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Management of Obesity and Metabolic Dysfunction-Associated Steatohepatitis (MASH) in Multimorbid Patients

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Article History	Abstract
Received: 20th March 2026 Accepted: 14th April, 2026	Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH), represents the progressive inflammatory phenotype of metabolic dysfunction-associated steatotic liver disease (MASLD). The recent nomenclature shift from NAFLD/NASH to MASLD/MASH reflects a fundamental reconceptualization of this condition not merely as a hepatic disorder, but as a systemic manifestation of metabolic dysregulation .

Keywords: Metabolic dysfunction-associated steatohepatitis; MASH; MASLD; obesity; multimorbidity; resmetirom; semaglutide; GLP-1 receptor agonist; thyroid hormone receptor beta agonist; non-invasive tests; fibrosis; bariatric surgery; cardiometabolic disease

1. Introduction

Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH), represents the progressive inflammatory phenotype of metabolic dysfunction-associated steatotic liver disease (MASLD). The recent nomenclature shift from NAFLD/NASH to MASLD/MASH reflects a fundamental reconceptualization of this condition not merely as a hepatic disorder, but as a systemic manifestation of metabolic dysregulation . MASH now stands as the leading cause of chronic liver disease globally, with an estimated prevalence approaching 5% of the general adult population and substantially higher rates among individuals with cardiometabolic risk factors .

The defining characteristic of MASH in contemporary clinical practice is its inextricable linkage with multimorbidity. The majority of patients presenting with MASH do not exhibit liver disease in isolation; rather, they present with a constellation of interrelated conditions including obesity, type 2 diabetes mellitus (T2DM), arterial hypertension, atherogenic dyslipidemia, chronic kidney disease (CKD), and elevated cardiovascular risk . This multimorbid phenotype creates a complex therapeutic landscape where management strategies must simultaneously address hepatic fibrosis progression, metabolic control, and extrahepatic organ protection. The 2024 joint European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO) guidelines explicitly frame MASLD as a multisystem disease requiring integrated care pathways .

The therapeutic paradigm for MASH has undergone transformative evolution. For decades, management remained confined to lifestyle modification with limited pharmacologic options. However, 2024 marked the FDA accelerated approval of resmetirom (Rezdiffra), a selective thyroid hormone receptor beta (THR-β) agonist, as the first disease-specific therapy for non-cirrhotic MASH with moderate-to-advanced fibrosis (stages F2–F3) . This milestone was followed in August 2025 by the FDA approval of semaglutide 2.4 mg (Wegovy), a glucagon-like peptide-1 receptor agonist (GLP-1RA), for the same indication based on the pivotal ESSENCE phase 3 trial results . These approvals have fundamentally altered the treatment algorithm, particularly for multimorbid patients in whom these agents offer dual hepatic and cardiometabolic benefits.

This narrative review examines the contemporary management of obesity and MASH in multimorbid patients, synthesizing evidence from recent clinical trials, international guidelines, and real-world therapeutic positioning. We address risk stratification methodologies, lifestyle and pharmacologic interventions, the role of metabolic surgery, and the imperative for multidisciplinary care coordination in this challenging patient population.

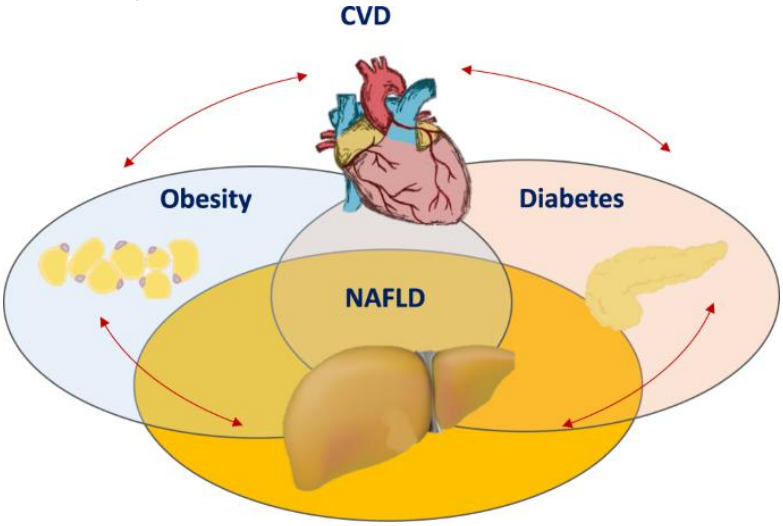
2. Pathophysiology and the Multimorbid Phenotype

