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Diabetes and Obesity as Catalysts in MASH Progression: Mechanisms and Emerging Therapies

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Abstract: Metabolically-dysfunction-associated steatohepatitis (MASH) has become a significant global health issue, closely associated with obesity and type 2 diabetes mellitus (T2DM). This review closely links the mechanistic interrelationships among these metabolic disorders and the progression of MASH, emphasising pathways such as insulin resistance, de novo lipogenesis, lipotoxicity, oxidative stress, and dysbiosis of the gut microbiota. Evidence from studies indicates that MASH is notably more common among those with T2DM, reflecting the metabolic links between the two conditions. Recent advances highlight Thyroid hormone receptor-β agonists, PPAR agonists, GLP-1/GIP receptor agonists, SGLT2 inhibitors, and gut microbiota modulators among the promising treatment options. It is essential to acknowledge that these pharmacological compounds primarily result in a partial alleviation of fibrosis. Key obstacles remain persistent gaps in non-invasive diagnostics and in individualized treatment strategies. A potential framework for enhancing MASH management and preventive strategies may be established by integrating multiomics-based biomarkers with combination therapies targeting metabolic and inflammatory pathways.

Keywords: MASH; MASLD; obesity; metabolic damage; diabetes; gut microbiome.

1. Introduction

MASH is often referred to as a ‘silent disease’ as it has few or no symptoms, especially in its early stages. The early stage of MASH progression is marked by steatosis, which is frequently linked to metabolic syndrome components like type 2 diabetes and obesity [1]. Various other mechanisms contribute to lipid accumulation in the liver, including increased lipolysis, hepatic lipogenesis, and consumption of high-calorie diets [1]. Insulin resistance is pivotal in the development of steatosis, as it leads to the release of free fatty acids from adipose tissue. Liver fibrosis serves as a significant predictor of MASH progression and Hepatocellular Carcinoma (HCC) development, [2] underscoring the need to target fibrosis in treatment approaches. Risk factors for MASH-associated HCC include advanced liver fibrosis, older age, male gender, metabolic syndrome, genetic predispositions, and dietary habits, underscoring the need for effective surveillance and diagnostic measures [1].

Insulin resistance (IR) and lipotoxicity are closely interconnected and fundamental in setting the stage for the development of MASLD/MASH [3]. (Figure 1) And from a metabolic perspective, MASLD is caused by an imbalance in hepatic energy metabolism, with excess

carbohydrates and fats; the liver is unable to oxidise them, resulting in their accumulation as triglycerides [3,4].

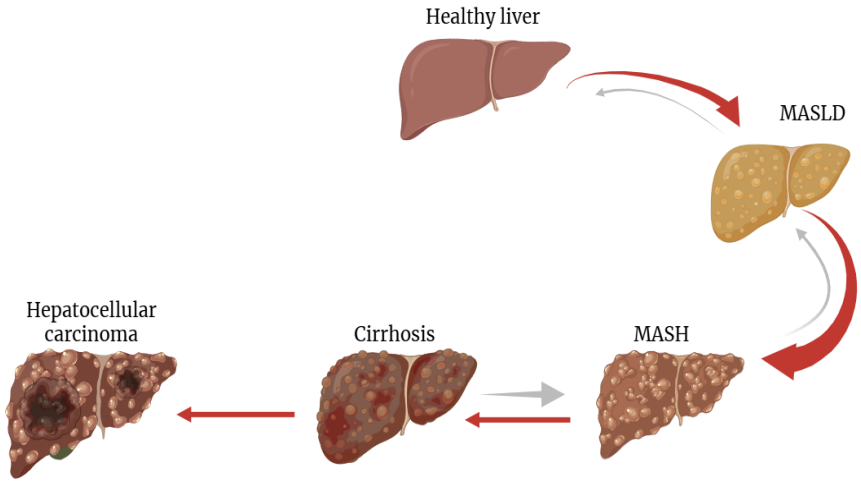

Figure 1. The progression spectrum of MASLD. A healthy liver can become steatotic due to obesity, lifestyle choices, or other factors. Steatohepatitis can arise from steatosis when inflammatory factors are present. Both MASLD and MASH can often be reversed, while cirrhosis may improve partially with treatment. If not addressed, this condition may lead to hepatocellular carcinoma and might eventually necessitate a liver transplant.

1.1. Epidemiology.

Metabolically-dysfunction-associated steatotic liver disease (MASLD), which was earlier classified under the more general term non-alcoholic fatty liver disease (NAFLD), signifies a notable change in our understanding, diagnosis, and treatment of liver diseases linked to metabolic dysfunction. MASLD, including its more severe variant called metabolic dysfunction-associated steatohepatitis (MASH), is increasingly acknowledged as a condition intrinsically connected to metabolic risk factors like obesity, type 2 diabetes mellitus (T2DM), dyslipidaemia, and IR [5]. Although epidemiological studies involving over 8 million individuals have found that the global prevalence of MASLD is around 25%, this figure varies significantly based on diagnostic methods and geographical regions. Notably, the two regions with the highest prevalence rates are the Middle East and South America, both estimated at about 30%. Approximately 60% of individuals who underwent liver biopsies were found to have MASH. Reflecting its metabolic characteristics, 42% of those with MASLD were also diagnosed with metabolic syndrome (MetS); 69% had hyperlipidaemia; 51% were classified as obese; 39% had hypertension; and 22% were diabetic [6].

The prevalence of MASLD/MASH rises alongside the growing rates of obesity, MetS, and T2D. Between 1975 and 2014, the global number of individuals with obesity has surged, with 11% of adult men and 15% of adult women diagnosed with this condition. In Brazil, obesity saw a 67.8% increase over a 13-year period, reaching 19.8% by 2018. MASLD/MASH prevalence varies from 60 to 95% in populations with obesity [7].

The way fat is distributed in the body plays a significant role in the development of metabolic diseases, and excess fat around the abdomen can pose different risks than a more uniform distribution. A recent agreement highlights the value of measuring waist circumference to provide a more accurate assessment of metabolic risk; however, the rate of abdominal obesity has risen more rapidly than that of general obesity, even when body mass index is considered [8]. Further, in a cohort of 2017 subjects monitored for 4.4 years, visceral

fat area, measured using ultrasonography or computed tomography, showed a longitudinal association with the incidence of MASLD/MASH, with an adjusted hazard ratio of 2.23 (95% CI 1.28–3.89) [9].

