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Interplay between MASLD, obesity and type 2 diabetes: epidemiology, shared pathways and clinical implications

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD), obesity and type 2 diabetes mellitus (T2DM) are interconnected global epidemics that frequently coexist and mutually reinforce disease progression and adverse clinical outcomes. MASLD, the most prevalent chronic liver disease worldwide, is now recognised as a hepatic manifestation of systemic metabolic dysfunction. The coexistence of the triad markedly accelerates MASLD progression, heightens cardiometabolic risk and shifts mortality patterns towards cardiovascular disease, the leading cause of death in affected populations. However, most available data describe MASLD in association with either obesity or T2DM individually, while robust epidemiological or mechanistic evidence for their combined overlap remains scarce. This review synthesises current evidence on the epidemiological overlap and shared risk architecture linking MASLD, obesity and T2DM. We examine integrated pathophysiological and molecular mechanisms underpinning this triad, including insulin resistance, lipotoxicity, mitochondrial dysfunction, endoplasmic reticulum stress, transcriptional and epigenetic dysregulation and gut–liver axis perturbations. We further discuss the clinical implications of this shared biology, emphasising integrated screening strategies and presenting an evidence-based algorithm for non-invasive identification of advanced hepatic fibrosis within the triad. We review evidence-based therapeutic approaches, including mechanism-based pharmacological therapies, and highlight their differential effects on weight, glycaemic control and liver disease severity. Emerging research priorities and future directions for integrated cardiometabolic care are also outlined. Collectively, the review underscores the need for integrated hepatic–cardiometabolic care to improve clinical outcomes across this metabolic triad.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), obesity and type 2 diabetes mellitus (T2DM) are distinct, yet interconnected global epidemics.[1–4] MASLD, the most prevalent chronic liver disease worldwide, is closely intertwined with the rising burden of obesity, insulin resistance and T2DM. They frequently co-occur and share core pathophysiological pathways that drive the progression of the liver disease from simple steatosis to hepatocellular carcinoma (HCC).

The clinical impact of this triad, however, extends well beyond the liver. Their coexistence also markedly heightens the risk of major adverse cardiovascular events (MACE) and other extrahepatic complications, with cardiovascular disease (CVD) now recognised as the leading cause of mortality in MASLD populations.[5–7] Meta-analyses demonstrate approximately a 1.4–1.7 fold higher risk of MACE in individuals with MASLD compared with those without steatotic liver disease.[7–9] In parallel, MASLD is increasingly viewed as a hepatic manifestation and complication of T2DM, while T2DM and obesity accelerate the natural history of MASLD, underscoring their bidirectional, mutually reinforcing relationship.

These insights have prompted a paradigm shift from disease-specific, organ-centred care towards integrated metabolic management, in which MASLD, obesity and T2DM are approached as components of a common cardiometabolic spectrum. Recent comprehensive reviews reaffirm MASLD as a major global health burden and highlight its close metabolic links with obesity and T2DM. However, these conditions are typically examined in isolation or in pairs. The concept of a unified 'triple overlap' remains underexplored, and the distinct clinical implications of this combined phenotype are seldom addressed.

This review addresses this gap by examining the epidemiological overlap of the triad, synthesising mechanistic pathways linking these conditions, and discussing integrated screening and mechanism-based therapeutic strategies. The review was informed by a structured search of PubMed, Scopus

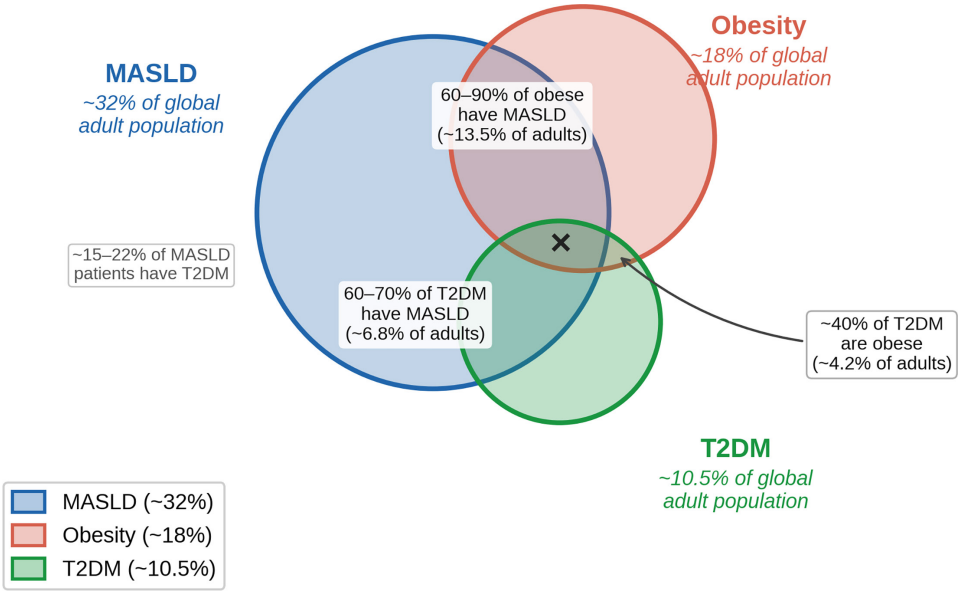

Figure 1 Global prevalence and overlap of MASLD, obesity and type 2 diabetes mellitus (T2DM). MASLD, metabolic dysfunction-associated steatotic liver disease.