The pathogenesis of MASH extends far beyond simple hepatic lipid accumulation. As illustrated in Figure 1, MASH arises from a complex interplay between adipose

tissue dysfunction, insulin resistance, genetic predisposition, gut microbiome alterations, and systemic inflammatory signaling . In multimorbid patients, these pathways create a self-perpetuating cycle wherein hepatic steatosis exacerbates systemic metabolic dysfunction, which in turn accelerates liver injury.

Figure 1. Interconnected pathophysiological drivers of MASH in multimorbid patients. Adipose dysfunction releases pro-inflammatory cytokines and free fatty acids, while insulin resistance promotes de novo lipogenesis. These systemic factors converge on the liver to drive steatosis, inflammation, and fibrogenesis.

The following image from Nature illustrates the bidirectional relationship between MASLD and its cardiometabolic comorbidities, emphasizing the central role of the liver in systemic disease:



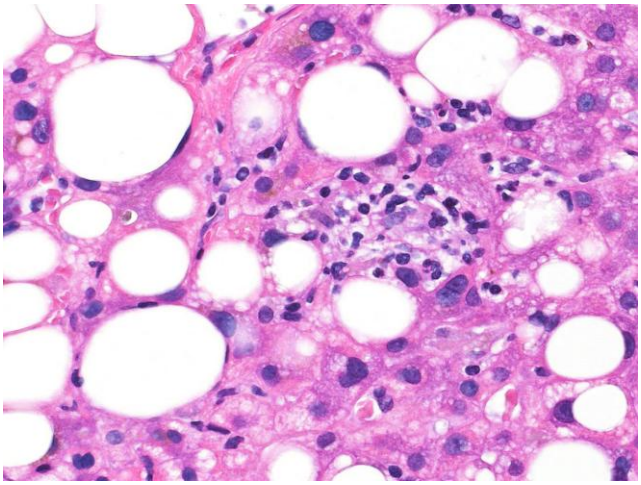
Multimorbidity Interconnections

Figure 1b. The interconnected cardiometabolic disease continuum. Obesity, diabetes, and cardiovascular disease form a bidirectional relationship with MASLD, creating a self-amplifying cycle of metabolic dysfunction.

Obesity serves as both a causal driver and a therapeutic target in MASH. Adipose tissue expansion, particularly visceral adiposity, promotes lipotoxicity through increased circulating free fatty acids and adipokine dysregulation . Concurrent T2DM, present in approximately 55% of MASH patients, amplifies hepatic insulin resistance and accelerates fibrosis progression . Hypertension and atherogenic dyslipidemia further compound cardiovascular risk, which represents the leading cause of mortality in this population rather than liver-related complications . The

American Heart Association's modified Delphi consensus emphasizes that MASLD should be systematically screened in all patients with cardiovascular disease, given this bidirectional relationship .

The histopathological progression from simple steatosis to steatohepatitis and fibrosis is clearly demonstrated in liver biopsy specimens:



MASH Histopathology

Figure 1c. Histopathological features of MASH on H&E staining, showing macrovesicular steatosis, hepatocyte ballooning, and lobular inflammatory infiltrates characteristic of steatohepatitis.

Understanding this interconnected pathophysiology is essential for therapeutic decision-making. Interventions that target shared molecular pathways—such as GLP-1 receptor signaling, which modulates both hepatic lipid metabolism and systemic glycemic control—offer particular promise in multimorbid patients . Conversely, liver-directed therapies that do not address systemic metabolic dysfunction may prove insufficient in isolation.