Diabetes is among the most rapidly escalating global health crises of the 21st century. In 2019, approximately 463 million individuals across the globe were affected by diabetes, with a projected increase of 51% by 2045, leading to a prevalence of 700 million cases [10]. Brazil ranks as the fifth nation globally in terms of the number of people living with diabetes, totalling 16.8 million [11].

Although the link between T2D and MASLD is well recognized, physicians may not fully appreciate the detrimental consequences of this association. [12]. According to two meta-analyses [13,14], MASLD is highly prevalent in T2DM patients [15]. A clinical model that predicted MASH and advanced fibrosis in MASLD patients with T2DM was developed by Bazick et al. [16] in 2015 and showed greater accuracy than the MASLD fibrosis score, with a specificity of 90.0% and a sensitivity of 56.8%. Pooled studies conducted in Europe showed a prevalence rate of 68% (95% CI 62.1–73.0), marking the highest rate worldwide. The prevalence of MASH and advanced fibrosis in individuals with MASLD and T2DM was estimated at 37.3% (95% CI 24.7–50.0) and 17.0% (95% CI 7.2–34.8), respectively [14]. Additionally, the overall mortality over a period of 5–10 year follow-up period was estimated at 585 per 100,000, which is higher than that observed in other chronic liver diseases. Most MASLD patients with T2DM met the criteria for MetS, underscoring the connection between these conditions within the metabolic risk continuum [9].

This review aims to provide a comprehensive overview of the mechanistic pathways through which diabetes and obesity accelerate the progression of MASH, while highlighting emerging therapeutic strategies that extend beyond conventional management approaches.

2. Methodology

A systematic literature search was performed using PubMed and Scopus to identify recent findings on the roles of diabetes and obesity in MASH progression and related emerging therapeutic strategies. Search terms included “MASH progression,” “diabetes and MASH,” “obesity and NAFLD/MASH,” “metabolic dysfunction steatohepatitis,” and keywords related to novel therapies such as metabolic regulators, anti-inflammatory agents, gut–liver axis modulators, nanomedicine-based interventions, regenerative approaches, and anti-fibrotic therapies. Data on ongoing and completed clinical trials were also retrieved from the National Library of Medicine (NIH) database. We included original research articles, clinical studies, and peer-reviewed publications addressing molecular mechanisms and innovative therapeutic approaches. Preclinical and clinical studies assessing efficacy, safety, and mechanistic pathways were considered. Only full-text articles published between 2015 and 2025 were included, while non-peer-reviewed sources, duplicates, and conventional-treatment-only papers were excluded. Emphasis was placed on incorporating high-quality and up-to-date evidence, though clinical data on emerging therapies remain limited.

3. The Complex Linkage Between Obesity, Diabetes, and MASH

The pathophysiology of MASH is complex, multifactorial, and still under investigation [17]. It is generally accepted that multiple pathways and mechanisms are involved in the pathogenesis of MASH. MASLD is the most common cause of chronic liver disease (>25% of

all adults). Over 1/2 to 2/3 of patients with MASLD have obesity, and over 3/4 of patients with MASH have obesity. Among patients with MASLD, 10–25% may have or develop MASH [18]. The risk of developing MASH is approximately 2-3 times higher in individuals with obesity and/or T2DM. The prevalence of MASH in patients with obesity is 30%, while the prevalence of MASH in patients with type 2 diabetes mellitus ranges between 30% to over 50% [14, 18, 19]. However, not all individuals with obesity are metabolically unhealthy, and not all normal-weight or lean individuals are metabolically healthy. Factors such as fat distribution, adipose tissue (AT) function, and insulin resistance (IR) play a central role in the development of metabolic disturbances, including MetS, diabetes, and MASLD [9].

MASH is characterized by hepatic fat accumulation, which can lead to inflammation and liver damage [18]. Therefore, the primary risk factor for MASH is obesity, as excess fat contributes to chronic liver inflammation [20]. Slowly increasing body weight is the fuse for subsequent metabolic disorders, among which T2DM is undoubtedly the one most closely related to obesity [21]. The outcome of metabolism-related T2DM is quite simple: hyperglycaemia resulting from declined insulin sensitivity owing to the reduction of functional β-cell mass, with obesity being a powerful driver in its development and progression, including strengthened genetic/epigenetic vulnerability [22], microenvironmental changes impairing insulin signalling, deteriorated β-cell function, and dysregulated microbiome-gut-brain axis. Obesity, particularly visceral adiposity, plays a central role by promoting insulin resistance (IR), a hallmark of T2DM and a critical driver of hepatic steatosis [9].

More than 10 years ago, Virtue and Puig [23] put forward the “AT expandability hypothesis”, by which the capacity for stock lipids by expanding AT is limited in an individualized fashion. Thus, when the storage capacity of AT is surpassed, excess lipids are deposited in ectopic sites, including the liver and skeletal muscle, leading to insulin resistance via lipotoxic mechanisms (Figure 2).

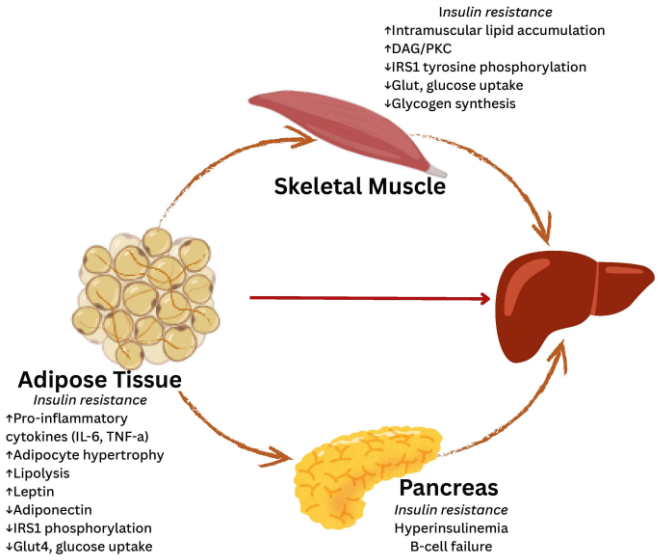

Figure 2. Changes associated with insulin resistance and lipotoxicity in various target organs. Alterations in adipose tissue, coupled with insulin resistance and lipotoxicity, work together to enhance lipolysis, reduce storage capacity, and increase the delivery of free fatty acids (FFAs) to organs such as the muscle and pancreas. This results in diminished glucose uptake, the release of pro-inflammatory cytokines, and a further decline in insulin sensitivity. Within skeletal muscle, the accumulation of excess lipids leads to an increase in harmful lipotoxic lipids, which exacerbates insulin resistance and results in reduced glucose uptake and glycogen levels. The failure of pancreatic β-cells can occur as an initial event (alternate hypothesis) or as a secondary effect from burnout (classic hypothesis), eventually leading to the inability to sustain glucose homeostasis. Consequently, surplus FFAs are directed to the liver, which is further complicated by hepatic insulin resistance.