and Web of Science using combinations of keywords including "MASLD", "NAFLD", "MASH", "obesity", "type 2 diabetes", "insulin resistance", "hepatic fibrosis", "pathophysiology", "non-invasive tests", "cardiovascular risk" and "treatment". Additional relevant publications were identified through manual screening of reference lists. We prioritised large epidemiological studies, meta-analyses, international guidelines and pivotal clinical trials. Much of the earlier literature used non-alcoholic fatty liver disease (NAFLD)/Non-alcoholic steatohepatitis (NASH terminology; these studies are interpreted as largely overlapping populations under the updated MASLD framework.

EPIDEMIOLOGY AND SHARED RISK FACTORS

MASLD, obesity and T2DM affect a substantial proportion of the global population, with estimated prevalences of 29%–38%, 16%–20% and 10%–11%, respectively.[3 10–14] Considerable epidemiological overlap exists among these conditions, reflecting their shared metabolic underpinnings (figure 1). This overlap is asymmetric, as MASLD prevalence is considerably higher among individuals with obesity or T2DM than the prevalence of obesity or diabetes among individuals with MASLD, underscoring the complex bidirectional nature of these metabolic disorders.[10 14 15]

MASLD, defined as hepatic steatosis occurring in the presence of at least one cardiometabolic risk factor, encompasses a disease spectrum from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), the progressive inflammatory phenotype that may advance to fibrosis, cirrhosis and HCC.[16] Current estimates suggest that MASLD alone affects about one-third of the global adult population.[3 15 17] This burden, however, varies across regions and populations and is strongly influenced by the presence of metabolic comorbidities, particularly obesity and T2DM.

The highest prevalence rates are reported in the Middle East and South America, followed by North America and parts of Asia, reflecting the parallel rise in obesity and T2DM.[4 10 12 13] In contrast, lower but steadily rising prevalence rates are observed in sub-Saharan Africa.[18] Ethnic disparities are also evident. Individuals of Hispanic ancestry show higher susceptibility to MASLD, partly driven by PNPLA3 variants, whereas individuals of African ancestry appear relatively protected despite similar obesity and T2DM prevalence.[19 20] This suggests genetic factors can modify the impact of metabolic risk within the triad. Sex differences are also observed, with higher prevalence in men during early adulthood and increasing rates among post-menopausal women, a pattern partly attributable to differences in visceral adiposity and diabetes risk but also reflecting loss of oestrogen-mediated metabolic protection after menopause.[21 22]

In individuals with obesity or T2DM, MASLD is 2–3 fold more common than in the general population, making it a leading hepatic manifestation of the global metabolic disease epidemic (figure 1).[15 17] Approximately 60%–70% of patients with T2DM have MASLD, and among those with MASLD, about half exhibit histological features of MASH.[17 23] T2DM not only increases the likelihood of MASLD but also accelerates progression to fibrosis and cirrhosis, nearly doubling the risk of advanced fibrosis and markedly increasing the risk of HCC compared with MASLD without diabetes.[24 25] The relationship is asymmetric, with only a 15%–22% overall proportion of those with MASLD having T2DM.[26] MASLD also worsens glycaemic control in people with established T2DM and independently increases the risk of incident T2DM in

those without diabetes, even after adjustment for body mass index.[27]

The epidemiological intersection with obesity is more striking. In obese populations, MASLD prevalence ranges from about 60% to over 90%, approaching near-universal in severe obesity (figure 1).[15 28] Visceral adiposity, in particular, is closely linked to more severe steatosis, higher rates of clinically significant fibrosis, decompensated cirrhosis and liver transplantation.[15 23 25]

The prevalence of the triple overlap—concurrent MASLD, obesity and type 2 diabetes—remains poorly quantified and represents an important knowledge gap. However, using established pairwise prevalences, we estimate ~3%–9% of adults worldwide are affected. These epidemiological patterns reflect shared pathogenic roots.

The shift in terminology from NAFLD to MASLD represents a shift in emphasis from alcohol exclusion to metabolic dysfunction, and a repositioning of steatotic liver disease within the broader cardiometabolic continuum.[16 29] This framework highlights the interconnected biology of the MASLD–obesity–T2DM triad, whose natural history remains heterogeneous. Obesity often precedes MASLD and T2DM, yet in some individuals, T2DM or MASLD may be diagnosed first.[30 31] This heterogeneity is also reflected in lean MASLD, where steatotic liver disease occurs in individuals without obesity but often with visceral adiposity and insulin resistance.[32] Genetic factors further contribute to the variability in disease susceptibility and progression. Heritable variants such as PNPLA3, TM6SF2 and MBOAT7 have been shown in recent genetic studies to contribute directly to hepatic fat accumulation and fibrosis independent of traditional metabolic risk factors, highlighting the multifactorial nature of MASLD.[32–34] These epidemiological and genetic observations collectively point to shared biological pathways linking MASLD, obesity and T2DM, at the molecular and cellular levels.

