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Metabolic-Dysfunction-Associated Steatotic Liver Disease in Type 2 Diabetes Mellitus: From Pathophysiology and Screening to Therapeutic Strategies

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Abstract

Metabolic-dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes mellitus (T2DM) share insulin-resistance-driven metabolic derangements that promote hepatic steatosis, systemic inflammation, and fibrogenesis. MASLD affects approximately 65% of adults with T2DM, with nearly half meeting histologic criteria for metabolic-dysfunction-associated steatohepatitis (MASH), significantly increasing the risk for cirrhosis, hepatocellular carcinoma, and cardiovascular events. Key pathophysiologic mechanisms include upregulated de novo lipogenesis, impaired β-oxidation, and lipotoxic signaling cascades, establishing a bidirectional relationship in which MASLD worsens glycemic control and T2DM accelerates fibrotic progression. Randomized clinical trials have shown that glucagon-like peptide-1 (GLP-1) receptor agonists reduce hepatic fat fraction by approximately 20% to 40% and improve aminotransferase levels, while sodium-glucose cotransporter 2 inhibitors achieve modest reductions in steatosis with additional cardiometabolic benefits; extending these metabolic effects into histologic disease modification, semaglutide has become the first GLP-1 receptor agonist to receive US Food and Drug Administration accelerated approval for anti-fibrotic benefit in MASH, based on fibrosis improvement demonstrated in the phase 3 ESSENCE trial among adults with moderate-to-advanced fibrosis (F2–F3) without cirrhosis, thereby establishing its role beyond metabolic control as a disease-modifying therapy. Dual and triple incretin agonists yield additive improvements in glycemic and hepatic endpoints in early disease, although histologic antifibrotic efficacy remains unproven. In advanced fibrosis, phase II and III trials of agents targeting apoptosis-signal-regulating kinase 1, farnesoid X receptor, and fibroblast growth factor 21 pathways have produced mixed results, emphasizing the need for more effective therapies. Integration of validated noninvasive fibrosis assessment (eg, fibrosis-4 index with transient elastography), sustained weight loss of ≥10%, evidence-based antidiabetic pharmacotherapy, and timely enrollment in clinical trials within multidisciplinary care frameworks offers the greatest potential to modify the MASLD-T2DM disease trajectory and improve long-term outcomes.

Key Words: Metabolic-dysfunction-associated steatotic liver disease, metabolic-dysfunction-associated steatohepatitis, type 2 diabetes mellitus, fibrosis-4 index, glucose lowering agents, insulin resistance

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a growing global health problem. By 2050, more than 1.31 billion people worldwide are expected to have diabetes, mostly T2DM[1]. Individuals with T2DM are at increased risk of a spectrum of complications, including cardiovascular disease (CVD), chronic kidney disease (CKD), heart failure, and metabolic-dysfunction-associated steatotic liver disease (MASLD)[2].

MASLD is defined by the presence of hepatic steatosis in conjunction with at least 1 of 5 cardiometabolic risk factors aligned with metabolic syndrome components.[3] Globally, approximately 65% of individuals with T2DM are affected by MASLD[4]. The disease spectrum ranges from simple steatosis to steatohepatitis, cirrhosis, liver decompensation, and ultimately hepatocellular carcinoma (HCC)[3].

MASLD and T2DM share a complex, bidirectional relationship in which each condition exacerbates the other. MASLD promotes both peripheral and hepatic insulin resistance (IR), leading to dyslipidemia, hyperglycemia, and hyperinsulinemia[5]. Consequently, individuals with MASLD are 2 to 3 times more likely to develop T2DM than are those without MASLD[6]. T2DM drives hepatic fibrogenesis, substantially increasing the risk of advanced fibrosis (stage F2 or higher) and HCC[7]. Approximately 15% to 25% of individuals with T2DM present with clinically significant liver fibrosis, histologically defined as moderate to severe (stage F2 or greater)[7]. T2DM not only doubles the risk of HCC but also increases HCC-related mortality by 1.5-fold in individuals with MASLD[8].

This article integrates emerging data on MASLD prevalence in T2DM populations, clarifies underlying mechanisms, and critically assesses approaches for early diagnosis and therapeutic intervention.

2. Epidemiology: The Prevalence and Incidence of MASLD in Prediabetes and T2DM

MASLD is the leading global cause of chronic liver disease. Recent evidence indicates that the prevalence of MASLD among individuals with prediabetes is 37% to 50% and that individuals with prediabetes have a 2.5-fold higher risk of MASLD, an 8.5-fold higher risk of significant fibrosis, and a nearly 6-fold higher risk of advanced fibrosis relative to normoglycemic individuals[9]. MASLD affects more than 38% of adults globally. Among individuals with T2DM, the prevalence rates of MASLD, metabolic-dysfunction-associated steatohepatitis (MASH), and cirrhosis are 70%, 35%, and 7%, respectively[10]. The bidirectional relationship between MASLD and T2DM is underscored by evidence indicating a 2- to 3-fold increased risk of T2DM in individuals with MASLD[6], with overweight, obesity, and MASLD identified as key contributors to both prediabetes and T2DM[11]. T2DM is associated with an increased risk of fibrosis progression, with 15% to 38% of affected individuals also exhibiting MASH and clinically significant fibrosis or cirrhosis; moreover, MASLD is linked to higher prevalence rates of metabolic comorbidities. For example, 69%, 38%, 43%, and 54% of individuals with MASLD have prediabetes, CKD, CVD, and cancer, respectively[10]. Prevalence rates of MASLD with comorbid T2DM differ by region. For example, prevalence rates of MASLD with comorbid T2DM are 80% in Eastern Europe, 71% in the Middle East, and 53% in Africa[12]. These differences are attributed to regional differences in metabolic comorbidities, acquired risk factors (eg, obesity, diabetes burden, and socioeconomic status), and genetic polymorphisms (eg, PNPLA3, TM6SF2, and MBOAT)[13].

In Taiwan and across East Asia, global metabolic trends are further accentuated by popula-

tion-specific characteristics that confer heightened metabolic vulnerability. Data from the National Nutrition and Health Survey in Taiwan (NAHSIT) demonstrate a high prevalence of central obesity and clustering of metabolic syndrome components at comparatively lower body mass index (BMI) thresholds among Taiwanese adults,[14] underscoring a population-level predisposition to metabolic dysfunction. Although NAHSIT does not directly assess hepatic steatosis or IR, these metabolic phenotypes are well-established contributors to MASLD pathogenesis and support the inference that this metabolic milieu is permissive to hepatic fat accumulation. Consistent with broader Asian epidemiology, hepatic steatosis affects approximately one-quarter to one-third of adults, with prevalence increasing sharply in the presence of dysglycemia;[15] within this context, MASLD is highly prevalent among Asian populations with metabolic risk factors and is increasingly recognized as an early hepatic manifestation of systemic insulin resistance. As glucose dysregulation progresses to overt T2DM, disease burden escalates substantially, with MASLD prevalence rising to approximately 60% to 75% and a markedly increased risk of progressive liver disease, including advanced fibrosis, cirrhosis, and liver-related morbidity.[15-17] Longitudinal studies in metabolically at-risk populations further indicate that hepatic steatosis develops at clinically meaningful rates among individuals with dysglycemia, while patients with T2DM experience substantially accelerated progression to advanced liver disease compared with metabolically healthy individuals.[4,15,18] Collectively, these observations highlight the importance of early MASLD screening, risk stratification, and timely metabolic intervention in Taiwanese and other Asian populations with prediabetes and T2DM, in whom visceral adiposity, ectopic fat deposition, and IR occur at lower BMI thresholds than in Western populations.[14,19]

3. MASLD as a Disease Modifier in Chronic Viral Hepatitis

MASLD increasingly functions as a clinically meaningful disease modifier in patients with chronic viral hepatitis, particularly hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. Evidence from epidemiologic and mechanistic studies indicates that MASLD can accelerate fibrosis progression, increase the risk of HCC, and contribute to persistent liver injury even when viral replication is controlled.[20-22] These interactions arise from the convergence of metabolic inflammation, lipotoxicity, and insulin resistance with viral-mediated necroinflammation, creating a synergistic environment that promotes hepatic fibrogenesis.

In chronic hepatitis B, steatosis is typically driven by host metabolic factors rather than viral mechanisms. Patients with HBV who also have MASLD or metabolic syndrome exhibit higher fibrosis stages and a greater likelihood of progression to cirrhosis compared with those without metabolic dysfunction.[22,23] In patients with chronic hepatitis B receiving nucleos(t)ide analogue therapy, the presence of concurrent hepatic steatosis has been shown to independently increase the risk of HCC.[22] These findings suggest that MASLD can blunt the antifibrotic benefits of viral suppression and should be considered a parallel therapeutic target in HBV management.

In chronic hepatitis C, the interaction between steatosis and viral injury is even more pronounced. HCV, particularly genotype 3, can directly induce steatosis, while MASLD contributes an additional metabolic burden that accelerates fibrosis progression.[24] Before the advent of direct-acting antivirals (DAAs), steatosis and IR were associated with reduced sustained virologic response to interferon-based therapy. Although DAAs achieve near-universal viral clearance, patients with persistent MASLD or metabolic risk factors remain at

elevated risk for fibrosis progression and HCC after cure, especially when advanced fibrosis is present at baseline.[25,26] These observations underscore that viral eradication does not fully normalize liver-related risk when metabolic dysfunction persists.

Taken together, MASLD acts not merely as a comorbidity but as a pathophysiologic amplifier of chronic viral hepatitis. Its presence alters disease trajectory, modifies treatment response, and influences long-term outcomes. For clinicians managing HBV or HCV, assessment and treatment of metabolic dysfunction should be integrated into routine care, with attention to weight reduction, glycemic control, and cardiometabolic risk modification. This dual-axis approach—targeting both viral and metabolic drivers—is essential for reducing fibrosis progression and HCC risk in patients with chronic viral liver disease complicated by MASLD.

4. Bidirectional Pathophysiological Interaction Between T2DM and MASLD

T2DM and MASLD are interrelated manifestations of metabolic syndrome that frequently coexist owing to overlapping pathophysiologic mechanisms. Shared determinants—including genetic susceptibility, overnutrition, sedentary behavior, physical inactivity, obesity, chronic low-grade inflammation, and IR—contribute to the onset and progression of both disorders[27,28]. Their bidirectional interaction exacerbates hyperglycemia, accelerates hepatic injury, and increases the risk of extrahepatic complications and mortality beyond that observed with T2DM alone[27,28].