The AT expandability hypothesis has relevant clinical implications. It explains the metabolic pattern usually observed in patients with lipodystrophies (a rare disorder characterized by a selective loss of adipose tissue, leading to a range of metabolic complications and changes in body appearance). Increased ectopic fat in the pancreas, liver, and muscles, as well as varying degrees of incapacity to expand subcutaneous adipose tissue, are characteristics of these genetic diseases [9]. Hence, severe IR in lipodystrophy patients can result in diabetes, MASLD, and MetS. Impaired peripheral fat storage capacity has both etiological and genetic associations with IR and metabolic disorders, thereby supporting the AT expandability hypothesis.

Hepatic lipid accumulation in MASH arises mainly from elevated FFAs, enhanced de novo lipogenesis driven by insulin resistance, and dietary lipids. Impaired glucose handling increases acetyl-CoA and malonyl-CoA synthesis, promoting steatosis and worsening hepatic insulin resistance. Concurrently, fasting hyperglucagonemia and altered amino acid metabolism indicate glucagon resistance, closely linked to liver fat content [24, 25]. Together, disrupted insulin and glucagon signaling pathways contribute to disease progression and heighten the risk of type 2 diabetes.

Oxidative stress, mitochondrial dysfunction, and pro-inflammatory cytokines drive the progression from simple steatosis to MASH and, ultimately, to fibrosis. While the classic "two-hit" hypothesis links hepatic fat accumulation and insulin resistance to subsequent inflammation and fibrosis, the "multi-hit" model better explains the complexity of MASLD, incorporating genetic, metabolic, and environmental influences. Insulin resistance accelerates lipolysis, FFA influx, and hepatic lipogenesis, while inflamed adipose tissue releases IL-6 and TNF-α and reduces adiponectin. These processes promote lipotoxicity, mitochondrial and ER stress, hepatocyte injury, and progressive fibrosis [26].

Obesity and T2DM accelerate MASLD progression by increasing visceral fat, FFA influx, and hepatic insulin resistance. Excess FFAs and hyperglycemia intensify ROS production by enhancing oxidative metabolism and activating NADPH oxidase, driving oxidative stress and hepatocyte injury. This environment activates Kupffer cells and stellate cells, promoting inflammation and fibrosis. Consequently, individuals with obesity and T2DM show more severe liver damage, making these conditions strong metabolic catalysts for the transition from steatosis to progressive MASH and advanced liver disease.

4. Essential Biomarkers Linked to MASH

In recent years, the investigation of biomarkers, especially in relation to MASH and T2DM, has attracted significant interest. The relationship among MASH, obesity, and T2DM underscores the necessity for a comprehensive management strategy that targets factors such as insulin resistance and chronic inflammation [27].

Biomarkers offer essential information regarding the existence and advancement of these conditions. These measurable indicators represent particular aspects of disease-related physiological processes, and their importance has increased in the area of metabolic disorders (Figure 3). Additionally, biomarkers can offer significant biomedical information and enhance decision-making in healthcare for various conditions, including movement-related disorders, breast cancer, and Alzheimer's disease [28].

As already seen earlier, obesity plays a major role in the onset of MASH due to lipid imbalance, insulin resistance, and ongoing inflammation. Targeting specific biomarkers presents an effective approach for identifying these associated conditions. Inflammatory

markers such as CRP, IL-6, and TNF-α act as signs of inflammation, whereas Homeostatic model assessment for insulin resistance (HOMA-IR), fasting insulin, and HbA1c are crucial for assessing IR [27].

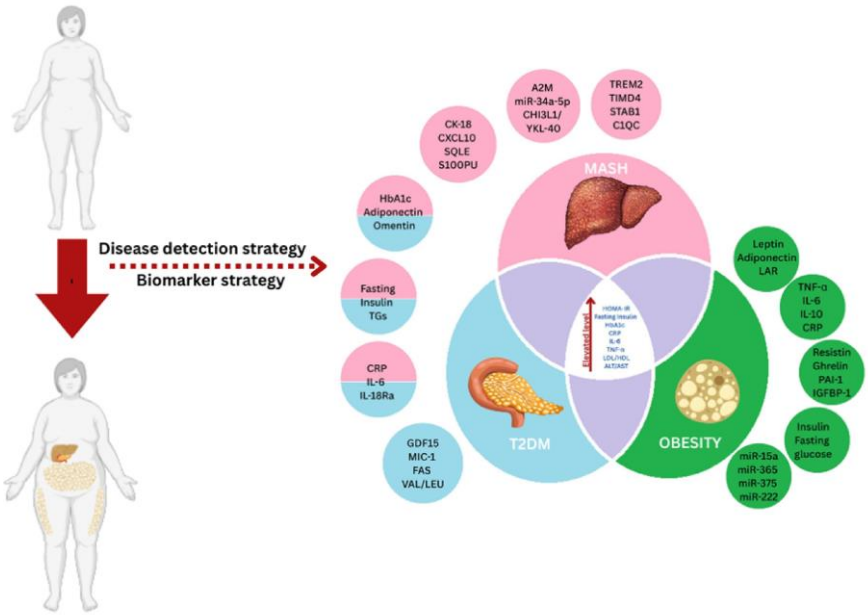

Figure 3. Overlapping biomarkers are responsible for metabolic disorders. This Venn diagram represents the common biomarkers used to diagnose MASH, T2D, and obesity in humans.

4.1. Biomarkers in insulin resistance.

Insulin resistance happens when tissues don't respond well to insulin, messing up glucose control and causing metabolic problems. To spot this early, assess risks, and develop targeted treatments, we need reliable biomarkers. Several biomarkers show how sensitive or resistant someone is to insulin, with HOMA-IR, fasting insulin levels, and HbA1c being key players. These biomarkers give us a peek into how a person's body handles glucose and help us spot and manage insulin-related issues [27].