INTEGRATED PATHOPHYSIOLOGICAL AND MOLECULAR MECHANISMS LINKING MASLD, OBESITY AND TYPE 2 DIABETES

The shared biological pathways involve disturbances in substrate flux, intracellular signalling and immunometabolic regulation that drive hepatic lipid accumulation and progressive metabolic dysfunction. The interconnected mechanisms linking MASLD, obesity and T2DM are summarised in figure 2.

Insulin resistance: the central driver

Hyperinsulinaemia in T2DM, excess free fatty acids (FFAs) and pro-inflammatory cytokines from visceral adiposity can reduce insulin receptor synthesis and impair signal transduction processes, such as activation of hepatic protein kinase C, thereby disrupting cellular insulin signalling and resulting in insulin resistance.[35–37] Insulin resistance in hepatic, adipose and skeletal muscle tissues is a central physiological abnormality that links MASLD to obesity and T2DM. In adipose tissue, it enhances lipolysis, increasing the release of FFA that subsequently accumulate in the liver as triglycerides.[38 39] Within the liver, selective insulin resistance disrupts glucose metabolism

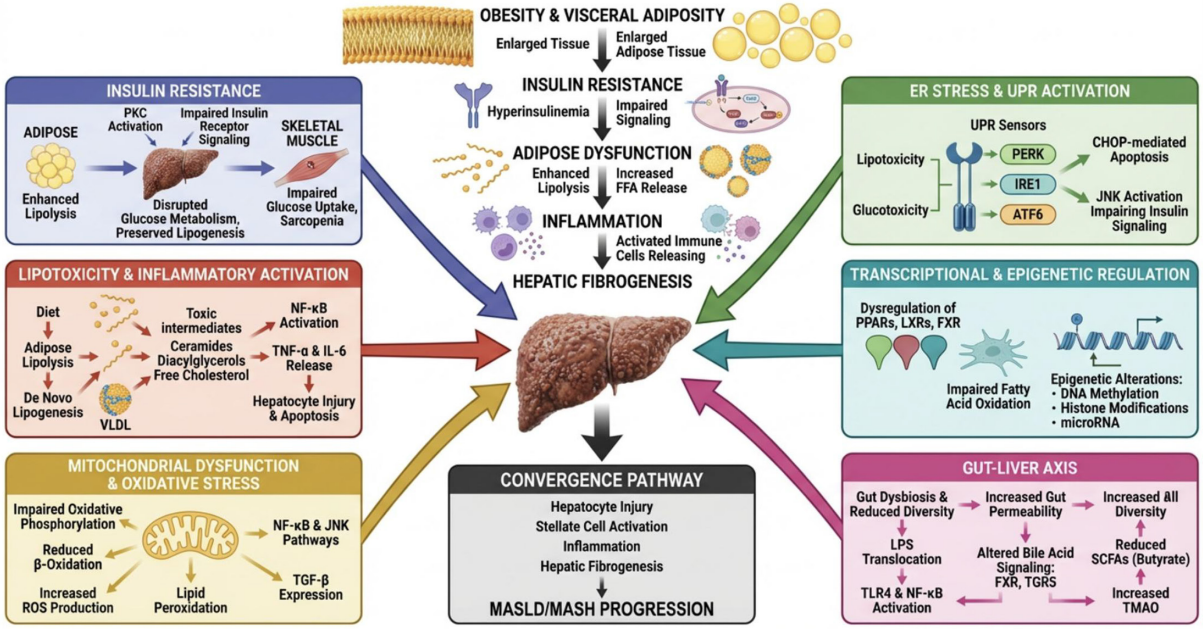

Figure 2 Integrated pathogenesis of the MASLD–obesity–T2DM triad. ER, endoplasmic reticulum; FFA, free fatty acid; FXR, farnesoid X receptor; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; LXRs, liver X receptors; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NF-κB, nuclear factor-κB; PPARs, proliferator-activated receptors; ROS, reactive oxygen species; SCFA, short-chain fatty acid; T2DM, type 2 diabetes mellitus; TGF-β, transforming growth factor-β; TGR5, Takeda G-protein-coupled receptor 5; TLR4, toll-like receptor 4; TMAO, trimethylamine N-oxide; TNF, tumour necrosis factor; UPR, unfolded protein response.

by diminishing glycogen synthesis and increasing gluconeogenesis while preserving lipogenesis, thereby promoting hyperglycaemia and hepatic steatosis.[38 40] In skeletal muscle, the primary site of insulin-mediated glucose disposal, impaired glucose uptake contributes to systemic hyperinsulinaemia. This is further exacerbated by sarcopenia and sarcopenic obesity, which worsen insulin resistance and promote hepatic fat accumulation.[32 41 42] Together, these disturbances form a vicious metabolic cycle that progressively amplifies insulin resistance, hepatic fat accumulation and glycaemic dysregulation, driving the parallel progression of MASLD, T2DM and obesity.