4.1 MASLD as a Driver of Incident T2DM

MASLD promotes systemic IR and glucose dysregulation, creating a metabolic milieu that drives T2DM development[29,30]. Through hepatic steatosis and inflammation, MASLD disrupts lipid and glucose homeostasis and alters endocrine crosstalk with peripheral tissues, destabilizing glycemic control[29,30]. MASLD is an upstream driver of T2DM. MASLD exerts lipotoxic, inflammatory, and hormonal signals that induce β-cell stress and systemic IR, key contributors to incident T2DM[29,30]. The mechanisms linking MASLD to T2DM are detailed in Figure 1.

4.1.1 Hepatic IR

In MASLD, excess free fatty acids (FFAs) and de novo lipogenesis (DNL) generate lipotoxic intermediates that impair insulin receptor signaling within hepatocytes, attenuating insulin-mediated suppression of hepatic glucose production and contributing to hyperglycemia[31]. Hepatic IR further exacerbates systemic IR by increasing very-low-density lipoprotein (VLDL) secretion and altering substrate fluxes, resulting in ectopic lipid accumulation in peripheral tissues[31]. Clinically, impaired hepatic insulin action is a central mechanism linking hepatic steatosis to high fasting plasma glucose levels and progressively abnormal oral glucose tolerance, ultimately leading to T2DM in susceptible individuals[29,31].

4.1.2 Lipotoxicity

When adipose tissue exceeds its storage capacity, FFAs overflow to the liver, where toxic lipid species—such as ceramides and diacylglycerols—accumulate and activate stress kinases that impair insulin signaling and injure hepatocytes [31]. Lipotoxicity induces oxidative stress and endoplasmic reticulum stress, intensifying cellular damage and initiating apoptotic pathways that perpetuate inflammation and fibrosis, thereby exacerbating both hepatic and systemic IR[31]. This self-reinforcing lipotoxic cycle—characterized by excessive lipid influx, impaired mitochondrial oxidation, and toxic lipid accumulation—establishes a mechanistic link between hepatic steatosis and the IR phenotype that precedes T2DM[29,31].

4.1.3 Inflammatory cytokine release

Steatosis and hepatocyte injury activate innate immune pathways and inflammasome complexes, leading to elevated levels of proinflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6), which disrupt insulin receptor substrate signaling in hepatic and peripheral tissues[31]. The resulting low-grade, chronic inflammation originating from the steatotic liver contributes to systemic IR, impairs glucose uptake in

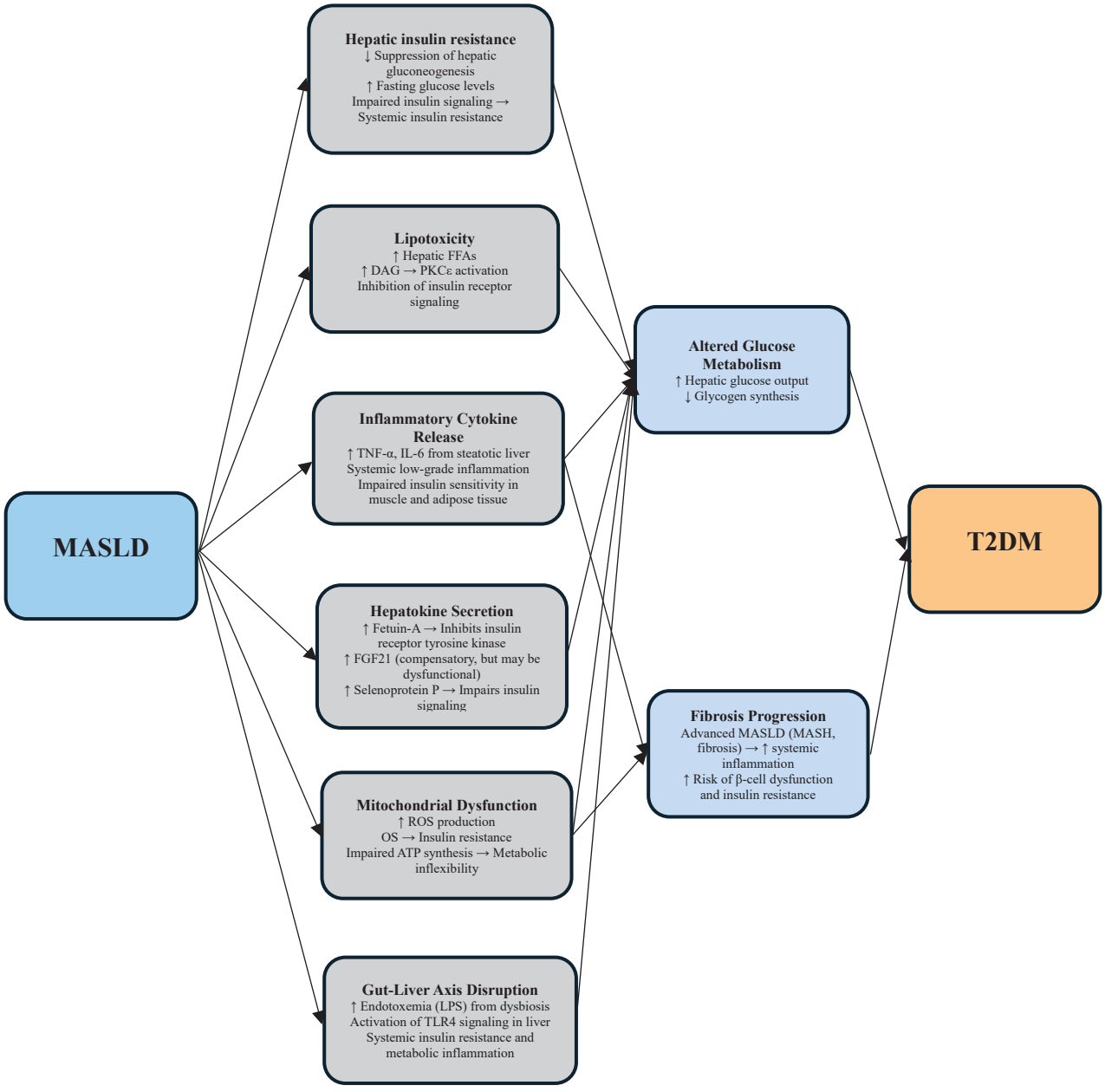

Figure 1. Mechanisms linking MASLD to T2DM onset. MASLD initiates hepatic insulin resistance, lipotoxicity, inflammatory cytokine release, hepatokine secretion, mitochondrial dysfunction, and gut-liver axis disruption, which collectively promote altered glucose metabolism and progressive hepatic fibrosis; these interrelated mechanisms ultimately converge on the pathogenesis of T2DM. Abbreviations: ROS, reactive oxygen species; OS, oxidative stress; T2DM, type 2 diabetes mellitus; MASLD, metabolic-dysfunction-associated steatotic liver disease; TLR4, toll-like receptor 4; LPS, lipopolysaccharide; MASH, metabolic-dysfunction-associated steatohepatitis; ATP, adenosine triphosphate; FGF21, fibroblast growth factor 21; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; DAG, diacylglycerol; PKCε, protein kinase C epsilon.

skeletal muscle, and exacerbates adipose tissue dysfunction[30,31]. These inflammatory mediators sustain a pathogenic cycle in which progressive IR enhances adipose lipolysis and FFA flux to the liver, further amplifying cytokine production and accelerating glycemic deterioration toward T2DM[29,31].

4.1.4 Hepatokine secretion

The steatotic and inflamed liver undergoes endocrine reprogramming, altering hepatokine secretion profiles that regulate insulin sensitivity in skeletal muscle and adipose tissue and modulate pancreatic β-cell stress responses[29,30]. Dysregulated hepatokine signaling converges with inflammatory cytokines and lipid-derived mediators to propagate whole-body IR, reinforcing both fasting and postprandial hyperglycemia[29,30]. Through endocrine crosstalk, MASLD acts as a systemic driver of metabolic deterioration rather than a localized hepatic condition, thereby facilitating progression to overt T2DM[29,30].

4.1.5 Mitochondrial dysfunction and cellular stress

In MASLD, mitochondrial overload with FFAs and impaired oxidative capacity lead to the excessive generation of reactive oxygen species, which damage cellular proteins and lipids and activate stress pathways that attenuate insulin signaling[31]. Mitochondrial dysfunction intersects with endoplasmic reticulum stress and inflammasome activation, amplifying hepatocyte injury, cytokine release, and lipid peroxidation—each contributing to the progression of IR[31]. These convergent stress responses impair hepatic metabolic flexibility, exacerbate gluconeogenic output, and promote systemic metabolic inflexibility, thereby accelerating the onset of T2DM[29,31].

4.1.6 Altered hepatic glucose metabolism

In MASLD, hepatic IR results in inappropriately elevated hepatic glucose production through increased gluconeogenesis and impaired glycogen synthesis, contributing to fasting hyperglycemia[31]. Simultaneously, the lipotoxic suppression of insulin signaling reduces hepatic responsiveness to postprandial insulin, allowing continued glucose output despite prevailing hyperinsulinemia[31]. This disruption of hepatic glucose regulation, in concert with peripheral IR, establishes the metabolic foundation for progressive dysglycemia and eventual diagnosis of T2DM[29,31].

4.1.7 Fibrosis progression

Persistent lipotoxic and inflammatory injury in MASLD activates hepatic stellate cells and fibrogenic signaling pathways, resulting in collagen deposition and architectural distortion that further compromise hepatic metabolic regulation[31]. Hepatic fibrosis is associated with more profound metabolic dysfunction, including intensified IR and impaired lipid handling, both of which heighten the risk of hyperglycemia[29,31]. As fibrosis progresses, the liver's ability to buffer against metabolic stress declines, amplifying systemic drivers of T2DM pathogenesis[29,31].

4.1.8 Gut-liver axis disruption

In MASLD, dysbiosis and low-grade intestinal inflammation disrupt gut-derived metabolites and immune signaling, exacerbating hepatic inflammation and IR.[17] Perturbations in the gut-liver axis reinforce systemic metabolic dysfunction, impair glucose tolerance, and promote progression toward T2DM[29,30]. The interactions between the gut, liver, and peripheral tissues highlight the mechanistic basis by which MASLD frequently precedes and predicts incident T2DM[29,30].

Taken together, these mechanisms establish MASLD as a metabolically active condition that not only reflects but actively drives the pathogenesis of T2DM. Early identification and targeted interven-

tion are essential to mitigate progression and reduce cardiometabolic risk[10,29].