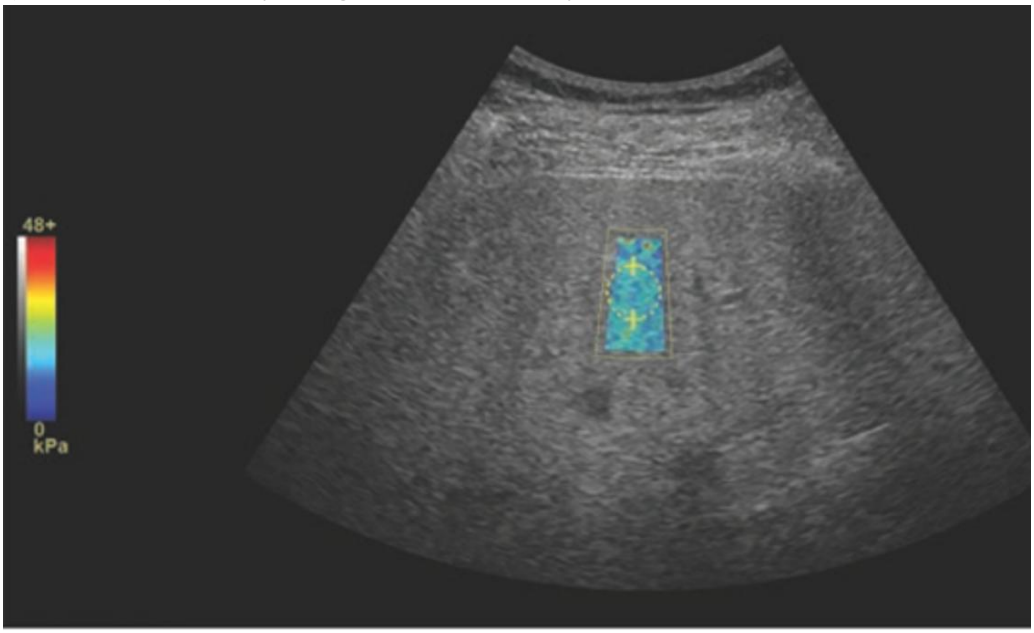
3. Risk Stratification and Non-Invasive Assessment

Effective management of MASH in multimorbid patients begins with accurate risk stratification. Given the invasive nature and sampling variability of liver biopsy, contemporary guidelines strongly advocate for non-invasive tests (NITs) as the cornerstone of fibrosis assessment . The stepwise algorithm typically employs serum-based scores followed by imaging-based elastography to identify patients at risk of progressive fibrosis who may benefit from pharmacotherapy.

Table 1. Non-Invasive Tests for MASH Risk Stratification in Multimorbid Patients

The Fibrosis-4 (FIB-4) index serves as the optimal initial screening tool due to its simplicity, cost-effectiveness, and high negative predictive value for excluding advanced fibrosis . In patients with indeterminate or high FIB-4 scores, vibration-controlled transient elastography (VCTE) provides quantitative liver stiffness measurement. The EASL-EASD-EASO guidelines recommend VCTE cut-offs of 8–15 kPa to identify F2–F3 fibrosis—the precise population eligible for FDA-approved MASH pharmacotherapy . Magnetic resonance elastography (MRE) offers superior accuracy in obese patients or those with ascites, though availability remains limited .

The following image demonstrates liver stiffness measurement using VCTE (FibroScan), a key diagnostic modality in MASH risk stratification:



Liver Elastography

Figure 2a. Vibration-controlled transient elastography (FibroScan) demonstrating liver stiffness measurement in a patient with suspected MASH. The color-coded scale indicates increasing stiffness values corresponding to fibrosis severity.

The 2025 American Diabetes Association consensus report specifically recommends that all adults with T2D or prediabetes undergo FIB-4 screening, even with normal liver enzymes, followed by VCTE or enhanced liver fibrosis (ELF) testing for those

with elevated scores . This proactive screening approach is critical in multimorbid patients who may remain asymptomatic despite significant underlying fibrosis.