Lipotoxicity and inflammatory activation

Lipotoxicity occurs when FFA influx from diet, adipose tissue lipolysis and hepatic de novo lipogenesis exceeds the liver's capacity to channel fatty acids into β-oxidation or esterification pathways.[43–45] Toxic lipid intermediates such as ceramides, diacylglycerols and free cholesterol accumulate and activate pro-inflammatory signalling pathways, notably nuclear factor-κB (NF-κB), with downstream induction of tumour necrosis factor (TNF)-α and interleukin-6.[44 46 47] These mediators promote hepatocyte injury and apoptosis, impair insulin receptor signalling and initiate hepatic stellate cell activation, which drives fibrosis.[46 47] Obesity magnifies lipotoxicity through increased fatty-acid flux from hypertrophied adipose tissue, while T2DM intensifies these processes via hyperinsulinaemia and enhanced de novo lipogenesis.[48]

Mitochondrial dysfunction and oxidative stress

In MASLD, excess delivery of FFA to the liver imposes metabolic stress on hepatic mitochondria, resulting in impaired oxidative phosphorylation, reduced β-oxidation capacity and increased generation of reactive oxygen species (ROS).[45 49 50] When ROS production exceeds endogenous antioxidant and autophagic defences, oxidative stress ensues, leading to lipid peroxidation and activation of stress-responsive signalling pathways, including NF-κB and c-Jun N-terminal kinase.[45 50–52] These pathways promote the expression of pro-inflammatory and profibrotic mediators such as TNF-α and transforming growth factor-β, contributing to hepatocellular injury, stellate cell activation and fibrogenesis.[53]

Mitochondrial dysfunction and oxidative stress reinforce one another in a self-perpetuating cycle, whereby oxidative damage further impairs mitochondrial structure and function, amplifying ROS production and metabolic inflexibility. These abnormalities are more pronounced in individuals with obesity or type 2 diabetes, in whom chronic lipid and glucose oversupply intensifies mitochondrial stress, oxidative injury and mitochondrial DNA damage.[54 55] Obesity-associated MASLD is therefore characterised by lower mitochondrial fatty acid oxidation and higher ROS levels, particularly in MASH compared with simple steatosis.[54]

Endoplasmic reticulum stress and cellular dysfunction

Chronic overnutrition, excess fatty acids, glucotoxicity and inflammation are established drivers of endoplasmic reticulum (ER) stress in the liver, adipose tissue and pancreas in obesity, MASLD and T2DM.[56–58] Lipotoxicity and glucotoxicity disrupt ER homeostasis, triggering activation of the unfolded protein response through its principal sensors: protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme-1α (IRE1α) and activating transcription factor-6 (ATF6).[56 58 59]

While initially adaptive, persistent activation of these pathways promotes maladaptive signalling characterised by C/EBP homologous protein-mediated apoptosis, c-Jun N-terminal kinase activation with consequent impairment of insulin signalling and amplification of inflammatory cascades.[58 60 61] In the liver, sustained ER stress exacerbates hepatocellular injury and fibrogenesis, while systemically it reinforces insulin resistance and glycaemic dysregulation.[61–63] Thus, ER stress links chronic overnutrition and lipotoxicity to both hepatic disease progression and metabolic deterioration across the MASLD–T2DM–obesity spectrum.

Transcriptional and epigenetic regulation

Nuclear receptors (NR), including peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs) and the farnesoid X receptor (FXR), regulate lipid metabolism, bile acid homeostasis and insulin signalling in the liver and other metabolically active tissues.[64 65] In obesity and T2DM, reduced activity of these pathways contributes to impaired fatty-acid oxidation, dyslipidaemia and worsened insulin resistance.[66–68] Dysregulation of FXR and LXR also disturbs bile acid and cholesterol handling, further impairing metabolic flexibility. This is compounded by epigenetic alterations, including DNA methylation, histone modifications and microRNA-mediated repression, that also arise in response to chronic overnutrition, hyperglycaemia and lipotoxic stress, and further sensitise hepatocytes to iron-dependent lipid peroxidation and ferroptosis.[69 70] Together, these mechanisms alter transcriptional regulation, increase susceptibility to lipotoxic injury and promote the development of more severe MASLD phenotypes.

Gut–liver axis and microbiome interactions

Obesity and T2DM are associated with gut microbiota dysbiosis, reduced microbial diversity and impaired intestinal barrier integrity.[71 72] Increased gut permeability facilitates translocation of microbial products, particularly lipopolysaccharide, into the portal circulation, triggering hepatic toll-like receptor 4 (TLR4) activation and downstream NF-κB signalling, which promotes inflammatory and profibrotic pathways, thereby contributing to MASLD progression.[71–73]

Dysbiosis also modifies bile acid composition and signalling.[74] In MASLD, altered bile acid pools and microbial metabolism are associated with disrupted FXR

and Takeda G-protein-coupled receptor 5 (TGR5) signalling.[75 76] Impaired FXR activity contributes to disordered lipid and cholesterol homeostasis, favouring hepatic lipid accumulation, while reduced intestinal TGR5 signalling is associated with diminished glucagon-like peptide-1 secretion, adversely affecting glucose regulation, satiety and energy balance.[75 76]

In parallel, obesity, T2DM and MASLD are characterised by reduced production of beneficial short-chain fatty acids, particularly butyrate, which further weakens gut barrier integrity and insulin sensitivity.[77 78] In addition, increased gut-derived metabolites such as trimethylamine N-oxide have been linked to oxidative stress, inflammation and cardiometabolic risk.[79 80] These gut–liver axis disturbances reinforce hepatic steatosis, systemic insulin resistance and progressive liver injury in MASLD.