4.2 T2DM as a Driver of Incident MASLD

MASLD affects nearly two-thirds of individuals with T2DM, and MASH affects up to 40% of individuals with T2DM. This underscores their shared pathobiology and highlights a need for integrated metabolic care[32]. Lipotoxicity and low-grade inflammation mechanistically connect glycemic dysregulation to hepatocellular injury, fibrosis, and adverse hepatic and cardiometabolic outcomes[29,33]. The mechanisms linking T2DM to MASLD are detailed in Figure 2.

4.2.1 IR

In T2DM, adipose tissue IR promotes increased lipolysis and FFA flux to the liver, generating substrate pressure for hepatic triglyceride synthesis and accumulation of lipotoxic intermediates that exacerbate hepatic IR[29,33]. This hepatic IR is marked by impaired suppression of endogenous glucose production coupled with persistent DNL—a "selective" pattern that perpetuates hyperglycemia while driving hepatic steatosis[29,32]. Elevated endogenous glucose production and fasting hepatic IR are hallmark features of MASLD and become further accentuated in T2DM, mechanistically linking systemic IR to hepatic steatosis and hyperglycemia[32].

4.2.2 Hyperinsulinemia

Compensatory hyperinsulinemia in early and established T2DM upregulates hepatic sterol regulatory element binding protein 1c (SREBP-1c) and carbohydrate response element binding protein (ChREBP), augmenting DNL and malonyl-CoA, which together increase triglyceride synthesis and impair fatty acid oxidation[29]. Elevated DNL is a defining feature of steatotic liver disease and links hyperinsulinemia to hepatic fat accrual in IR states[34]. Reduced hepatic insulin clearance, commonly observed in the context of steatosis, further sustains hyperinsulinemia, thereby reinforcing lipogenesis and intensifying hepatic fat accretion[32]. Collectively, hyperinsulinemia and selective hepatic IR establish a feed-forward loop that links glucose dysregulation to lipid deposition and lipotoxic stress within hepatocytes[29].

4.2.3 Chronic inflammation

Low-grade systemic inflammation characteristic of T2DM (eg, TNF-α, IL-6, NLRP3 signaling) impairs insulin action across tissues and activates hepatic innate immunity, accelerating steatosis and steatohepatitis[35,36]. Inflammation synergizes with lipotoxicity to worsen hepatic IR and fibrogenic signaling, worsening MASLD[36,37].

4.2.4 Adipokine dysregulation

T2DM-associated hypoadiponectinemia eliminates a critical insulin-sensitizing and antisteatotic signal, predisposing the liver to lipid accumulation and inflammation.[38,39] The concurrent dysregulation of leptin, resistin, and other adipokines further disrupts hepatic lipid metabolism and immune homeostasis, promoting the progression from metabolic dysfunction to MASLD[37,38].

4.2.5 Gut-liver axis

In metabolic disease, gut dysbiosis and increased intestinal permeability permit the translocation of microbe-associated molecular patterns into portal circulation, activating hepatic innate immune pathways that intensify IR and steatosis[33]. Altered bile acid signaling and microbial metabolites further influence hepatic lipid and glucose metabolism, embedding gut-liver crosstalk within the pathogenesis of MASLD in T2DM[29,33]. These gut-derived signals converge with hepatic inflammation and mitochondrial stress, accelerating disease progres-

sion beyond simple hepatic fat accumulation[29,33].

4.2.6 Ectopic fat deposition

T2DM promotes ectopic lipid deposition, which in the liver manifests as excessive triglyceride storage and accumulation of lipotoxic species that impair insulin signaling and injure hepatocytes[29]. Intrahepatic lipid accumulation, in turn, feeds forward to worsening hepatic IR and VLDL overproduction, deepening steatosis[29].

4.2.7 Mitochondrial dysfunction

Hepatic mitochondrial overload and incomplete fatty acid oxidation in IR states increase reac-

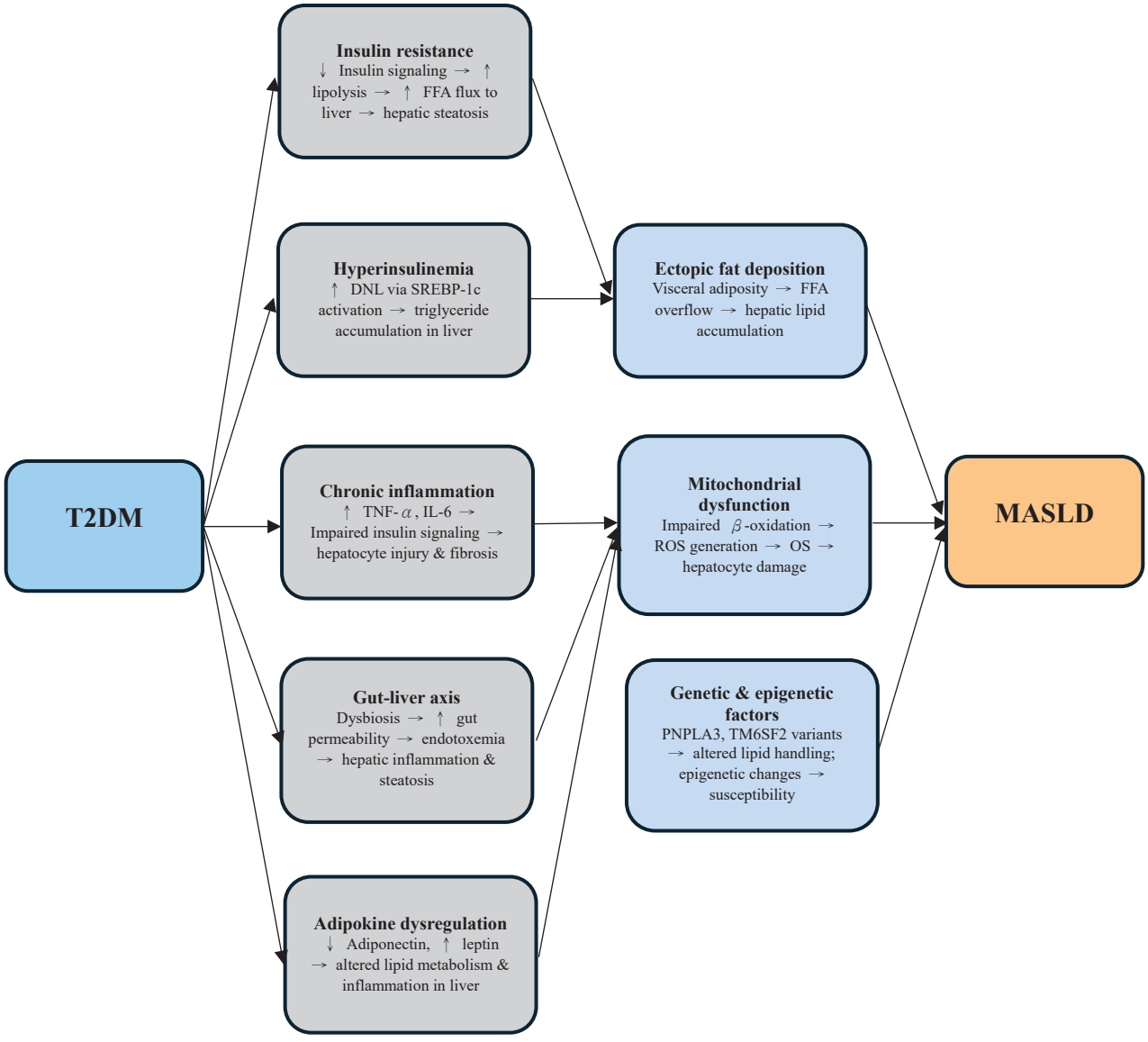

Figure 2. Mechanisms linking T2DM to MASLD onset. T2DM initiates several upstream disturbances—including insulin resistance, hyperinsulinemia, chronic inflammation, adipokine dysregulation, and gut-liver axis disruption—which drive downstream effects such as ectopic fat deposition and mitochondrial dysfunction; genetic and epigenetic factors further modulate susceptibility, with all pathways converging toward MASLD onset in a unified pathogenic continuum. Abbreviations: T2DM, type 2 diabetes mellitus; MASLD, metabolic-dysfunction-associated steatotic liver disease; ROS, reactive oxygen species; OS, oxidative stress; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; DNL, de novo lipogenesis; FFA, free fatty acid; SREBP-1c, sterol regulatory element binding protein 1c.