HOMA-IR, a widely studied biomarker of insulin resistance, strongly correlates with the gold-standard hyperinsulinemic–euglycemic clamp. Large cohort studies and meta-analyses show that elevated HOMA-IR significantly increases the risk of developing type 2 diabetes and is also associated with a higher risk of MASLD, cardiovascular disease, chronic kidney disease, and increased carotid intima-media thickness [29].

4.2. Biomarkers in chronic inflammation.

Insulin resistance frequently induces a mild, persistent inflammatory state that activates immune cells and leads to the secretion of pro-inflammatory cytokines, such as C-reactive protein (CRP), IL-6, and TNF-α. This inflammatory response worsens liver injury in MASH, contributing to steatohepatitis, and intensifies IR in T2D.

Elevated C-reactive protein (CRP) reflects systemic inflammation and is associated with a higher risk of developing type 2 diabetes, as supported by large prospective studies and meta-analyses. Increased CRP and IL-6 levels also correlate with greater risk of cardiovascular disease and all-cause mortality, highlighting their value as inflammatory markers linked to metabolic and vascular complications [29].

4.3. Biomarkers in lipid dysregulation.

Lipid imbalance, characterized by unusual lipid levels in the blood, significantly increases the risk for several diseases, including cardiovascular disease, metabolic syndrome, obesity, and T2DM. Monitoring lipid markers is essential for the early detection and management of lipid imbalances and heart-related conditions. Grasping the key processes involved in lipid metabolism and identifying individuals at high risk enables healthcare professionals to apply preventive measures and commence suitable treatment strategies, which may include lifestyle modifications, medication, or a combination of both [30].

4.4. MicroRNAs (miRNAs) as biomarkers.

MicroRNAs (miRNAs) are small non-coding RNA molecules that are key regulators of gene expression and have come to be recognized as potential biomarkers for a range of diseases, such as T2DM and MASH. Certain biomarkers are only evident in obesity, for instance, mir-15a, mir-365, mir-375, and mir-222 [31].

Nonetheless, multiple miRNAs have been recognized as promising biomarkers for both MASH and T2DM. The shared miRNA biomarkers consist of miR-122, miR-126, miR-144, miR-29a, miR-203, and miR-223.Reduced levels of miR-122 and miR-126 have been observed in T2DM and are linked to cardiovascular issues, which can arise in both MASH and T2DM.[27] miR-144 has been recognized as a possible biomarker for insulin resistance, while alterations in miR-29a levels have been noted in both prediabetic and diabetic individuals, and it may also contribute to liver fibrosis related to MASH [32]. miR-103 is associated with the regulation of adipose tissue and glucose metabolism, both of which are pertinent to MASH and T2DM. Additionally, changes in miR-223 levels have been observed in T2DM patients and may also play a role in liver inflammation associated with MASH [33]. These miRNAs appear to have potential as biomarkers for both MASH and T2DM, as they underscore the shared metabolic issues underlying these disorders. As miRNAs are easily measurable, highly specific, and mechanistically relevant, they offer potential for early diagnosis, disease monitoring, and therapeutic targeting in MASH.

5. Pathways and Rationale for Treatment Options in MASH

The pathophysiology of MASH is characterized by steatosis, lipotoxicity, apoptosis, and inflammation, together with insulin resistance and progressive fibrosis, and these disturbances, importantly, provide the rationale for targeted therapeutic intervention [9, 26]. Genetic predispositions, such as single-nucleotide polymorphisms, also impact susceptibility to MASLD and its progression and present further avenues for the development of novel therapeutics (Figure 4). Due to their initial asymptomatic presentation and the lack of widely available, accurate, and accessible non-invasive tests, early diagnosis of MASLD and MASH is challenging [17].

PPAR agonists, such as glitazones, have demonstrated positive outcomes in patients with MASH and MAFLD. For example, regardless of a patient's T2DM status, pioglitazone has been shown to improve liver function and liver fat content, which can result in the resolution of MASH [1,9,17,26,34]. Rosiglitazone, on the other hand, has shown limited effectiveness, and its trials were discontinued due to increased cardiovascular risk [1]. Despite these promising results, the application of pioglitazone for MASH is currently not approved outside of the treatment of T2DM due to potential side effects like weight gain, fluid retention,

and risk of bone fractures or bladder cancer [35]. However, pioglitazone has been demonstrated to lower myocardial infarction and stroke risk in patients with T2DM or prediabetes, making it a potential treatment for MASH patients at cardiovascular risk.

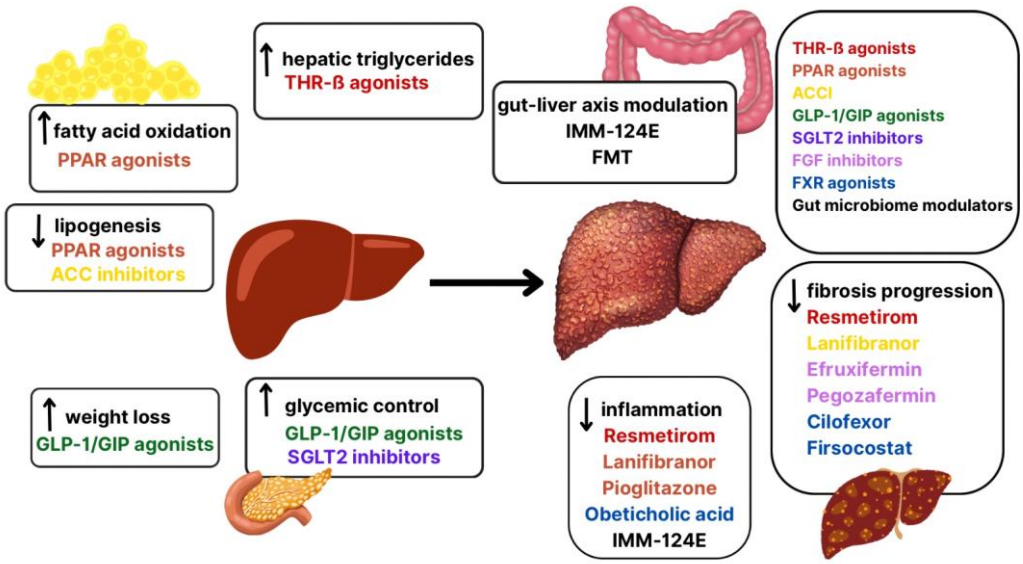

Figure 4. Pharmacological interventions in MASLD and MASH progression.