4. Lifestyle Intervention: The Foundational Pillar

Despite the advent of pharmacotherapy, lifestyle modification remains the indispensable foundation of MASH management. Weight reduction operates in a dose-dependent manner to improve hepatic histology: a 3–5% body weight loss improves steatosis, 7–10% resolution reduces inflammation and MASH activity, while ≥10% weight loss offers the potential for fibrosis regression . Figure 4 illustrates these graduated therapeutic targets.

Dietary interventions should prioritize the Mediterranean dietary pattern, characterized by high consumption of monounsaturated fats, polyunsaturated fatty acids, fiber-rich vegetables, whole grains, and lean proteins while restricting processed carbohydrates, fructose-sweetened beverages, and saturated fats . This dietary approach demonstrates particular efficacy in multimorbid patients by simultaneously improving glycemic control, lipid profiles, and blood pressure.

Physical activity recommendations align with standard guidelines: at least 150–200 minutes of moderate-intensity aerobic exercise weekly, supplemented by resistance training two to three times weekly to preserve lean muscle mass and mitigate sarcopenic obesity . High-intensity interval training may offer superior benefits for MASH and fibrosis specifically . Behavioral health interventions, including cognitive behavioral therapy and mindfulness-based approaches, address the psychological comorbidities frequently accompanying obesity and chronic disease .

However, the reality of sustained lifestyle modification remains challenging. Real-world adherence to dietary and exercise programs is frequently suboptimal, with weight regain common following initial success . This limitation underscores the necessity of adjunctive pharmacologic and surgical interventions in appropriately selected multimorbid patients.

5. Pharmacologic Management of Comorbidities

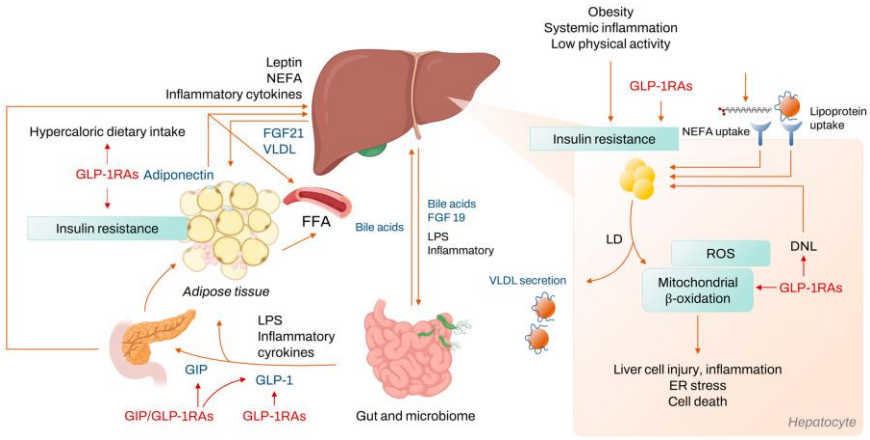
In multimorbid MASH patients, pharmacotherapy for associated conditions should be selected with awareness of hepatic and extrahepatic effects. The 2024

cardiovascular-liver-metabolic Delphi consensus provides specific guidance on medication selection in this population .

For T2DM management, incretin-based therapies—including GLP-1 receptor agonists and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists—have emerged as preferred agents . The mechanism of GLP-1 receptor agonists in liver protection involves multiple pathways, as illustrated below:

GLP-1 Mechanism

Figure 5a. Mechanism of GLP-1 receptor agonists in MASH pathophysiology. GLP-1RAs modulate hepatic lipid metabolism, reduce de novo lipogenesis, decrease oxidative stress, and improve mitochondrial function through direct and indirect pathways.



Semaglutide and tirzepatide demonstrate robust glycemic efficacy while promoting weight loss and reducing major adverse cardiovascular events (MACE) . Sodium-glucose cotransporter-2 (SGLT2) inhibitors offer complementary benefits for heart failure and renal protection, with modest reductions in hepatic fat content observed in imaging studies . Pioglitazone, a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist, retains utility for MASH with prediabetes or T2DM, though requires monitoring for weight gain and fluid retention .

Hypertension management should prioritize angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), which offer renal protection and may attenuate hepatic fibrogenesis . For atherogenic dyslipidemia, statins remain the cornerstone of therapy and are safe in compensated MASH-related cirrhosis, though they should be discontinued in decompensated disease . The lipid-

lowering effects of resmetirom provide additional atherogenic risk reduction in patients receiving this MASH-directed therapy .