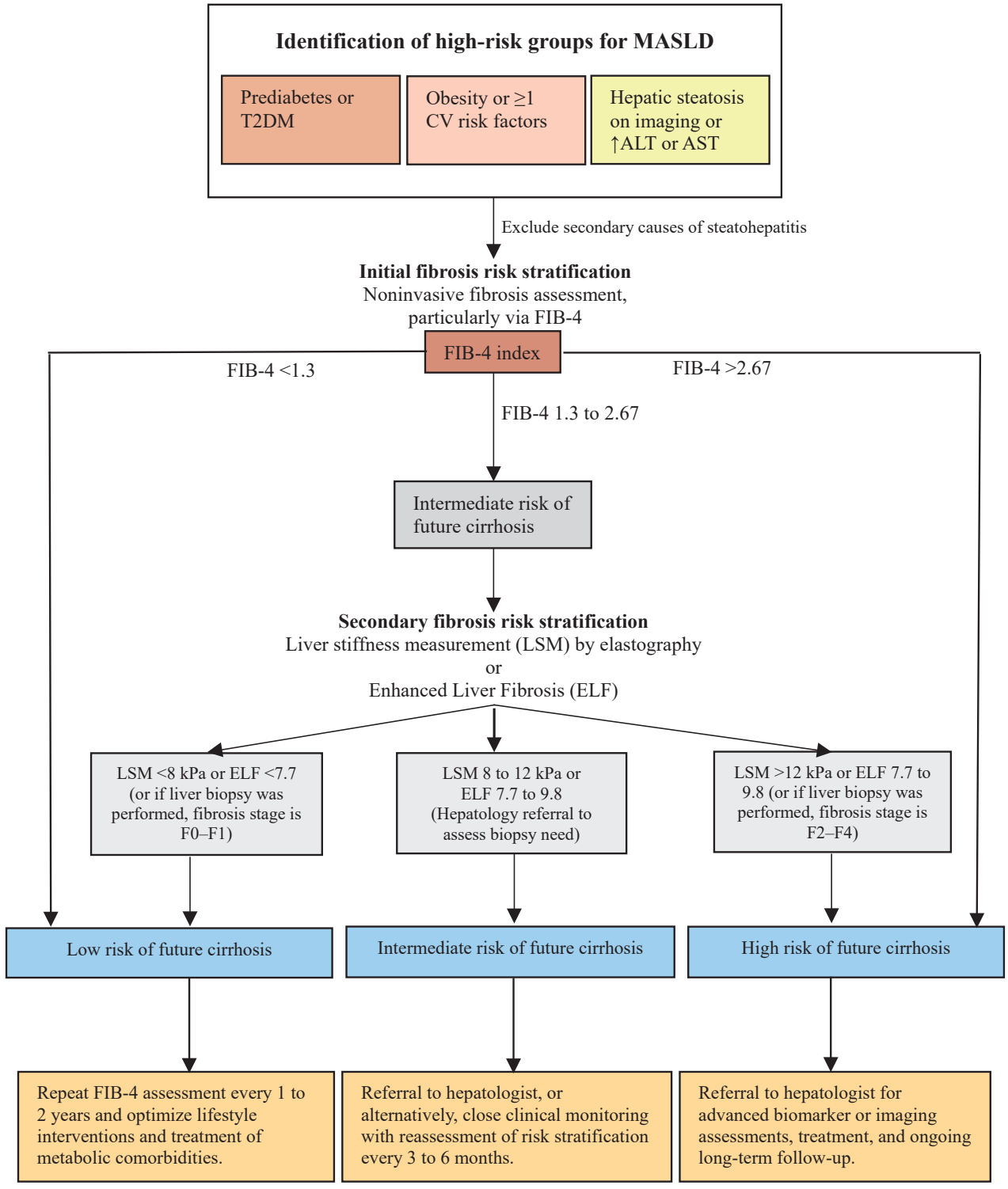

Figure 3. Algorithmic approach to screening and fibrosis risk stratification in MASLD. Note. Adapted from "Metabolic-dysfunction-associated steatotic liver disease (MASLD) in people with diabetes: The need for screening and early intervention. A consensus report of the American Diabetes Association" by Cusi K, et al, 2025, Diabetes Care, 48, p. 1057-82. "Clinical care guidance in patients with diabetes and metabolic-dysfunction-associated steatotic liver disease: A joint consensus. Hepatology Communications" by Huang JF, et al, 2024, Hepatology Communications, 8, p. e0571. Abbreviations: MASLD, metabolic-dysfunction-associated steatotic liver disease; T2DM, type 2 diabetes mellitus; CV, cardiovascular; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

tive oxygen species and redox stress, damaging organelles and promoting steatosis[40,41]. Mitochondrial inefficiency and altered tricarboxylic acid cycle flux reduce metabolic flexibility and amplify IR, accelerating MASLD onset and progression[40-42].

4.2.8 Genetic and epigenetic factors

Common genetic variants (eg, PNPLA3 I148M, TM6SF2 E167K, and GCKR P446L) influence susceptibility to hepatic steatosis and disease progression, interacting with IR and lipid metabolism to modulate MASLD risk in individuals with T2DM[29]. Epigenetic modifications linked to IR and hepatic lipid metabolism likely integrate diabetic milieu and environmental exposures to promote MASLD initiation and progression[43].

Take together, the convergence of IR, hyperinsulinemia, adipokine imbalance, chronic inflammation, and gut-derived endotoxemia creates a prosteatotic and proinflammatory hepatic environment. This integrative pathway leads to triglyceride accumulation, hepatocyte ballooning, and fibrotic remodeling, culminating in incident MASLD in individuals with T2DM[29,32,33].

5. Screening for MASLD and T2DM

The bidirectional relationship between T2DM and MASLD necessitates routine screening for both conditions given their ability to increase risks of mortality and liver-related complications[44]. Recent guidelines recommend evaluating MASLD fibrosis in all individuals with T2DM by using noninvasive tests with high negative predictive value to effectively rule out advanced fibrosis[5]. A variety of noninvasive modalities, including serum biomarkers and advanced imaging techniques, are available to evaluate fibrosis risk in individuals with T2DM[44]. Examples of advanced imaging techniques include vibration-controlled transient elastography (VCTE), liver stiffness measurement (LSM), shear wave elastography, and magnetic resonance imaging (MRI)-based elastography.

Adults with T2DM should be screened for MASH, given that fibrosis stage is a strong prognostic marker reflecting proximity to cirrhosis[10]. Assessments should initially involve serologic markers, including the fibrosis-4 (FIB-4) index, aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio, AST-to-platelet ratio index (APRI), and MASLD fibrosis score[45]. The FIB-4 index, calculated from age, AST, ALT, and platelet count by using the formula (age×AST)/(platelet count×√ALT), is a widely validated first-tier test that demonstrates greater sensitivity than ALT alone for detecting liver fibrosis in patients with MASLD, including those with T2DM[5,10].

FIB-4 scores of <1.3, with a negative predictive value of ≥90%, can reliably indicate the absence of advanced fibrosis (defined as bridging fibrosis or compensated fibrosis). The predictive ability of FIB-4 scores is associated with patient age. FIB-4 scores are less predictive for patients aged ≤35 or ≥65 years, prompting some to propose a 2.0 cutoff in older adults; however, due to limited evidence, a simplified threshold of 1.3 is generally recommended [10]. Individuals with low risk may repeat FIB-4 testing every 1 to 2 years and optimize lifestyle and treatment of comorbidities. Those with FIB-4 scores of >2.67 are considered at high risk of advanced fibrosis[10]. Among individuals with obesity and prediabetes or T2DM, 30% to 40% have FIB-4 scores of >1.3 and should undergo further assessments; those with scores of >2.67 (≤5%) face significantly elevated risk for advanced fibrosis (positive predictive value 60% to 80%) and may be referred directly to specialists for evaluation of at-risk MASH or cirrhosis[10]. LSM by transient elastography is widely endorsed as a second-tier test; a stepwise FIB-4 plus VCTE approach effectively stratifies liver-related risk, with LSM < 8.0 kPa reliably excluding advanced fibrosis and guiding follow-up in primary care and endocrinology clinics with repeat surveil-

lance in 1 to 2 years and LSM > 8.0 kPa warranting specialist referral[10].

The Enhanced Liver Fibrosis (ELF) test is also a validated second-tier, noninvasive biomarker panel used when advanced fibrosis is suspected or when VCTE is unavailable, integrating type III procollagen peptide, hyaluronic acid, and tissue inhibitor of metalloproteinase-1 to stratify fibrosis risk.[10] ELF scores <7.7 indicate very low likelihood of significant fibrosis, whereas scores ≥9.8 identify individuals with MASLD at increased risk for advanced fibrosis and liver-related clinical events, and values >11.3 denote the highest risk for hepatic decompensation and warrant hepatology referral. In primary care and diabetes settings, ELF <9.8 generally supports continued follow-up with periodic reassessment, while scores ≥9.8 should prompt secondary evaluation; intermediate values (9.2–9.7) require individualized interpretation based on overall cardiometabolic and fibrosis-progression risk.[10]

Current guidelines recommend routine screening for MASLD in individuals with prediabetes and T2DM[10,46]. The 2025 American Diabetes Association (ADA) consensus advocates early fibrosis detection and management in prediabetes or T2DM, emphasizing interprofessional care and supportive policies to improve outcomes in MASLD[10]. FIB-4 score is used to monitor fibrosis even with normal liver enzymes; in patients with diabetes with indeterminate or high FIB-4 scores, further stratification through transient elastography or fibrosis biomarkers is recommended, with referral to a hepatologist for additional evaluation[10,47]. Liver biopsy is typically considered when noninvasive assessments are inconclusive or when alternative diagnoses are suspected[46]. Figure 3 summarizes the preferred noninvasive tests for initial and secondary fibrosis risk stratification and optimal management in individuals at high risk of MASLD.

6. Management of MASLD in T2DM

6.1 Nonpharmacological Interventions

6.1.1 Weight loss

Lifestyle modification is central to managing MASLD and T2DM. Weight loss is the primary determinant of diabetes risk reduction; in adults with overweight or obesity, a reduction of >5% leads to improved outcomes on various metabolic parameters, and an early reduction of ≥10% doubles 5-year remission odds in newly diagnosed cases[48]. Weight loss also leads to improvements in liver enzyme health, steatosis status, liver stiffness, and MASLD histology outcomes, with greater reductions yielding stronger benefits[10,49]. Evidence regarding the effect of weight reduction on advanced fibrosis is limited. In MASH, ≥5% weight loss may reduce steatosis, >5% may reverse steatohepatitis, and ≥10% can improve fibrosis, although histologic change may not be correlated proportionally with weight loss[10]. Given the challenges of achieving and sustaining weight loss, patients should receive individualized targets (7% to 10% gradual reduction) and referral to structured weight-loss programs when accessible[5].

6.1.2 Physical activity

Guidelines for physical activity and exercise are similar for individuals with diabetes and individuals with diabetes complicated by MASLD; these guidelines recommend ≥150 min/week of moderate or ≥75 min/week of vigorous aerobic activity plus resistance training 2 to 3 times/week. Exercise should be tailored to enhance self-efficacy and long-term adherence[10]. Various modalities—including aerobic, resistance, and high-intensity interval training—effectively reduce hepatic steatosis[29]. Structured exercise reduces IR, aminotransferases, and steatosis in MASLD[10]. Aerobic exercise may yield superior hepatic benefits. High-intensity approaches

have shown improvement in MASH and fibrosis[10]. A meta-analysis of 19 randomized controlled trials (RCTs) found comparable efficacy between moderate-intensity continuous training and high-intensity interval training in reducing hepatic steatosis[50]. For patients with impaired cardiorespiratory function who cannot tolerate aerobic activity, resistance training—which is associated with lower energy expenditure than other exercise modalities—may be more appropriate[51].

6.1.3 Dieting

Individualized nutritional strategies for MASLD should integrate culturally relevant dietary modifications and family counseling to address its familial clustering[52]. Dietary patterns high in saturated fats and simple sugars—particularly fructose—are associated with increased risk of IR, hypertriglyceridemia, and hepatic fibrosis[10]. Accordingly, reducing fructose intake, especially through the elimination of sugar-sweetened beverages, constitutes a critical therapeutic goal in MASLD management[53].

An optimal dietary framework should lead to the reduced intake of ultraprocessed foods, saturated fats, and refined sugars. Fiber-rich carbohydrates and unsaturated fatty acids should be prioritized to enhance metabolic and hepatic outcomes[10,54]. Omega-3 fatty acids have demonstrated efficacy in reducing hepatic fat content. Nevertheless, their effect on fibrosis progression remains limited[53]. Several dietary models, including the Mediterranean, Dietary Approaches to Stop Hypertension, low-fat/low-carbohydrate, and intermittent fasting regimens, have shown promise in improving hepatic steatosis, although evidence supporting their efficacy in treating steatohepatitis or fibrosis is currently insufficient[10].