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have demonstrated beneficial effects on liver steatosis, inflammation, and fibrosis, making them a potential therapy for MASH [6,9,26]. However, most of the randomized controlled trials that have been done to date have been few in number and have not examined the effect of SGLT-2 inhibitors on liver histology [9].

Resmetirom, a selective agonist of the thyroid hormone receptor beta (THR-β), presents a promising strategy by reducing systemic effects and specifically increasing hepatic metabolism. Even though Resmetirom represents a significant advancement in the treatment of non-cirrhotic MASH, further long-term research is needed to fully assess its clinical benefits and secure regulatory approval for broader use in MASLD and MASH [36]. Even though new treatments are being developed, regulatory bodies have only recently begun to define clear diagnostic pathways to reliably and economically identify patients eligible for treatment without the need for liver biopsies [14]. In the prescribing information for Resmetirom, the FDA highlights F2–F3 fibrosis as the therapeutic window, supports the use of NITs, and waives the need for a biopsy [37]. As a result, it is up to the practicing doctors to choose the best diagnostic approach and determine how well it fits the clinical context. As outlined in the latest 2024 joint 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) guidelines on the management of MASLD, imaging or biomarker-based NITs capable of detecting MASH F2-F3 are encouraged based on expert opinion alone although no actual data on NIT performance in MASH F2-F3 is specifically provided [38]. However, the Foundation for the National Institutes of Health Biomarkers Consortium "NonInvasive Biomarkers of Metabolic Liver Disease" (NIMBLE) has highlighted the need to develop new NITs for subjects with at-risk MASH, which includes cirrhosis, and for which Resmetirom is not currently recommended. Consequently, the absence of consistently tested and validated non-invasive tests for MASH F2-F3 that can effectively identify individuals likely to meet histopathological criteria for non-alcoholic steatohepatitis with fibrosis presents a considerable challenge [17]. This existing obstacle is further exacerbated by the reality that most currently

available biomarkers are inadequate and that there is no definitive test established to effectively screen for MASH with F2–F3 [17].

As per the FDA-mandated pathways, medications are only approved once the drugs have successfully completed phase III study, commonly a large-scale randomized placebo-controlled clinical trial. This requires more than a decade of effort, which can be shortened by several years if breakthrough or accelerated approval designations are achieved [39]. Current research indicates the potential of gut–liver axis modulation as a therapeutic approach strategy for MASH. Dysbiosis of the gut microbiome, a key factor in disease progression, increases intestinal permeability and induces liver inflammation. Among hopeful supplementary treatments, IMM-124E, the bovine colostrum-based drug, has exhibited a dramatic decrease in AST levels. and ALT levels of MASH patients following treatment for 24 weeks, but no effect on liver lipid levels [26].

Despite the widespread occurrence of MASH among people with obesity and/or T2D, finding effective treatments has long been a significant medical challenge. Until recently, Vitamin E and Pioglitazone were considered off-label options for patients with histologically confirmed MASH and considerable hepatic fibrosis, particularly those with diabetes, although there is experimental evidence indicating their potential benefit for individuals without diabetes [40]. On March 14, 2024, the FDA granted accelerated approval for Resmetirom, marking it as the first drug specifically for patients with MASH and stages F2 to F3 of moderate to advanced hepatic fibrosis. It is expected that this approval will soon be accompanied by several other treatments currently undergoing various phases of clinical trials [37].

6. Gut Microbiome Modulators as an Emerging Promising Probiotic for Preventing and Treating MASH

Recent studies have associated alterations in the gut microbiome with the development of NAFLD [41]. Although the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) currently lack guidelines regarding the role of probiotics in patients with NAFLD and/or NASH, probiotics are a promising therapeutic option for patients with NAFLD because they can restore a natural and healthy gut microbiome [18].

The gut microbiome has already been clinically proven and is linked to many diseases, including obesity, cardiovascular disease, inflammatory bowel disease, malnutrition, osteoporosis, colorectal cancer, and Clostridium difficile infection [42]. Individuals with MASH frequently exhibit a higher prevalence of Proteobacteria and Enterobacteriaceae, along with a reduced abundance of beneficial bacteria such as Bacteroidetes and Firmicutes [43]. Alterations in microbial populations can affect metabolic and inflammatory processes, contributing to the development of liver disease [44]. One of the primary processes includes the generation and movement of endotoxins, especially lipopolysaccharides [44]. In patients with MASLD/MASH, the gut microbiome typically generates elevated amounts of endotoxins [45]. Because of a compromised intestinal barrier, frequently seen in obesity and metabolic syndrome, these endotoxins migrate into the portal circulation, reach the liver, and elicit inflammatory responses [44].

The gut microbiome interacts with the immune system of the host, affecting the development of MASLD/MASH [26]. Bacterial components, such as peptidoglycans and flagellin, can stimulate immune cells via pattern recognition receptors, including toll-like receptors and nucleotide-binding oligomerization domain-like receptors [46, 47]. This

stimulation results in the secretion of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which contribute to liver inflammation and fibrosis [26]. Dietary elements play a crucial role in shaping the composition and function of the gut microbiota, thereby influencing the progression of MASLD/MASH [48].

Recent studies underline the potential of modulating the gut–liver axis as a treatment strategy for MASH. Dysbiosis of the gut microbiome, which plays a crucial role in the progression of the disease, leads to increased gut permeability and initiates liver inflammation. Among the promising adjunct therapies, IMM-124E, a product derived from bovine colostrum, has demonstrated a noteworthy reduction in AST and ALT levels in MASH patients after 24 weeks of treatment [49]; however, it did not affect liver fat content [43].

Furthermore, fecal microbiota transplantation (FMT) is under investigation, but the clinical data supporting both treatments are still in the early stages. Importantly, IMM-124E has demonstrated a favorable safety profile, with no adverse effects reported [26, 43]. Table 1 summarizes the therapeutic options available for the treatment of MASH.

Table 1. An overview of the therapeutic options for the treatment of MASLD and MASH.