Collectively, these interconnected mechanisms form a network of self-reinforcing pathophysiological pathways. Understanding these integrated pathways is essential for identifying therapeutic targets that can disrupt these cycles and modify disease trajectories across the triad.

CLINICAL IMPLICATIONS AND INTEGRATED SCREENING

The frequent co-occurrence of MASLD, obesity and type 2 diabetes has important implications for clinical practice. Risk stratification based on single-organ paradigms may underestimate overall cardiometabolic burden. Contemporary care pathways, therefore, increasingly support integrated screening strategies that assess hepatic disease severity alongside cardiometabolic risk factors, enabling earlier identification of high-risk individuals and more coordinated preventive interventions.

Cardiometabolic risk assessment

CVD is the leading cause of mortality in MASLD, with increased risks of coronary artery disease, heart failure and arrhythmias.[5 16 81 82] The coexistence of obesity and T2DM further amplifies these risks.[16 83] Accordingly, international guidelines advocate routine cardiometabolic assessment for all individuals with MASLD, including evaluation for obesity, T2DM, hypertension and dyslipidaemia, rather than a liver-focused approach in isolation.[6 16]

Identification of high-risk liver disease

T2DM and obesity are the strongest predictors of progression to advanced fibrosis, cirrhosis and HCC in MASLD.[16 84] Epidemiological data also indicate a graded increase in mortality when MASLD coexists with T2DM and/or obesity, underscoring the importance of early identification of high-risk liver disease within this triad.[16 85] Accordingly, major societies, including European Association for the study of the Liver- European Association for the study of Diabetes,European Association for the study of Obesity EASL-EASD-EASO and the ADA, endorse screening for MASLD with clinically significant fibrosis in all adults with T2DM and in adults with obesity, particularly when additional metabolic risk factors are present.[16 86]

Current clinical pathways favour a stepwise approach in which initial risk stratification with simple fibrosis risk scores such as Fibrosis-4 (FIB-4) is followed, when indeterminate or elevated, by second-line assessment using vibration-controlled transient elastography or specialised serum fibrosis panels.[16 87 88] However, uncertainties remain regarding optimal cut-off values and diagnostic performance, particularly in obesity and T2DM, where accuracy may be attenuated.[87–89] To address inconsistencies across existing guidelines and to support practical implementation of fibrosis risk-stratification in high-risk metabolic populations, we developed an evidence-based clinical algorithm that synthesises recommendations from AASLD, EASL–EASD–EASO, AGA and ADA guidance documents, together with supporting validation studies (figure 3).[16 86 90–94]

Emerging indices such as the Fibrotic NASH Index, metabolomics-based scores (eg, MASEF) and the FIB-C3 model show promising diagnostic performance in high-risk metabolic cohorts but require further external validation.[95–97] Future risk-stratification frameworks are likely to integrate clinical scores with genetic susceptibility variants (eg, PNPLA3, TM6SF2, MBOAT7), imaging-derived adiposity measures and novel metabolic or inflammatory biomarkers to enable more precise and personalised risk assessment.

However, in LMIC, access to second-line non-invasive fibrosis assessment tools and the emerging indices remains limited. In such settings, FIB-4—a simple, widely available and low-cost test—can be used as the sole triage tool. Patients with intermediate (FIB-4 ≥1.3) or high-risk scores can then be referred to specialist hepatology services (figure 3). This approach can still reduce unnecessary consultations and prioritise specialist care for those at the highest risk of advanced fibrosis.

THERAPEUTIC INTERVENTIONS AND MANAGEMENT STRATEGIES

The intertwined pathways of the triad also have important therapeutic implications, as interventions targeting one component can often improve the others. Lifestyle, pharmacological and surgical interventions act on shared pathways and can produce synergistic improvements in weight, glycaemic control and liver disease severity.

Lifestyle interventions

Lifestyle modification, encompassing weight loss, dietary changes and physical activity, remains first-line therapy for MASLD and related metabolic diseases due to its safety, accessibility and cost-effectiveness.[98 99] In MASLD, a modest weight loss of 5%–10% improves hepatic steatosis and metabolic parameters, whereas a ≥10% loss is associated with resolution of steatohepatitis and regression of mild-to-moderate fibrosis.[100 101] Evidence for reversal of advanced fibrosis is, however, limited.