The Mediterranean diet, endorsed by both the American Association for the Study of Liver Diseases and the ADA, remains the preferred long-term strategy because of its wide-ranging benefits on cardiometabolic and hepatic health[10,54]. Traditional Japanese dietary patterns have demonstrated potential in reducing BMI and mitigating fibrosis severity[53].

Annual diabetes self-management education and support sessions led by diabetes care and education specialists, in collaboration with registered dietitian nutritionists, facilitate sustained behavioral change and enable delivery of personalized nutritional therapy[10]. Such structured lifestyle interventions not only benefit patients with MASLD but also complement standard management protocols for T2DM[10]. Increasing patient awareness about fibrosis risk may further enhance engagement and compliance with therapeutic recommendations[10].

Poor dietary quality independently contributes to MASLD-related mortality. Therefore, robust public health initiatives aimed at safeguarding current and future populations are urgently needed[55].

6.1.4 Metabolic Surgery

Metabolic surgery has become an important therapeutic consideration for patients with obesity, T2DM, and MASLD or MASH. Contemporary clinical pathways and practice guidelines increasingly recognize surgery as a disease-modifying intervention when lifestyle modification and pharmacologic therapy fail to achieve adequate metabolic control[46,56-58]. The metabolic effects of surgery—including substantial and durable weight loss, improved insulin sensitivity, and reductions in systemic inflammation—directly target the mechanisms driving hepatic steatosis, lipotoxicity, and fibrogenesis[59-62].

Histologic improvement following metabolic surgery is well documented. Meta-analyses demonstrate reductions in hepatic steatosis in approximately 70% to 80% of patients, resolution of lobular inflammation and hepatocyte ballooning in 50% to 75%, and fibrosis regression in 30% to 40%[63,64].

These histologic changes translate into clinically meaningful reductions in HCC incidence and other obesity-associated malignancies[64,65].

RCT data further support the efficacy of metabolic surgery in MASH. In a trial of 288 adults with biopsy-proven disease, Roux-en-Y gastric bypass or sleeve gastrectomy combined with standard medical therapy resulted in significantly higher rates of MASH resolution without fibrosis progression at 1 year compared with lifestyle intervention alone. Resolution occurred in 56% of patients undergoing Roux-en-Y gastric bypass and 57% undergoing sleeve gastrectomy, compared with 16% in the lifestyle group (p<0.0001). Among participants completing follow-up (82%), the primary endpoint was achieved in 70% of surgical patients versus 19% of those receiving lifestyle modification (p<0.0001)[66]. These findings demonstrate that metabolic surgery can reverse steatohepatitis within a clinically relevant timeframe.

Long-term observational data confirm sustained hepatic and cardiometabolic benefit. In a matched cohort of adults with obesity and noncirrhotic MASH followed for a median of 7 years, metabolic surgery was associated with significantly lower rates of major adverse liver outcomes (2.3% vs 9.6%; p=0.01) and cardiovascular events (8.5% vs 15.7%; p=0.007) [66]. Persistent steatohepatitis or fibrosis was more common among individuals who did not achieve adequate postoperative weight loss, underscoring the importance of sustained metabolic improvement for long-term hepatic protection.

The role of metabolic surgery in advanced liver disease requires careful patient selection. In compensated MASLD-related cirrhosis, surgery can be performed safely at experienced centers, with perioperative risks comparable to those observed in less advanced disease[67,68]. Emerging evidence suggests that metabolic surgery may even promote recompensation in selected patients with MASLD-related cirrhosis[68]. In contrast, outcomes are significantly worse in individuals with clinically significant portal hypertension or decompensated cirrhosis. In these populations, metabolic surgery is not recommended outside the context of liver transplantation at specialized tertiary centers because of increased postoperative liver-related risk and limited outcome data[46,56,57].

Take together, the evidence positions metabolic surgery as a highly effective therapeutic modality capable of reversing steatohepatitis, improving fibrosis, and reducing long-term hepatic and cardiometabolic complications. Its integration into MASLD management should be guided by disease severity, metabolic risk profile, and surgical candidacy, with multidisciplinary evaluation central to optimizing outcomes.

6.2 Pharmacological Interventions

Approximately 15% to 20% of adults with T2DM are estimated to be at risk of MASH, which may progress to cirrhosis if left untreated[10]. Although no glucose-lowering agents (GLAs) are currently approved specifically for MASLD, the condition's strong associations with obesity, metabolic syndrome, and T2DM underscore the need for a multifaceted management strategy[10]. GLAs such as peroxisome proliferator-activated receptor (PPAR) agonists, glucagon-like peptide-1 (GLP-1) receptor agonists (RAs), the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1RA tirzepatide, and sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated efficacy in improving glycemic control, hepatic steatosis, liver enzyme levels, and inflammation while also offering cardiovascular protection and potential antifibrotic effects[7,10]. Robust RCTs support the histologic benefits of these agents, and ongoing studies continue to evaluate targeted pharmacologic strategies for MASLD and MASH in individuals with T2DM[69,70]. The histologic efficacy of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas, and insulin

remains inadequately defined[7]. In addition to glucose-lowering therapies, nuclear receptor modulators have entered the treatment landscape, with the thyroid hormone receptor-β (THR-β) agonist resmetirom receiving US Food and Drug Administration (FDA) approval in March 2024 for individuals with MASH and fibrosis stages 2 or 3. The following sections summarize recent evidence on the efficacy of approved GLAs for treating MASLD; their effects on MASLD are illustrated in Table 1.

6.2.1 Thiazolidinediones

Pioglitazone, a PPAR-γ agonist, was the first GLA to have demonstrated efficacy in treating MASH in an RCT[71]. In a real-world retrospective study involving 279 patients with T2DM and MASLD, 1 year of pioglitazone therapy led to significant reductions in FIB-4 score from 1.92 to 1.68 and APRI score from 0.42 to 0.33, and the concomitant use of SGLT2 inhibitors led to greater improvements[72].

A first-in-Asia RCT demonstrated that 24 weeks of pioglitazone therapy was well tolerated and led to significant histological improvements, including reduced hepatic steatosis and fat content on MRI-derived proton density fat fraction[73]. Liver enzyme normalization and favorable changes in lipid profiles were also observed, without worsening hepatic fibrosis in Asian patients with MASH[73]. Further RCTs in T2DM or prediabetic populations consistently showed improvements in steatosis, inflammation, and hepatocellular ballooning, although fibrosis outcomes varied[7].

In a meta-analysis of 4 RCTs, pioglitazone significantly improved ballooning (odds ratio [OR], 2.11; 95% confidence interval [CI], 1.33 to 3.36), steatosis (OR, 3.39; 95% CI, 2.19 to 5.25), inflammation (OR, 2.58; 95% CI, 1.68 to 3.97), and fibrosis (OR, 1.68; 95% CI, 1.02 to 2.77) in biopsy-confirmed patients with MASH, with long-term use promoting the resolution of MASH without worsening fibrosis regardless of diabetes status[74]. Similarly, a meta-analysis of 8 RCTs—5 involving pioglitazone and 3 involving rosiglitazone—in 516 patients with MASH revealed that pioglitazone, but not rosiglitazone, significantly reduced rates of advanced fibrosis (OR, 3.15; 95% CI, 1.25 to 7.93; p=0.01) and fibrosis across any stage (OR, 1.66; 95% CI, 1.12 to 2.47; p=0.01) and promoted the resolution of MASH (OR, 3.22; 95% CI, 2.17 to 4.79; p<0.001)[75]. A subsequent meta-analysis further validated pioglitazone's benefits across insulin sensitivity, glycemic control, liver enzyme levels, and histologic parameters, although uncertainties regarding long-term efficacy and safety remain[76]. PPAR agonists more broadly improve hepatic steatosis, inflammation, and insulin sensitivity in MASLD; however, their clinical utility is constrained by adverse effects. The major toxicities include fluid retention, weight gain, and a rare but clinically meaningful risk of precipitating heart failure, with additional concerns such as edema and dose-related weight gain that may offset metabolic benefits and complicate long-term management.

Given its affordability and clinical benefits, pioglitazone remains a cost-effective therapeutic option for patients with MASLD and T2DM. Interest in PPAR agonism continues to expand, with novel agents such as the deuterium-stabilized pioglitazone enantiomer PXL065[77] and pan-PPAR agonists like lanifibranor[78] showing promise in improving hepatic histology, metabolic profiles, and cardiovascular outcomes in MASH populations[79].

6.2.2 GLP-1 RAs and dual GLP-1/GIP RAs

Animal models demonstrate that GLP-1 analogs suppress hepatic lipogenesis via cAMP-activated kinase pathway activation and reduce hepatic fat accumulation and nutrient-induced proinflammatory signaling, supporting their potential as novel therapies for MASLD[80]. GLP-1 RAs confer benefits in atherosclerotic CVD, contribute to weight reduc-

Table 1. Hepatic effects of glucose-lowering agents in MASLD and MASH.