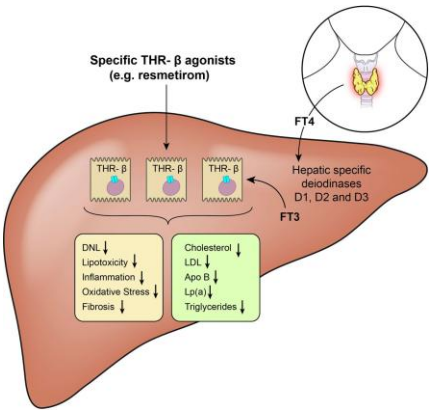
6. MASH-Targeted Pharmacotherapy

The contemporary treatment algorithm for multimorbid MASH patients now incorporates two FDA-approved disease-specific therapies, with selection based on individual patient phenotype, comorbidity profile, and treatment goals 6.1 Resmetirom (Rezdiffra)

Resmetirom, approved in March 2024, functions as a selective THR-β agonist that enhances mitochondrial β-oxidation, promotes lipophagy, and reduces hepatic lipogenesis without systemic hyperthyroidism . The MAESTRO-NASH phase 3 trial demonstrated that 52 weeks of treatment achieved MASH resolution without fibrosis worsening in 26% (80 mg) and 30% (100 mg) of patients versus 10% with placebo, with fibrosis improvement of ≥1 stage in 24% and 26%, respectively . Importantly, resmetirom is weight-neutral, making it particularly suitable for patients who are lean or have stable weight with progressive fibrogenesis.

The drug significantly improves atherogenic lipid parameters, reducing LDL-C by approximately 19%, triglycerides, ApoB, and lipoprotein(a) . Real-world evidence suggests associations with reduced MACE and all-cause mortality . Adverse events are predominantly mild gastrointestinal symptoms and pruritus; thyroid function testing at baseline is recommended given the mechanism of action .

The hepatic mechanism of resmetirom is illustrated in the following diagram:



Resmetirom Mechanism

Figure 6a. Mechanism of selective THR-β agonism by resmetirom. Activation of hepatic THR-β receptors enhances mitochondrial β-oxidation, reduces de novo

lipogenesis, decreases lipotoxicity and inflammation, and improves lipid profiles through hepatic-specific pathways.

6.2 Semaglutide (Wegovy)

Semaglutide 2.4 mg received FDA approval in August 2025 based on the ESSENCE trial interim analysis . At 72 weeks, semaglutide achieved MASH resolution without fibrosis worsening in 62.9% versus 34.3% with placebo, and ≥1-stage fibrosis improvement in 36.8% versus 22.4% . The agent additionally produced 10.5% mean weight loss and demonstrated established cardiovascular benefit from the SELECT trial in patients with overweight/obesity and established cardiovascular disease .

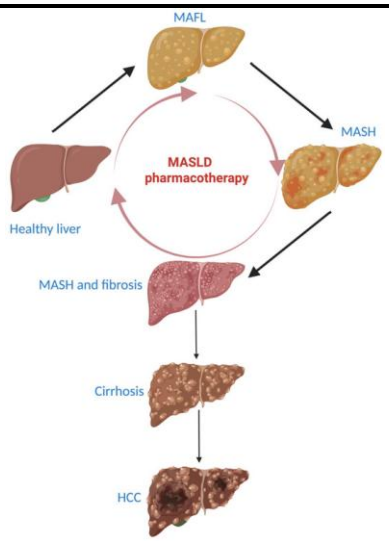
Semaglutide is ideally positioned for multimorbid patients with obesity and T2DM, where it simultaneously addresses hepatic histology, glycemic control, weight management, and cardiovascular risk reduction . Gastrointestinal adverse events (nausea, vomiting, diarrhea, constipation) are common but generally transient; dose titration and patient education improve tolerability .

Table 2 provides a direct comparison of these agents to guide clinical selection.