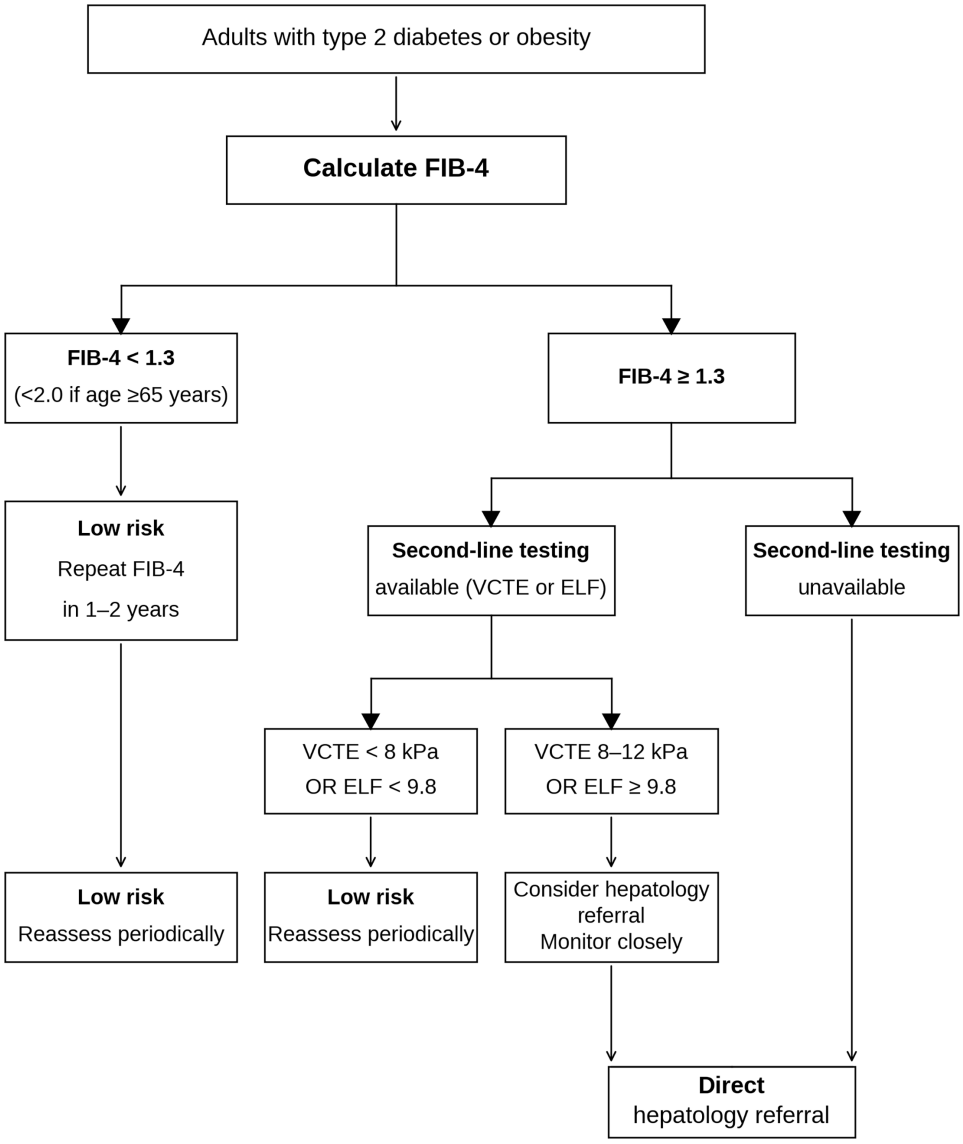

Figure 3 Screening algorithm for advanced fibrosis in MASLD among adults with T2DM or obesity. FIB-4, Fibrosis-4; MASLD, metabolic dysfunction-associated steatotic liver disease; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

In T2DM, weight loss of 5%–10% improves insulin sensitivity and glycaemic control, whereas ≥10%–15% loss can induce T2DM remission.[100 102] A 2025 meta-analysis confirmed the dose-dependent relationship between weight reduction and T2DM remission.[103]

Mediterranean and low-carbohydrate diets improve insulin sensitivity, lipid profiles, inflammation and cardiometabolic risk, often independent of weight loss.[104 105] Combined aerobic and resistance exercises, including high-intensity interval training, also enhance insulin sensitivity, improve mitochondrial function, reduce oxidative stress and decrease hepatic and visceral fat.[106 107] However, long-term adherence is challenging, and the benefits may diminish over time, highlighting the need for sustainable and structured lifestyle programmes.[16 104]

Pharmacological interventions

The pharmacotherapy landscape for MASLD, obesity and T2DM includes both established and emerging metabolic therapies alongside liver-specific agents. In this review, we classify therapies according to their primary mechanistic targets, namely metabolic or insulin-sensitising, transcription-modulating therapies and other mechanism-based classes that are under active investigation. We also distinguish therapies with biopsy-proven histological benefit from those with evidence based primarily on metabolic or surrogate endpoints to guide clinical decision-making. Table 1 provides an evidence-based summary of the therapeutic roles and strength of evidence for currently available agents, integrating major society guidance and pivotal clinical trial data.