S. No	Drug	Mechanism of Action	Advantage	Disadvantage	Trial Status	References
Thyroid Hormone Receptor (THRβ) agonist						
1.	Resmetirom	A thyroid hormone receptor beta (THR-β) agonist that affects lipid metabolism and cholesterol levels	enhances fatty acid oxidation and reduces lipogenesis in the liver; reduces lipid accumulation, inflammation, and fibrosis; decreases triglyceride synthesis, promotes LDL cholesterol uptake, and reduces hepatic lipotoxicity	mild gastrointestinal side effects, such as nausea and diarrhea, and a slight decrease in free T4 at high dosages.	Phase IV. FDA-approved	[30,50]
2.	VK2809	prodrug that selectively binds to the thyroid hormone receptor beta (THR-β) after being activated in the liver. In MASH, this activation lowers inflammation and hepatic steatosis by improving cholesterol and triglyceride levels, increasing fat metabolism, and decreasing lipogenesis	Reduces hepatic lipogenesis, lowers lipid levels with minimal systemic impact	Mild or moderate gastrointestinal -related events	Phase II completed	[51,52]
Acetyl-CoA Carboxylase (ACC) inhibitors						
3.	PF-05221304	inhibits acetyl-CoA carboxylase (ACC), which targets pathways involved in lipid synthesis	Minimal adverse events; phase 2a trials showed effectiveness in reducing liver fat percentage, with a significant reduction in liver fat	N/A	Phase IIa	[53]
4.	IMA-1	suppresses indoleamine 2,3-dioxygenase 1 (IDO1), adjusting the immune system and tryptophan metabolism.	does not induce hyperlipidemia; halting diet-induced NASH progression in male mice and macaque models; avoids side effects	N/A	Preclinical /Early-phase	[54]
Diacylglycerol O-acyltransferase 2 (DGAT2) inhibitor						
5.	PF-06865571	limits the production of triglycerides by	Combined therapy with PF-05221304 showed a	potential for off-target	Phase II	[55]

S. No	Drug	Mechanism of Action	Advantage	Disadvantage	Trial Status	References
Thyroid Hormone Receptor (THRβ) agonist						
		inhibiting diacylglycerol O-acyltransferase 2 (DGAT2).	significant reduction in liver fat	effects and unknown long-term safety due to limited clinical data.		
Fibroblast Growth Factor (FGF) Analogs						
6.	Aldafermin (NGM282)	FGF19 analog that regulates the synthesis of bile acids, the metabolism of glucose, and the metabolism of fats	The peptide, phase 2 study showed fibrosis improvement without worsening NASH. Reduces liver fat	Diarrhoea	Phase II and IIb	[56]
7.	Efruxifermin (EFX, also known as AKR-001 or AMG876)	Fc-FGF21 fusion protein targets the FGF21 receptor pathways that are involved in the metabolism of fats and carbohydrates.	Peptide: improved pharmacokinetics and pharmacodynamics; showed potential in improving glycemic control; has a good safety profile; demonstrated antifibrotic effects meeting FDA criteria for phase 3 trials.	Mild to moderate gastrointestinal events	Phase II	[17,57]
Farnesoid X Receptor (FXR) agonists						
8.	Obeticholic Acid (OCA)	semi-synthetic bile acid, strong agonist of FXR.	Improves insulin sensitivity and reduces inflammatory markers.Regulates bile acid synthesis; reduces liver fat, demonstrating significant histological improvements in clinical trials	investigated in phase 2 and phase 3 trials; linked to adverse effects such as fatigue, constipation, abdominal distention, pruritus, and changed lipid profiles	Phase II	[58]
9.	Tropifexor (LJN452)	Non-bile acid FXR agonist	Significantly reduces ALT, liver fat, and NAS	Pruritus	Phase II	[59]
10.	Cilofexor (GS-9674)	Non-bile acid FXR agonist	enhancement of liver parameters in patients suffering from compensated cirrhosis or advanced fibrosis.	Headache	Phase II	[60,61]
11.	Vonafexor (EYP001)	Non-bile acid FXR agonist	Preclinical studies of a selective FXR agonist showed encouraging reductions in inflammation, fibrosis, and liver fat; phase 2 studies showed decreased liver enzymes and liver fat content.	At higher dosages, mild pruritus was noted.	Phase II	[62]
Peroxisome Proliferator-Activated Receptor (PPAR) agonists						
12.	Pioglitazone	Gamma agonists of peroxisome proliferator-activated receptors improve glucose utilization and lipid storage/redistribution, which lowers insulin resistance.	In an early randomized clinical trial (RCT) with 55 participants who had biopsy-proven MASH and prediabetes/T2DM, it was the first anti-hyperglycemic medication to demonstrate efficacy. Lowers liver inflammation, increases insulin sensitivity, and resolves 51% of MASH.	Weight gain and fluid retention	Completed Phase IV	[63]

S. No	Drug	Mechanism of Action	Advantage	Disadvantage	Trial Status	References
Thyroid Hormone Receptor (THRβ) agonist						
13.	Lanifibranor	pan-PPAR agonist that targets glucose and lipid metabolism (PPARγ, PPARδ, and PPARγ).	In highly active NASH, small-molecule clinical studies demonstrated notable improvements in liver histology without exacerbating fibrosis and anti-inflammatory effects.	Gastrointestinal-related events, peripheral edema, anemia, and weight gain	Phase II	[64]
14.	Saroglitazar	Dual PPARα/γ agonist, lipid and glucose metabolism modulator.	Approved in India for NASH, this small molecule improved metabolic parameters, hepatic fat content, and liver enzyme levels. Wider international approval is still pending.	Gastritis, asthenia, and pyrexia	Phase II and Phase III (India, US)	[65,66]
Stearoyl-CoA Desaturase 1 (SCD1) modulators						
15.	Dexmedetomidine (DEX)	Selective α2-adrenergic agonist that affects the CNS and sedation pathways	In NAFLD mice, the small molecule decreased inflammation and hepatic steatosis while also increasing insulin sensitivity.	cause bradycardia and hypotension as a result of central sympatholysis. limited use in individuals with serious cardiac disorders.	Clinical Phase III (Japan)	[67]
Antisense Oligonucleotides (ASOs)						
16.	AZD2693 (ION839)	targets the PNPLA3 gene, more especially the I148M variant that is associated with a higher accumulation of triglycerides in the liver.	Targets NASH patients with the PNPLA3 I148M variant, a genetic risk factor, in phase 2 trials; lowers hepatic lipid storage by reducing the expression of the mutated PNPLA3 protein; has been demonstrated to lower liver triglyceride levels and alleviate steatosis in animal models.	Its long-term safety and fibrosis impact are still unknown, and it may limit its use by posing risks of injection site reactions, immune responses, and off-target effects that only affect patients with the PNPLA3 I148M mutation.	Phase II b	[68]
Glucagon-like Peptide 1 (GLP-1) and Glucose-dependent Insulinotropic Polypeptide (GIP) receptor agonists						
17.	Liraglutide	GLP-1 receptor agonist, improving glucose homeostasis and insulin secretion.	lowers weight, hepatocyte apoptosis, and hepatic steatosis.	benefits that are lost when treatment is stopped.	Phase II	[69]
18.	Semaglutide	GLP-1 receptor agonist, improving glucose homeostasis and insulin secretion.	improves weight loss, hepatic steatosis reduction, and glycemic control.	nausea, vomiting, and limited improvement in fibrosis.	Phase II	[70–72]
19.	Tirzepatide	GLP-1 receptor agonist, improving glucose homeostasis and insulin secretion	Improves weight loss, insulin resistance, and reduces liver fat	increased gastrointestinal-related events in a dose-dependent manner.	Phase II	[73,74]