Class	Agent(s)	Hepatic mechanism	Study design & population (n)	Duration (weeks)	Intervention	Hepatic Steatosis	Steatohepatitis	Fibrosis regression	Fibrosis progression	Ref
PPAR-γ agonist	Pioglitazone	Enhances insulin sensitivity; reduces hepatic lipotoxicity and inflammation via PPAR-γ activation	RCT; MASH; T2DM or prediabetes (n=55)	24	Pioglitazone vs. placebo	↓ steatosis	↑ resolution of MASH	↑ fibrosis improvement	No worsening	71
			Retrospective real-world study; T2DM + MASLD (n = 279)	52	Pioglitazone ± SGLT2i vs. baseline	↓ FIB-4, ↓ APRI	Not assessed	Not directly assessed	↓ fibrosis indices	72
			First-in-Asian RCT; MASH (n=90)	24	Pioglitazone vs. placebo	↓ MRI-PDFF	↓ inflammation	No worsening	No worsening	73
			4 RCTs; MASH; T2DM or prediabetic (n=61)	24 - 144	Pioglitazone vs. placebo	↓ steatosis	↓ ballooning	Variable	Variable	7
			Meta-analysis of 4 RCTs; MASH; T2DM or nondiabetic (n=334)	24 - 96	Pioglitazone vs. placebo	↓ (OR 3.39)	↓ (OR 2.58)	↓ (OR 1.68)	↓ progression	74
			Meta-analysis of 8 RCTs (5 pioglitazone, 3 rosiglitazone; n= 516)	14 - 96	Pioglitazone vs. placebo	↑ steatosis resolution	↓ (OR 3.22; ↑ MASH resolution)	↓ (OR 3.15; advanced fibrosis)	OR 1.66 (any stage)	75
			Meta-analysis; MASLD with prediabetes T2DM (n=343)	16 - 144	Pioglitazone vs. placebo	↓ liver enzymes	↓ inflammation	Improved histology	Safety concerns noted	76
	PXL065 (R-pioglitazone)	Deuterium-stabilized enantiomer; retains hepatic benefits with reduced systemic exposure	Phase II RCT; MASH (n=117; 41% T2DM)	36	PXL065 vs. placebo	↓ steatosis	↓ inflammation	Improved histology	Not reported	77
Pan-PPAR agonist	Lanifibranor	Activates PPAR-α/δ/γ; improves lipid metabolism, inflammation, and fibrogenesis	RCT; MASH (n= 247; 42% T2DM; 76% moderate or advanced fibrosis)	24	Lanifibranor vs. placebo	↓ steatosis	↓ inflammation	↓ fibrosis	↓ progression	78
			Extension study; MASH (n=228; 42% T2DM)	24	Lanifibranor vs. placebo	↓ liver fat	↑ cardiometabolic profile	↑ histologic improvement	↓ progression	79
GLP-1 RA	Semaglutide	↓ hepatic lipogenesis via cAMP/AMPK activation; ↓ nutrient-induced inflammation; ↓ hepatic fat	Phase II RCT; MASH (n = 320; 65% T2DM)	72	Semaglutide vs. placebo	↓ steatosis	59% vs.17% resolution (P<0.001)	43% vs 33% (NS)	↓ (4.9% vs 18.8%)	81
			Phase II RCT; MASH; cirrhosis (n=71)	72	Semaglutide 2.4 mg vs. placebo	Improved fibrosis markers	NS (P=0.29)	OR 0.28 (P=0.087)	Not reported	82
			Phase II post hoc analysis; MASH (n=251)	72	Semaglutide vs placebo	Continuous score improvements	Improved necroinflammation	Improved fibrosis	NS	85
			Phase III RCT; MASH (n = 800)	72	Semaglutide 2.4 mg vs. placebo	NS	62.9% vs. 34.3% resolution (P<0.001)	36.8% vs 22.4% (P<0.001)	NS	86
	Liraglutide	↓ hepatic steatosis, ↓ inflammation, ↓ lipotoxicity	Phase II RCT; MASH (n=52)	48	Liraglutide vs. placebo	↓ Steatosis	Slowed progression	NS	NS	83
			Phase II RCT; obese T2DM; MASLD (n=128)	26	Liraglutide vs. placebo	↓ hepatic fat	NS	NS	NS	84

Class	Agent(s)	Hepatic mechanism	Study design & population (n)	Duration (weeks)	Intervention	Hepatic Steatosis	Steatohepatitis	Fibrosis regression	Fibrosis progression	Ref
Dual GIP/GLP-1 RA	Tirzepatide	↓ liver fat via enhanced adipose insulin sensitivity, ↓ DNL	Phase III sub-study; T2DM; MASLD (n=296)	52	Tirzepatide vs. insulin degludec	↓ Liver fat by 47% vs. 11% (P<0.001)	NS	NS	NS	87
			Phase II RCT; MASH (n = 190; 50–60% T2DM)	52	Tirzepatide (5/10/15 mg) vs. placebo	NS	44–62% resolution vs 10% placebo (P<0.001)	51–55% vs. 30% placebo	NS	88
Dual GLP-1/Glucagon RA	Survodutide	↓ hepatic fat via ↑ lipolysis, ↓ DNL, ↓ inflammation	Phase II RCT; MASH (n = 293)	48	Survodutide (2.4/4.8/6.0 mg) vs. placebo	≥30% fat reduction in 57–67% vs. 14% placebo	43–62% resolution vs. 14% placebo (P<0.001)	34–36% vs. 22% placebo	NS	89
	Efinopegdutide		Phase IIa RCT; MASLD (n=145; 33.1% T2DM)	24	Efinopegdutide vs. semaglutide	↓ liver fat by 72.7% vs 42.3% (P<0.001)	NS	NS	NS	90
Dual GLP-1/FGF21 RA	HEC88473	↓ hepatic fat via ↑ β-oxidation, ↓ lipogenesis, ↑ adiponectin	Phase Ib/IIa RCT; MASLD; T2DM (n=60)	5	HEC88473 30.6 mg vs. placebo	−47.21% hepatic fat vs. −15.05% placebo (P=0.0143)	NS	NS	NS	91
Triple GIP/GLP-1/Glucagon RA	Retatrutide	↑ energy expenditure, ↓ hepatic fat, ↓ inflammation, ↑ insulin sensitivity	Phase II RCT; MASLD subgroup (n = 98)	48	Retatrutide 12 mg vs. placebo	90% achieved liver fat normalization	Improved biomarkers	NS	NS	10
SGLT2 inhibitor	Various (meta-analysis)	↓ hepatic fat via glycosuria, weight loss, insulin sensitivity	Meta-analysis of 12 RCTs; MASLD overweight / obese (n=850; 90% T2DM)	24 (median)	SGLT2i vs. placebo or active comparators	−2.05% fat on MRI	Not assessed	Not assessed	Not assessed	92
	Various (claims-based, US)	↓ hepatic inflammation and fibrosis via metabolic modulation	Retrospective cohort (2007–2021); T2DM + MASLD; large US claims database (n not specified)	N/A	SGLT2i vs. other GLAs	↓ cirrhosis risk	Not assessed	Not assessed	↓ fibrosis-related events	93
	Various (claims-based, Korea)	↓ hepatic decompensation via metabolic stabilization	Nationwide Korean cohort (2014–2022); T2DM; MASLD (n=22550)	N/A	SGLT2i vs. thiazolidinediones	↓ hepatic decompensation	Not assessed	Not assessed	↓ progression risk	94
	Various (prospective)	↓ fibrosis via weight loss, improved glycemic control	Prospective observational; T2DM; MASLD (n=237)	~260	SGLT2i use vs. non-use	Not assessed	Not assessed	Not assessed	HR 0.34 (95% CI, 0.13–0.88)	95
	Ipragliflozin	↓ steatohepatitis and fibrosis via metabolic effects	Open-label biopsy study; T2DM; MASLD (n=55)	72	Ipragliflozin vs. baseline	Not reported	↑ ballooning (52% vs. 24%; p =0.02)	↑ fibrosis (57% vs. 16%; p =0.01)	Not reported	96
	Tofogliflozin	Glycosuria-mediated metabolic effects	Open-label RCT; T2DM; MASLD (n not specified)	48	Tofogliflozin vs. glimepiride	No significant change	No significant change	No significant change	No significant change	97

Class	Agent(s)	Hepatic mechanism	Study design & population (n)	Duration (weeks)	Intervention	Hepatic Steatosis	Steatohepatitis	Fibrosis regression	Fibrosis progression	Ref
Biguanide	Metformin	↓ hepatic gluconeogenesis; ↑ insulin sensitivity; possible indirect hepatoprotection via weight loss	Pilot RCT; MASH (n=48)	48	Metformin vs. placebo	Minimal histologic change; correlation with weight loss	NS	NS	NS	98
			TONIC RCT; pediatric MASLD (n=173)	96	Metformin vs. placebo/ vitamin E	No significant steatosis reduction vs. placebo	NS	No improvement	No difference	99
			Systematic review & meta-analysis; mixed MASLD/MASH (n=417)	12–96	Various metformin regimens vs. placebo	↓ ALT, IR, BMI; minimal histologic change	NS	No effect	No effect	100
			Pooled 6 RCTs; mostly nonT2DM (n=573)	12–96	Metformin vs. placebo	Modest steatosis & inflammation ↓; ALT improved	No MASH resolution	No effect	No effect	101
			Meta-analysis (rigorous criteria)	Various	Metformin vs. placebo	No meaningful histologic benefit	No benefit	No benefit	No benefit	102
Sulfonylureas	Various	↑ insulin secretion; hepatic effects poorly defined	Narrative review; MASLD	N/A	N/A	Not established	Not established	Not established	Not established	57
DPP-4 inhibitors	Sitagliptin	Inhibit GLP-1 degradation → ↑ incretin activity; experimental ↓ steatosis, inflammation, fibrosis	Observational T2DM cohorts	Variable	DPP-4 inhibitor vs. standard care	↓ aminotransferases (inconsistent)	Not established	Not established	Not established	28, 103
			RCT; MASLD (n=50)	24	Sitagliptin vs. placebo	No improvement	No improvement	No change	No change	104
			RCT; T2DM (n=44)	12	Sitagliptin vs. placebo	No change in MRI-PDFF	N/A	N/A	N/A	105
			RCT; MASH (n=40)	48	Sitagliptin vs. placebo	No histologic change	No change	No change	No change	106
Insulin	Basal insulin (various), insulin glargine	↓ FFA & glucose flux to liver; ↓ hepatic TG synthesis	Cross-sectional MRI study; T2DM (n≈2000)	N/A	Insulin users vs. non-users	Lower prevalence & fat fraction	N/A	N/A	N/A	107
	Basal insulin		RCT; T2DM (n=1452)	52	Peglispro vs. glargine	↓ liver fat & enzymes	N/A	N/A	N/A	108

Abbreviations: MASLD, metabolic-dysfunction-associated steatotic liver disease; T2DM, type 2 diabetes mellitus; NS, not significant; DNL, de novo lipogenesis; MRI, magnetic resonance imaging; PDFF, proton density fat fraction; RCT, randomized controlled trial; MASH, metabolic-dysfunction-associated steatohepatitis; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GIP-RA, gastric inhibitory polypeptide receptor agonist; PPAR, peroxisome proliferator-activated receptor; FGF21 RA, fibroblast growth factor 21 receptor agonist; SGLT2, sodium-glucose cotransporter 2; N/A: data not available; GLAs, glucose-lowering agents; CI, confidence interval; ALT, alanine transaminase; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FFA, free fatty acid; TG, triglycerides; IR, insulin resistance.

tion, and have shown promising efficacy in phase II and phase III RCTs. Nevertheless, no related drugs have been approved for the treatment of MASLD.