Metabolic or insulin sensitisers

Incretin-based therapies

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are now a central treatment for T2DM and obesity and are increasingly used to target MASLD/MASH. In MASLD, they reduce hepatic steatosis and liver injury primarily

Table 1 Evidence-based pharmacotherapy options for the MASLD-obesity-T2DM triad

Therapy class	Weight loss	HbA1c reduction	Effect on steatosis	Evidence for fibrosis improvement	Clinical notes
Metabolic or insulin sensitisers					
GLP-1 receptor agonists	Moderate–high	Strong	Strong	Moderate (liraglutide); emerging (semaglutide)	Biopsy-proven NASH resolution; cardiovascular benefit
Dual incretin agonists	High	Strong	Strong	Emerging (phase 2/3 ongoing)	Superior metabolic effects; investigational
Triple incretin agonists	High	Strong	Strong	Emerging	Investigational next-generation incretin therapies
SGLT2 inhibitors	Modest–moderate	Moderate	Moderate	Limited: surrogate markers only	Cardiovascular and renal benefits; oral therapy
Transcription-modulating therapies					
PPARγ agonists (pioglitazone)	Weight gain	Strong	Strong	Moderate	Biopsy-proven in T2DM with MASH; tolerability concerns
Pan-PPAR agonists	None	Modest	Strong	Strong	Lanifibranor—most promising investigational NR modulator; phase 3 ongoing
Dual PPARα/γ agonists	None	Moderate	Moderate	Limited biopsy data	Saroglitazar approved in India
FXR agonists	None	None	Modest	Moderate but safety concerns	Obeticholic acid limited by tolerability: not approved
THR-β agonists (Resmetirom)	None	None	Strong	Strong	First FDA-approved MASH-specific therapy; biopsy-proven

Effect size categories: None–no clinically meaningful effect; Modest–small but measurable effect; Moderate–clinically meaningful improvement; High–large effect with substantial clinical impact.
Evidence descriptors: Strong–consistent evidence from randomised trials or histological outcomes; Moderate–supportive randomised trial data, but limited consistency; Limited–indirect evidence, small studies or surrogate endpoints only; Emerging–early-phase or ongoing trial data without definitive outcomes.
FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NR, nuclear receptor; PPAR, peroxisome proliferator-activated receptor; SGLT2, sodium-glucose cotransporter-2; T2DM, type 2 diabetes mellitus; THR-β, thyroid hormone receptor beta.

through weight loss and improvements in insulin resistance, complemented by additional anti-inflammatory and metabolic effects.[108 109] First-generation GLP-1 RAs, liraglutide and semaglutide, have demonstrated biopsy-proven MASH resolution in phase 2 trials, with modest effects on fibrosis.[110 111] Their established cardiovascular benefits and regulatory approval for T2DM and obesity support use when metabolic comorbidities predominate, although they are not yet approved specifically for MASH.[112 113]

Next-generation dual and triple incretin agonists that co-target GLP-1, GIP and/or glucagon receptors, such as tirzepatide, survodutide, pemvidutide and retatrutide, produce greater weight loss of about 15%–25% and glycated haemoglobin reductions of 1.9%–2.4% than the first-generation GLP-1 RAs.[114 115] These multi-agonists produce marked reductions in liver fat of >50%–60% and have demonstrated early signals of improved fibrosis in phase 2 studies.[116–118] Histological outcomes from phase 3 trials are awaited, but these agents represent promising disease-modifying options for the triad.

Sodium-glucose co-transporter-2 inhibitors

Sodium-glucose co-transporter-2 inhibitors improve glycaemic control and induce modest weight loss through urinary glucose excretion.[119] Clinical studies in patients with T2DM and MASLD demonstrate reductions in hepatic steatosis and improvements in fibrosis biomarkers, although evidence is largely based on surrogate endpoints rather than biopsy outcomes.[120 121] Their established cardiovascular and renal benefits, combined with favourable metabolic effects, support their use in patients with MASLD and T2DM, particularly when cardiometabolic comorbidities predominate.

Transcription-modulating therapies

NR modulators

NR modulators are mechanistically important to MASLD/MASH therapeutics because they regulate lipid metabolism, insulin sensitivity, inflammation and fibrogenesis at the transcriptional level.[122 123]

Pioglitazone, a PPARγ agonist, has the longest clinical experience and most robust biopsy data among currently

available agents for MASH. It has demonstrated MASH resolution and modest fibrosis improvement in T2DM in patients with biopsy-proven MASH in randomised controlled trials.[123–125] Although weight gain, fluid retention and fracture risk limit its broader use, it remains a low-cost option for consideration by clinicians.[126] PXL065, a deuterium-stabilised pioglitazone derivative, achieved significant liver fat reductions and fibrosis marker improvements without weight gain or oedema in phase 2 trials.[127 128]

Lanifibranor, a pan-PPAR agonist, has shown the most promising phase 2 results with both NASH resolution and fibrosis improvement; phase 3 trials are ongoing.[125 129 130] Saroglitazar, a dual PPARα/γ agonist, has shown antisteatotic and metabolic benefits in clinical studies and is now approved for MASH in India.[126 131 132] Despite evidence that FXR therapies have some of the most effective anti-inflammatory and antifibrotic effects in MASH, obeticholic acid has not been approved due to safety concerns.[133 134] Several newer agents are under development.[122 125]

Thyroid hormone receptor-β agonists

Thyroid hormone receptor-β (THR-β) agonists target hepatic lipid metabolism. In March 2024, resmetirom, a liver-directed selective THR-β agonist, became the first Food and Drug Authority-approved pharmacotherapy for MASH with moderate-to-advanced fibrosis.[135] In the pivotal MAESTRO-NASH phase 3 trial, resmetirom caused significant reductions in liver fat, increased MASH resolution, improved fibrosis, reduced Low density lipoprotein cholesterol and had a favourable safety profile.[135 136] Resmetirom, therefore, is suitable for patients with established fibrotic disease where metabolic optimisation alone may be insufficient.