S. No	Drug	Mechanism of Action	Advantage	Disadvantage	Trial Status	References
Thyroid Hormone Receptor (THRβ) agonist						
20.	Retatrutide	GLP-1 receptor agonist, improving glucose homeostasis and insulin secretion	increases weight reduction and enhances metabolic parameters.	Increased heart rate that is dose-dependent and gastrointestinal problems linked to higher doses	Phase II	[75]
21.	Dulaglutide	Fc fragment fused to a GLP-1 receptor agonist, improving glucose homeostasis and insulin secretion	Peptide improves glycemic management and lowers hepatic glucose synthesis; increases insulin sensitivity by inducing insulin secretion and inhibiting glucagon release; and aids in weight loss by reducing appetite.	gastrointestinal side effects like nausea and vomiting.	Phase II explorator y	[76,77]
22.	Exenatide	Synthetic version of exendin-4, a GLP-1 receptor agonist, improving glucose homeostasis and insulin secretion	Peptide targets GLP-1 receptor, insulin signaling, AMPK, and inflammatory pathways, reducing hepatic inflammation and oxidative stress	frequent GI side effects and twice-daily dosing, reducing patient compliance	Phase II (limited efficacy)	[78–80]
Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors						
23.	Empagliflozi n	SGLT2 inhibitor specifically targeting the insulin signaling pathway	Small molecule; preclinical research showed reduced insulin resistance and decreased hepatic fat formation in a variety of animal models of NAFLD, including obese humans and mice brought on by a high-fat diet.	N/A	Phase IV	[81]
24.	Canagliflozi n	SGLT2 inhibitors target processes related to fatty acid oxidation and de novo lipogenesis	By altering important metabolic pathways in preclinical mouse models, this small drug decreased inflammation and hepatic fat accumulation	genital infections, dehydration, and rare diabetic ketoacidosis.	Research is needed, particularl y in phase 3 trials	[82–84]
25.	Dapagliflozi n	An insulin signaling system implicated in fatty acid oxidation, inflammation reduction, and fibrosis mitigation is targeted by SGLT2 inhibitors.	Small drug; lower serum levels of γ-glutamyltranspeptidase and alanine aminotransferase, as well as hepatic steatosis, inflammation, and liver fat content in mice models of obesity and diabetes produced by a high-fat diet	Acute kidney injury	Phase III	[85]
Anti-Fibrotic and Anti-Inflammatory Agents						
26.	Selonsertib	inhibits the inflammatory and apoptotic enzyme apoptosis signal-regulating kinase 1 (ASK1).	Small drug; lowers hepatic inflammation and fibrosis by reducing the activation of hepatic macrophages and stellate cells	Failed in phase 3 trials due to lack of efficacy in improving fibrosis, despite targeting ASK1 (apoptosis signal-	Phase II, but in Phase III showed no activity, so it is no longer under clinical developm	[86]

S. No	Drug	Mechanism of Action	Advantage	Disadvantage	Trial Status	References
				regulating kinase 1).	ent for this indication.	
27.	Cenicriviroc (CVC)	An antagonist of dual CCR2/CCR5 that targets fibrotic and inflammatory pathways	Hepatic inflammation is lessened by this small drug that decreases the influx and activation of these immune cells.	Did not meet primary endpoints in phase 3 trials (AURORA study), showing no significant improvement in fibrosis or inflammation long-term	Phase III	[87]
28.	Bela Pectin	Targets the fibrosis and inflammatory pathways by inhibiting galectin-3	By blocking the production of oligomeric structures and lattice-like assemblies that are necessary for activating pro-fibrotic signaling pathways, this large molecule galactoarabino-rhamnogalacturonan polysaccharide inhibitor, which is generated from natural sources, stops fibrosis and lowers liver inflammation	Limited to non-cirrhotic MASH with portal hypertension; no effect in advanced fibrosis or cirrhosis, and overall narrow patient applicability.	Phase IIb/III	[18]
29.	GB1107	Targets the fibrosis and inflammatory pathways by inhibiting galectin-3	Small molecule thiogalactoside inhibitor targeting carbohydrate recognition domain (CRD) of galectin-3	Still in early-stage development with limited human data, and potential off-target effects due to Galectin-3 inhibition remain uncertain.	Phase I/II	[88]
30.	Relaxin and its mimetics	Activates relaxin family peptide receptor 1 (RXFP1), a GPCR that binds to the hormone relaxin 2	Induces multiple effects, including anti-fibrosis, anti-inflammatory, and vasoprotective actions in various organs	cause pregnancy-related discomfort, bloating, or constipation. Additionally, relaxin can weaken your pelvic floor, which could affect how well you regulate your bladder	Preclinical /Early clinical	[89–92]
Gut–Liver Axis Modulators (Microbiome-Targeted Therapies)						
31.	IMM-124E	Targets gut-liver axis dysfunction in MASH, neutralizes gut-derived LPS, a key endotoxin implicated in triggering hepatic inflammation through Toll-like receptor 4 (TLR4)	Reduces inflammation, improves liver enzymes (AST and ALT), and has no reported adverse effects	A 24-week experiment showed no effect on liver fat	Phase II	[93]