In a phase II RCT of 320 patients with MASH, 65% of whom also had T2DM, semaglutide achieved MASH resolution without fibrosis worsening in 59% of these patients vs 17% on placebo (p<0.001), although fibrosis improvement was not significant (43% vs 33%; p=0.48), and fewer semaglutide-treated individuals exhibited fibrosis progression at 72 weeks (4.9% vs 18.8%)[81]. In another phase II trial involving patients with MASH and compensated cirrhosis, once-weekly semaglutide (2.4 mg) did not significantly improve fibrosis (OR 0.28; 95% CI 0.06 to 1.24; p=0.087) or resolve MASH (p=0.29) but was well tolerated and improved cardiometabolic parameters and noninvasive markers associated with fibrosis progression[82]. Likewise, liraglutide has been shown to slow MASH progression in phase II RCTs[83,84]. A post hoc analysis of a phase II study revealed significant efficacy of GLP-1 RAs in MASH, with continuous score improvements in steatosis, necroinflammation, and fibrosis[85].

In the phase III Effect of Semaglutide in Subjects with Noncirrhotic Nonalcoholic Steatohepatitis trial (N=800), 36.8% of patients with MASH treated with semaglutide 2.4 mg once weekly for 72 weeks achieved liver fibrosis improvement without steatohepatitis worsening (vs 22.4% on placebo; p<0.001), and 62.9% attained steatohepatitis resolution without fibrosis progression (vs 34.3% on placebo; p<0.001) [86]. Hence, in August 2025, the US FDA approved semaglutide as the first GLP-1 RA for adults with MASH and moderate-to-advanced fibrosis (F2–F3), reflecting growing evidence that incretin-based therapies can modulate steatohepatitis activity, improve metabolic dysfunction, and attenuate fibrosis progression in high-risk populations.

Tirzepatide, a dual GIP/GLP-1 RA, has been investigated for MASH treatment; in an early study of adults with T2DM and MASLD, 52 weeks of therapy reduced liver fat by up to 47%, compared with 11% achieved using insulin degludec (p<0.001)[87]. In the phase II SYNERGY-NASH trial, tirzepatide administered for 52 weeks at 5, 10, and 15 mg/day doses in 190 adults with MASH (50% to 60% of whom also had T2DM) achieved steatohepatitis resolution without fibrosis worsening in 44%, 56%, and 62% of participants at the aforementioned 3 doses versus in 10% with placebo (p<0.001), respectively, and ≥1-stage fibrosis improvement without MASH worsening in 55%, 51%, and 51% of participants at the aforementioned 3 doses versus 30% with placebo, respectively[88]. In a phase II RCT of 293 patients, survodutide (2.4, 4.8, and 6.0 mg/week)—a dual glucagon and GLP-1 RA—resulted in MASH improvement without worsening fibrosis in 47%, 62%, and 43% of participants at the aforementioned 3 doses, respectively, versus 14% in the placebo group (p<0.001); ≥30% liver fat reduction in 63%, 67%, and 57% of treated patients at the aforementioned 3 doses, respectively, versus 14% in the placebo group, and ≥1-stage fibrosis improvement in 34%, 36%, and 34% of treated patients at the aforementioned 3 doses, respectively, versus 22% in the placebo group[89].

In a phase IIa RCT, efinopegdutide (dual GLP-1/glucagon RA) yielded a significantly greater least squares mean relative reduction in liver fat content after 24 weeks in adults with or without T2DM (72.7% [90% CI, 66.8 to 78.7]) compared with semaglutide (42.3% [90% CI, 36.5 to 48.1]; p<0.001)[90]. Similarly, HEC88473, a dual GLP-1/fibroblast growth factor 21 RA, demonstrated metabolic improvements in patients with T2DM and MASLD in a phase Ib/IIa RCT, including enhanced glycemic control and lipid profiles, and a 47.21% mean relative reduction in hepatic fat fraction (indicated by the MRI-proton density fat fraction [PDFF]) in a 30.6-mg cohort versus 15.05% in a placebo cohort

(p=0.0143); notably, more patients with baseline PDFF > 8% achieved >30% reductions[91].

Finally, retatrutide, a triple agonist of GIP, GLP-1, and glucagon receptors, is undergoing tests on its efficacy in the treatment of MASH; in phase II RCTs, retatrutide produced dose-dependent weight loss in individuals with T2DM or obesity, and in a MASLD subgroup (N=98; ≥10% liver fat by MRI-PDFF), 90% receiving 12 mg (subcutaneously) per week achieved liver fat normalization with concurrent improvement in steatohepatitis biomarkers at 48 weeks[10].

GLP-1 RAs and dual GIP/GLP-1 agonists reduce hepatic fat, improve glycemic control, and induce substantial weight loss; however, their use is frequently limited by gastrointestinal intolerance. The most common adverse effects include nausea, vomiting, and diarrhea, with rare cases of pancreatitis reported. High cost may further constrain long-term use despite their dual metabolic and hepatic benefits.

6.2.3 SGLT2 inhibitors

SGLT2 inhibitors have not been evaluated in paired biopsy studies of MASLD. Nevertheless, multiple placebo- or active-controlled trials have assessed the effects of SGLT2 inhibitors by using surrogate endpoints, including reductions in serum liver enzyme levels and hepatic fat content on imaging. Across multiple trials, SGLT2 inhibitors demonstrated beneficial effects in patients with T2DM and MASLD, with improvements in hepatic steatosis, liver enzymes, fibrosis, body weight, and glycemic control; several agents showed superior performance in combination therapy settings and in comparison to established treatments such as pioglitazone and metformin[29]. A meta-analysis of 12 RCTs evaluated SGLT2 inhibitors for MASLD over a median of 24 weeks in 850 overweight or obese participants (90% with T2DM); treatment significantly reduced serum ALT (weighted mean difference [WMD], −10.0 IU/L; 95% CI, −12.2 to −7.79 IU/L; I^2=10.5%) and gamma-glutamyltransferase (WMD, −14.49 IU/L; 95% CI, −19.35 to −9.63 IU/L; I^2=38.7%), and liver fat content on imaging (WMD, −2.05%; 95% CI, −2.61 to −1.48%; I^2=0%), supporting their therapeutic potential in MASLD[92].

In a large U.S. claims-based cohort of patients with T2DM and MASLD between 2007 and 2021, SGLT2 inhibitors were associated with reduced risks of HCC (24%), cirrhosis (20%), nonliver cancers (39%), CVD (18%), and CKD (34%) relative to other GLAs, with a synergistic benefit from metformin[93]. These findings are consistent with a nationwide Korean cohort study using claims data from 2014 to 2022, which demonstrated that SGLT2 inhibitors were associated with a reduced risk of hepatic decompensation in patients with MASLD compared with thiazolidinediones[94]. At an approximately 5-year follow-up time point in a recent prospective study of 237 patients with T2DM and MASLD, liver stiffness was found to significantly increase (6.0±2.8 vs 5.8±2.7 kPa; p=0.02), with 56% of patients experiencing fibrosis progression; worsening was associated with higher BMI and a lower usage of SGLT2 inhibitors. Furthermore, a multivariate analysis revealed that SGLT2 inhibitors reduced the risk of fibrosis progression (hazard ratio, 0.34; 95% CI, 0.13 to 0.88), suggesting a potential protective role[95].

Two open-label studies—ipragliflozin[96] over 72 weeks and tofogliflozin[97] over 48 weeks—explored histological effects in patients with T2DM and MASLD; ipragliflozin was associated with improvements in steatohepatitis features such as ballooning (52% vs 24%; p=0.02) and liver fibrosis (57% vs 16%; p=0.01), and tofogliflozin showed no significant histological differences compared with glimepiride.

Despite a lack of histological data regarding the use of SGLT2 inhibitors in the treatment of MASH, the cardiometabolic benefits and consistent perfor-

mance of SGLT2 inhibitors across clinical endpoints suggest therapeutic promise in MASLD. Further RCTs incorporating paired liver biopsies are essential to confirm their efficacy and define their role in managing MASH. SGLT2 inhibitors reduce hepatic fat, visceral adiposity, and improve cardiometabolic outcomes; however, their use is limited by adverse effects, including urinary tract and genital mycotic infections and a rare risk of euglycemic diabetic ketoacidosis.

6.2.4 Other GLAs

Metformin remains a cornerstone oral agent for T2DM because of its broad metabolic benefits and protective effects against related comorbidities. Nevertheless, its direct effect on hepatic histology is limited. Histological improvements in MASLD associated with metformin are largely attributable to concurrent weight loss, as demonstrated by a strong correlation in early studies (r=0.79; p<0.0001)[98] and confirmed by a pediatric RCT evaluating metformin, vitamin E, and placebo over 96 weeks[99]. A systematic review and meta-analysis encompassing 417 participants reported improvements in liver enzyme levels, IR, and BMI but observed minimal histologic changes, with limited effects on steatosis, inflammation, hepatocellular ballooning, and fibrosis[100]. Similarly, pooled data from 6 RCTs involving 573 predominantly nondiabetic individuals indicated modest improvements in steatosis, inflammation, and ALT levels and no significant effect on fibrosis, MASH resolution, or body weight[101]. Meta-analyses employing rigorous methodological criteria concluded metformin lacks efficacy in treating MASH[102]. Although current evidence and clinical guidelines support its limited histologic utility, emerging data suggest possible hepatoprotective roles against cirrhosis and HCC[101]. Given metformin's complex pharmacological profile, further investigation is warranted to elucidate its potential hepatoprotective mechanisms. Metformin is generally well tolerated; however, adverse effects remain an important consideration, including gastrointestinal discomfort and, more rarely, vitamin B12 deficiency or lactic acidosis in high-risk clinical settings.

The hepatic effects of sulfonylureas in MASLD remain poorly defined and insufficiently investigated[57]. By contrast, experimental models support a hepatoprotective role for DPP-4 inhibitors, demonstrating reductions in steatosis, inflammation, and fibrosis[28]. Observational studies have reported reductions in aminotransferase levels with DPP-4 inhibitor treatment, although findings are inconsistent[28]. Sitagliptin has been associated with improved hepatic biomarkers in patients with T2DM; however, outcomes are frequently confounded by lifestyle-associated weight loss[103]. RCTs assessing DPP-4 inhibitors have not demonstrated efficacy in improving hepatic steatosis or fibrosis among individuals with T2DM or prediabetes[104-106]. DPP-4 inhibitors provide modest glycemic benefit but have limited impact on MASLD. Their overall safety profile is favorable; however, adverse effects include mild gastrointestinal discomfort and rare hypersensitivity reactions, which remain the primary safety considerations with this class.