Other mechanism-based classes

Other mechanism-based classes, including antioxidants, mitochondrial-targeted therapies and emerging microbiome-directed interventions, are under active investigation and may address pathophysiologic components not directly targeted by current metabolic or transcription-modulating agents.[125] Vitamin E has shown histological improvement in non-diabetic MASH, but its benefits are limited in T2DM and remain controversial due to inconsistent fibrosis outcomes and safety concerns.[92 126] Probiotics, prebiotics, postbiotics and engineered bacteria, although promising mechanistically, remain investigational and lack robust biopsy-proven efficacy in MASLD/MASH and T2DM.[137 138]

Bariatric surgery

Bariatric surgery remains the most effective intervention for severe obesity, producing sustained total weight loss of approximately 25%–30% and T2DM remission in around 50%–70% of patients.[139 140] These metabolic improvements translate into substantial hepatic benefits, including reductions in steatosis, necroinflammation and fibrosis.[141–143] The underlying mechanisms extend beyond the weight loss and improved insulin sensitivity to enhanced incretin (notably GLP-1) secretion, altered bile-acid signalling and shifts in gut microbiota.[143 144]

Both Roux-en-Y gastric bypass and sleeve gastrectomy demonstrate comparable improvements in liver fat, disease activity and MASH resolution with fibrosis reductions in a subset of patients.[140 141 145 146] Meta-analyses report about 70% reductions in liver fat by MRI-Proton density fat fraction, 40%–60% reductions in disease activity over 1–5 years and a 17%–25% decrease in the prevalence of significant fibrosis.[142 147 148]

Contemporary guidance, therefore, increasingly considers MASLD severity and T2DM when evaluating bariatric surgery eligibility.[16 149] Although MASLD alone is not yet an independent indication, early referral for surgical assessment should be considered in appropriate candidates with the metabolic triad.

Despite improvements in steatosis and steatohepatitis with multiple interventions, robust data on long-term clinical outcomes remain limited. Many trials rely on surrogate endpoints, including reductions in liver fat and histological improvement in MASH or fibrosis, often over relatively short follow-up periods. Evidence demonstrating their efficacy in the prevention of cirrhosis, HCC or liver-related mortality is sparse. Additionally, the availability and affordability of several of these emerging therapies are limited in many resource-constrained settings. These pose challenges for global implementation efforts to address the expanding burden of the triad.

FUTURE DIRECTIONS AND RESEARCH PRIORITIES

Future strategies for managing the interconnected triad of MASLD, obesity and T2DM should begin by addressing the lack of robust epidemiological data on the combined overlap of all three conditions. This will strengthen the shift in care models from disease-specific silos towards integrated cardiometabolic management.

A key priority should be the development and validation of accessible, scalable, non-invasive biomarkers and imaging tools to improve risk stratification, guide treatment selection and support longitudinal monitoring. Therapeutic innovation should focus on multitarget pharmacotherapies capable of simultaneously improving metabolic dysfunction, hepatic inflammation and advanced fibrosis. Parallel efforts should advance rational combination approaches that integrate metabolic therapies and liver-directed agents. Longer-term studies would be needed to determine whether these therapies translate into clinically meaningful liver-related outcomes.

Digital health platforms, including mobile applications, continuous glucose monitoring and wearable sensors, offer a scalable opportunity to support sustained lifestyle modification, enhance self-management and monitor metabolic parameters. Precision medicine approaches leveraging genomic, metabolomic, transcriptomic and

microbiome data may further refine patient stratification and guide individualised therapy.

Finally, a broader adoption of multidisciplinary care models that link hepatology, endocrinology, cardiology, nutrition and primary care will be critical for delivering holistic, cost-effective management of this metabolic triad. Future research should also address implementation strategies and equitable access to therapies, particularly in LMIC settings.

CONCLUSIONS

The convergence of MASLD, obesity and T2DM reflects a shared pathophysiological foundation rooted in insulin resistance, lipotoxicity, inflammation, oxidative stress, mitochondrial dysfunction and gut microbiome alterations. Recognising this interconnectedness supports a shift from disease-specific management to coordinated, multidisciplinary care aimed at modifying risk across the entire cardiometabolic–hepatic spectrum.

Lifestyle modification remains the cornerstone of therapy, supported by emerging pharmacotherapies and bariatric surgery for selected patients. Precision medicine approaches and integrated care pathways offer opportunities for earlier detection and targeted intervention. Future research should focus on biomarker discovery, therapeutic synergy and equitable implementation of integrated care models to improve long-term outcomes across this metabolic continuum.

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