7. Metabolic and Bariatric Surgery

For multimorbid patients with severe obesity who fail lifestyle and pharmacologic interventions, metabolic/bariatric surgery (MBS) represents the most effective long-term weight loss strategy and offers profound hepatic benefits . Current guidelines recommend MBS for patients with BMI >35 kg/m² regardless of comorbidities, or BMI >30 kg/m² with MASH, T2DM, or failure of non-surgical treatments .

The natural history of MASLD progression from healthy liver through steatosis, fibrosis, cirrhosis, and ultimately hepatocellular carcinoma is illustrated below, underscoring the importance of early intervention:



MASLD Disease Progression

Figure 7a. Natural history of MASLD progression. The spectrum extends from simple steatosis (MAFL) through MASH with inflammation, progressive fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Pharmacotherapy aims to interrupt this progression at the MASH/fibrosis stage.

Multiple meta-analyses demonstrate that bariatric intervention significantly improves MASLD histology, with reductions in steatosis, inflammation, and fibrosis observed across surgical modalities . Roux-en-Y gastric bypass and sleeve gastrectomy produce comparable hepatic benefits, though long-term data on fibrosis reversal remain evolving. The decision to pursue MBS in MASH patients requires multidisciplinary evaluation, particularly in those with advanced fibrosis where surgical risk may be elevated .

8. Emerging Therapeutics and Pipeline

The MASH therapeutic pipeline continues to expand beyond the currently approved agents. Tirzepatide, the dual GIP/GLP-1RA, demonstrated MASH resolution in up to 62% and fibrosis improvement in 51% of patients in the SYNERGY-NASH phase 2 trial . Survodutide, a dual glucagon/GLP-1 receptor agonist, showed dose-dependent histological benefits with significant antifibrotic activity . FGF21 analogs (efruxifermin, pegozafermin) and pan-PPAR agonists (lanifibranor) represent additional promising classes in phase 3 development .

Combination therapy strategies—pairing liver-directed agents with metabolic modulators—may ultimately prove necessary for optimal management of complex multimorbid phenotypes. However, long-term safety and efficacy data for sequential or combination regimens remain limited, representing a critical area for future investigation .

9. Multidisciplinary Care Coordination

The management of multimorbid MASH patients fundamentally requires an integrated, multidisciplinary approach. The Global NASH Council consensus emphasizes collaboration between hepatologists, endocrinologists, cardiologists, bariatric surgeons, dietitians, and behavioral health specialists . This model ensures that hepatic fibrosis assessment, metabolic optimization, cardiovascular risk reduction, and psychosocial support proceed in parallel rather than in siloed succession.

Key performance indicators for multidisciplinary MASH care include systematic screening for liver fibrosis in cardiometabolic clinics, annual assessment for T2DM and dyslipidemia in all MASLD patients, and structured referral pathways for pharmacotherapy initiation . Shared decision-making regarding treatment selection should incorporate patient preferences, cost considerations, insurance coverage, and anticipated adherence to dosing regimens—particularly when choosing between daily oral (resmetirom) and weekly injectable (semaglutide) formulations .

10. Conclusion

The management of obesity and MASH in multimorbid patients has entered a transformative era with the availability of FDA-approved disease-specific pharmacotherapies. Resmetirom and semaglutide offer distinct but complementary profiles: the former provides liver-directed metabolic enhancement with lipid-lowering benefits in weight-stable patients, while the latter delivers potent weight reduction, glycemic control, and cardiovascular protection in obese, diabetic populations. Neither agent, however, supersedes the foundational importance of lifestyle modification, comorbidity optimization, and multidisciplinary care coordination.

Future directions must focus on long-term outcome data to determine whether histologic improvements translate into reduced cirrhosis, hepatocellular carcinoma, and liver-related mortality. Additionally, the development of combination regimens,

refinement of non-invasive monitoring strategies, and expansion of access to integrated care models will be essential to address the growing global burden of MASH in multimorbid populations. As therapeutic options multiply, personalized treatment algorithms based on fibrosis stage, metabolic phenotype, and comorbidity burden will define the next standard of care in this challenging yet increasingly treatable disease.

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