Insulin therapy may ameliorate hepatic steatosis and normalize liver enzyme levels in MASLD[7]. Among patients with T2DM, hepatic steatosis was present in 76% and 62% of those not receiving insulin and those receiving insulin, respectively. Further, the median hepatic fat fraction was 13% and 10.2% in these 2 cohorts, respectively (both p<0.01)[107]. Basal exogenous insulin appears to reduce hepatic fat accumulation by suppressing FFA and glucose flux to the liver in patients with T2DM and MASLD[108]. Notably, a head-to-head RCT found insulin glargine and liraglutide similarly reduced MRI-derived hepatic fat content[109]. Nevertheless, insulin's effects on hepatic fibrosis and MASH remain inadequately documented[57]. Adverse effects

remain a central limitation of insulin therapy, particularly hypoglycemia and weight gain, which are more pronounced with intensive regimens and may complicate long-term metabolic and hepatic management.

6.2.5 THR-β agonist: Resmetirom

Thyroid hormone receptors regulate hepatic gene transcription through thyroid hormone response elements, with the liver-enriched THR-β isoform serving as a key regulator of lipid and cholesterol metabolism[110]. In hypothyroidism, reduced intrahepatic T3 availability contributes to MASLD progression by impairing mitochondrial turnover and disrupting lipid homeostasis through autophagy-dependent pathways[111,112]. Preclinical models demonstrate that selective THR-β activation enhances mitochondrial respiration and β-oxidation, leading to reductions in hepatic steatosis and supporting THR-β as a mechanistically targeted therapeutic pathway in MASH[113,114]. Resmetirom, a selective THR-β agonist approved by the US FDA in March 2024 for MASH with fibrosis (stages F2 or F3), produced marked reductions in hepatic fat by MRI-PDFF (−32.9% vs −10.4% at 12 weeks; −37.3% vs −8.5% at 36 weeks; both $p<0.0001$), alongside improvements in aminotransferases, atherogenic lipids, inflammatory markers, and fibrosis biomarkers, with predominantly mild gastrointestinal adverse effects in a phase II RCT[115]. In the MAESTRO-MASH phase III trial, resmetirom (80 mg and 100 mg) significantly increased rates of MASH resolution without fibrosis worsening (25.9 to 29.9% vs 9.7% with placebo; $p<0.001$) and fibrosis improvement by ≥1 stage (24.2 to 25.9% vs 14.2% with placebo)[116]. Although resmetirom favorably modified dyslipidemia and fibrosis-related biomarkers, it did not meaningfully alter glucose homeostasis or insulin resistance, with nausea and diarrhea being the most common adverse events.

7. Perspectives

Given the intertwined pathophysiologies of MASLD and T2DM, recent investigational therapies have pursued dual-target strategies to optimize metabolic and hepatic outcomes[117]. Given that CVD remains the leading cause of mortality among individuals with MASLD, including those with MASH, therapeutic strategies should also encompass features of metabolic syndrome.

Multiple pharmacologic strategies are under investigation for MASLD and T2DM, notably those targeting metabolic substrate disposal and hormonal pathways. Dual PPAR agonists, including PPARα/δ and PPARα/γ modulators, have shown mixed results: elafibranor demonstrated histologic improvement in MASH but failed to meet endpoints in intention-to-treat analysis due to off-target effects and limited selectivity[118,119]. Newer agents, such as lanifibranor and saroglitazar, have exhibited enhanced isoform selectivity and promising preclinical and clinical efficacy[78,118,120]. Glucagon receptor agonists also offer metabolic benefits but are constrained by adverse effects. GLP-1/glucagon receptor dual agonists (eg, MEDI0382 and oxyntomodulin) have demonstrated hepatoprotective and antidiabetic effects in early studies[121,122]. Additional therapeutic avenues include SGLT2 inhibitors (eg, NGI001) that reduce steatosis and inflammation[123] and novel agents, such as imeglimin and protein tyrosine phosphatase 1B (PTP1B) inhibitors, both of which exert metabolic and hepatic benefits via mitochondrial and STAT3-mediated mechanisms[124,125]. Orforglipron, a once-daily oral GLP-1 RA, offers substantial weight loss and glycemic control, supporting its potential role in MASLD management[126].

Beyond conventional glucose-lowering therapies, emerging agents have been formulated with a focus on modulating fibrosis, bile acid signaling, lipid metabolism, immune response, and oxidative stress[7,120,127-129]. Lanifibranor (pan-PPAR

agonist) and efruxifermin (FGF21 analog) are undergoing phase 3 and phase 2/3 trials, respectively, for their potential in reducing steatosis and inflammation[127,128]. Obeticholic acid, a farnesoid X receptor agonist, remains under FDA review due to its bile acid modulation and antifibrotic properties[120,129]. Additional candidates—including aramchol, NGM282, cenicriviroc, belapectin, and IMM-124e—target diverse metabolic and immunologic pathways and continue to advance in clinical trials[7,120,127-129]. Collectively, these therapies represent a paradigm shift in MASH management, advancing beyond glycemic control to encompass broader disease-modifying strategies.

8. Indications for Hepatology Referral

Patients living with T2DM and MASLD should be referred to a hepatologist when there is evidence of advanced or progressive liver involvement, diagnostic uncertainty, or features suggesting alternative or concomitant liver disease. Given the high prevalence of MASLD and advanced fibrosis among individuals with diabetes, current diabetes care recommendations emphasize systematic assessment for liver disease and appropriate referral in high-risk patients[130]. Referral is appropriate in individuals with persistently elevated aminotransferase levels despite optimization of metabolic risk factors, noninvasive fibrosis assessments indicating significant fibrosis (stage ≥F2) or yielding indeterminate or high-risk results, or clinical or imaging findings suggestive of cirrhosis or portal hypertension[44]. In patients with diabetes, hepatology consultation is also warranted when steatohepatitis is suspected, and disease-modifying pharmacotherapy or liver biopsy is being considered to clarify diagnosis or stage disease[44]. Additional indications include atypical biochemical or serologic profiles, such as disproportionately elevated aminotransferase elevations, cholestatic features, or hypergammaglobulinemia, which raise concern for autoimmune or other non-MASLD liver etiologies. Autoimmune hepatitis should be considered in this setting, particularly in patients with positive autoantibodies or elevated immunoglobulin G levels, and diagnosis is based on established clinical, serologic, and histologic criteria, including the simplified International Autoimmune Hepatitis Group scoring system [131,132]. Early referral to hepatology facilitates accurate diagnosis, exclusion of competing liver diseases, appropriate staging, and timely initiation of disease-specific management.

9. Conclusions

MASLD and T2DM share a bidirectional relationship that accelerates hepatic histologic progression and increases the risk of HCC, extrahepatic malignancies, and CVD, with disproportionate burden observed in lean Asian populations[133]. The absence of approved pharmacologic therapies underlines the urgent need for integrative strategies targeting hepatic steatosis, inflammation, fibrosis, and metabolic dysfunction—particularly IR—in individuals with prediabetes, T2DM, or obesity. Emerging evidence supports the use of GLP-1 RAs, SGLT2 inhibitors, tirzepatide, and pioglitazone, indicating their effectiveness in improving hepatic and cardiometabolic outcomes. Current clinical guidelines recommend pioglitazone or GLP-1 RAs for the treatment of T2DM and MASH[57] and jointly endorse GLP-1 RAs, tirzepatide, or SGLT2 inhibitors based on hepatic and metabolic profiles[134], signaling a paradigm shift toward liver-centered therapeutic frameworks. Nevertheless, unresolved questions remain regarding the integration of these agents into standard care and their long-term impact on MASLD epidemiology. Barriers—including concerns regarding advanced liver disease, low provider awareness, and limited longitudinal hepatic outcome data—necessitate multifaceted interventions involving early diagnostics (eg, FIB-4,

transient elastography), lifestyle modification, pharmacologic optimization, and multidisciplinary care. Given the escalating global prevalence of MASLD and T2DM, continued investigation into pathophysiology-guided therapeutic approaches, refined risk stratification tools, and novel agents capable of disrupting this pathogenic axis is imperative. Moving forward, longitudinal data on hepatic endpoints will be essential to inform evidence-based clinical recommendations. Future research must advance mechanistic understanding, optimize predictive algorithms, and develop personalized intervention strategies to address the rising heterogeneity of MASLD across a diverse range of populations.

Conflicts of interest

No conflicts of interest associated with this manuscript to declare.

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第二型糖尿病患者中的代謝功能異常相關脂肪肝疾病：從病理生理機轉與篩檢策略到治療方針

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摘要

代謝功能異常相關脂肪肝疾病（MASLD）與第二型糖尿病（T2DM）共享由胰島素阻抗所驅動的代謝失衡，促進肝臟脂肪堆積、全身性發炎反應及纖維化進程。MASLD 盛行率高達 T2DM 成人族群的 65%，其中近半數符合代謝功能異常相關脂肪肝炎（MASH）之組織學診斷標準，顯著提升肝硬化、肝細胞癌及心血管事件之風險。主要病理生理機轉包括去氧脂肪酸合成上調、β 細胞氧化受損，以及脂毒性訊號傳導活化，形成 MASLD 惡化血糖控制、T2DM 加速肝纖維化進展之雙向交互關係。隨機臨床試驗顯示，胰高血糖素樣胜肽 -1 受體促效劑（GLP-1 RAs）可降低肝脂肪含量 20% 至 40%，並改善轉氨酶指數；鈉 - 葡萄糖共轉運蛋白 2 抑制劑（SGLT2i）則可適度減少肝脂肪堆積，並具額外心血管代謝益處；將這些代謝效果延伸至組織學疾病的改變，Semaglutide 成為第一個獲得美國食品藥品管理局加速批准用於 MASH 抗纖維化益處的 GLP-1 RA，基於在第 3 期 ESSENCE 試驗中證明對中度至重度（F2–F3）且無肝硬化成人纖維化改善的結果，從而確立其作為一種改善病程進展治療疾病的地位，超越了單純代謝控制的範疇。雙重與三重促胰素受體促效劑在疾病早期可提供血糖與肝臟指標之加乘改善，惟其組織學抗纖維化療效尚未確立。針對晚期肝纖維化，第二及第三期臨床試驗中，標靶凋亡訊號調節激酶 1（ASK1）、法尼醇 X 受體（farnesoid X receptor）及纖維母細胞生長因子 21（FGF21）等途徑之藥物療效不一，凸顯對更有效治療策略之迫切需求。整合經驗證之非侵入性纖維化評估工具（如 Fibrosis-4 指數與瞬時彈性影像）、維持 ≥10% 之體重減輕、循證抗糖尿病藥物治療，以及於多專科照護架構中及時納入臨床試驗，可望改變 MASLD 與 T2DM 之疾病進程，並改善長期預後。