Thyroid Hormone Receptor (THRβ) agonist

Thyroid Hormone Receptor (THRβ) agonist						
S. No	**Drug**	**Mechanism of Action**	**Advantage**	**Disadvantage**	**Trial Status**	**References**
		activation on Kupffer cells and hepatocytes. By binding to LPS in the gut lumen, IMM-124E prevents translocation of these endotoxins into the portal circulation, thereby reducing systemic inflammation and interrupting the cascade of immune activation that contributes to hepatic injury and fibrogenesis.				
32.	Lactobacillus and Bifidobacterium species; probiotics and prebiotics such as inulin and FOS	alters the intestinal microbiome to enhance liver function	Clinical investigations have demonstrated that lowering liver fat content and raising liver enzyme levels improve liver health outcomes	Rare infections in immunocompromised patients may exacerbate SIBO symptoms	Multiple Phase II studies and some under Observational/pilot trials	[94–96]
33.	Short-chain fatty acids (SCFAs)	Anti-inflammatory substances are generated when dietary fibers are fermented by bacteria	have anti-inflammatory qualities and improve the function of the intestinal barrier, which will improve liver health	Relies on specific gut bacteria, which may be reduced in dysbiosis	Preclinical /early clinical	[97]
34.	Mediterranean diet, rich in fiber, polyphenols, and healthy fats	uses eating habits that are beneficial to the intestines to support liver health	promotes a healthy gut microbiota, which enhances liver function and is associated with less liver fat and better liver health outcomes in NASH/MASH patients	Needs dietary adjustments in liver disease	Clinical guideline-supported	[98]
35.	Rifaximin	Reduces endotoxin-producing bacteria in the gut	reduces dangerous germs to improve liver function; nevertheless, long-term use is debatable because of possible antibiotic resistance	Potential for antibiotic resistance Non-specific impact on microbiota	Phase 2 trials are ongoing	[99]
36.	Fecal Microbiota Transplantation (FMT)	restores a balanced gut flora by transferring feces from donors who are in good health	Lowers liver fat and increases insulin sensitivity; early clinical trials in MASH/NASH patients have shown promising results	risk of transmitting infectious agents or antibiotic-resistant bacteria from donor to recipient, particularly given that standard screening methods may not capture all potential pathogens.	Early-phase trials	[100]

7. Future Directions

A large prospective cohort study conducted in China revealed that the presence of multiple metabolic risk factors, including obesity, T2DM, and other comorbidities, was associated with a higher mortality rate for patients with MASLD [9, 14, 101]. Based on this study result, the authors concluded that in the future it may be necessary to subcategorize MASLD depending on the severity of the patient's metabolic syndrome symptoms in order to ensure more effective treatment. Therefore, grouping MASLD patients according to liver histology (steatosis, steatohepatitis, and fibrosis) may be less useful than grouping them by the main pathological mechanism involved, which is more suitable for predicting disease outcome. In addition, MASLD is a multisystemic disease; a multidisciplinary approach is required, and it is likely that monotherapy (in combination with lifestyle modification) to treat MASLD will not [102] provide complete treatment success. Thus, to achieve this, combination therapy targeting different pathological pathways and organ systems needs to be more intensively explored [14, 103, 104].

Future treatment strategies will likely incorporate genetically based technologies [6]. In particular, siRNA-based therapeutics provide a personalized medicine approach [105]. This will be especially relevant to genetically-associated liver disease, where a number of single-nucleotide polymorphisms have already been identified. Related therapeutics targeting signalling pathways in lipogenesis, inflammation, apoptosis, and fibrosis are in development [106]. Nevertheless, there is still a number of factors need to be taken into account in addition to stringent regulatory requirements before such combination therapies can be implemented in clinical practice: first and foremost, monotherapy must be well-established in patients; the second is that clinical trials must be carefully planned and conducted with a large number of participants; and the third is that the dosage and safety of such preparations must be thoroughly investigated [107]. And last but not least, the treatment of patients who do not respond to "conventional" treatment or are noncompliant must also be considered, so that it would be useful to develop a more personalized treatment approach [108].

Another effective method to manage patients with T2DM and MASH is the strategic use of overlapping biomarkers. This enables risk assessment using non-invasive biomarker panels for early diagnosis. The effectiveness of addressing cardiometabolic comorbidities and the efficacy of MASH-targeted therapies in individuals with MetALD must be rigorously evaluated, emphasizing liver-related outcomes or their appropriate surrogates. Thus, finding the initial stages of MASH and T2DM is the ultimate objective. It would be very beneficial for researchers to employ "multiomics" techniques, which combine knowledge from multiple biological databases (such as proteomics and genomics), and to tailor lifestyle and pharmacological interventions in accordance with the unique biomarker profiles of each patient as individualized treatments.

8. Conclusions

Metabolically–dysfunction–associated steatohepatitis remains a major global health burden, especially among individuals with obesity and type 2 diabetes. This study underscores how chronic metabolic stress, lipotoxicity, insulin resistance, and gut dysbiosis interact to accelerate hepatic injury and fibrosis. Although recent pharmacological advancements—such as Resmetirom, the first FDA-approved drug for non-cirrhotic MASH—represent meaningful progress, current therapeutic strategies still face significant limitations. Most investigational

drugs, including pioglitazone, THR-β agonists, GLP-1/GIP receptor agonists, and SGLT2 inhibitors, show promise in improving hepatic steatosis and metabolic parameters. Yet, their capacity to reverse or halt fibrosis remains inconclusive.

Considering that MASH and MASLD are multisystemic disorders, forthcoming therapeutic approaches should transition from monotherapy to combination regimens that address metabolic, inflammatory, and fibrotic pathways. The absence of universally validated non-invasive diagnostic biomarkers and standardized endpoints continues to hinder timely diagnosis and therapeutic evaluation. Future research should therefore focus on integrating multiomics-based biomarker discovery, modulation of the gut–liver axis, and personalized medicine approaches to better stratify patients and predict treatment response. Furthermore, combination therapies targeting multiple metabolic and inflammatory pathways simultaneously may offer a more holistic and durable disease resolution. Furthermore, a thorough assessment of therapeutic effectiveness in patients with concurrent metabolic comorbidities, such as MetALD, will be crucial for establishing clinical endpoints.

Overall, bridging the translational gap between mechanistic understanding and clinical application remains the key challenge. A multidisciplinary, patient-centered approach—combining metabolic management, pharmacotherapy, and microbiome modulation—will be essential to transform MASH therapy from disease control toward true reversal and prevention.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

Abbreviations

Abbreviation	Definition
MASH	Metabolic Dysfunction Associated Steatohepatitis
MAFLD	Metabolic Dysfunction Associated Fatty Liver Disease
MASLD	Metabolic Dysfunction Associated Steatotic Liver Disease
T2DM	Type II Diabetes Mellitus
MetS	Metabolic Syndrome
AT	Adipose Tissue
IR	Insulin resistance
miRNA	Micro RNA
SGLT-2	Sodium Glucose Co-transporter-2
FMT	Fecal Microbiota Transplantation

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