

Metabolic Dysfunction-Associated Steatotic Liver Disease: A Review and Cases Regarding Liver Transplantation

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INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), is a large global public health issue. MASLD encompasses a spectrum ranging from steatosis to metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The nomenclature change reflects the recognition that metabolic dysfunction is the primary driver of this disease.¹ This review synthesizes current understanding of MASLD epidemiology, pathophysiology, screening strategies, and management approaches with particular emphasis on recently approved therapeutics and clinical scenarios including liver transplantation.

EPIDEMIOLOGY AND BURDEN OF DISEASE

The global prevalence of MASLD has increased dramatically over the last three decades, rising to more than 50% in some populations.² The current estimated global prevalence is 38.2%.² Per the Global Burden of Disease (GBD) 2021 data, there are increasing rates and trends of point prevalence, annual incidence, and disability-adjusted life-years (DALYs) across 204 countries with approximately 2.2 times as many DALYs in 2021 compared to three decades prior.³

The prevalence of MASLD is substantially higher among specific subgroups. A meta-analysis of 156 studies including 1.8 million people with type 2 diabetes (T2DM) found a global MASLD prevalence of 65% and MASH 32%.⁴ The bidirectional relationship is clinically significant as well. MASLD increases the risk of new-onset T2DM by a factor of 2.2 or 3.4 in the presence of advanced liver disease.⁵

MASLD increases the risk of cirrhosis and HCC. A meta-analysis of 64 studies showed a pooled incidence rate of HCC of 1.25 per 1000 person-years among persons with MASLD, but 20 per 1000 person-years among persons with MASLD-related cirrhosis.⁶ Beyond hepatic complications, MASLD increases the risk of fatal and nonfatal cardiovascular disease (CVD) by a factor of 1.5 independent of traditional risk factors and by 2.5 in the presence of severe liver disease.⁷ Additional extrahepatic manifestations include increase risk of new-onset heart failure,⁸ atrial fibrillation,⁹ CKD,¹⁰ and other extrahepatic cancers by a factor of 1.2–1.5.¹¹ The leading causes of death in MASLD are CVD, extrahepatic cancers, and cirrhosis-related complications, in that order.¹

NATURAL HISTORY

The highest number of coexisting metabolic disorders in MASLD patients includes T2DM, obesity, and hypertension.¹ In roughly 30% of MASLD patients, disease progression is driven by lipotoxic effects (i.e., adiposity, or accumulation of visceral fat, and insulin resistance) leading to hepatocellular damage and lobular inflammation, which are the hallmark features of MASH that progress to fibrosis and cirrhosis.¹²

Liver fibrosis is staged on a five-point scale from F0 to F4. Patients with F0 (no fibrosis) or F1 (perisinusoidal or portal fibrosis) have an estimated time to cirrhosis of 30 to 35 years. F2 (perisinusoidal and portal or periportal fibrosis) represents a critical threshold since it is a strong predictor of death from any cause and liver-related complications. Progression to cirrhosis from F2 is approximately 20 years. F3 (septal and bridging fibrosis) progresses to cirrhosis in about five years. Once cirrhosis (F4) develops, there is less than 10% chance per year of reversing to MASH with a 0.5–2.5% annual risk of HCC and 10% annual risk of hepatic decompensation.¹

Additional factors that hasten MASLD progression include alcohol, genetic variants (i.e., PNPLA3, TM6SF2, APOB), and hepatitis B and C infection.¹

PATHOPHYSIOLOGY

The pathophysiology of MASLD is multifactorial. Insulin resistance in adipose tissue increases intracellular lipid droplets and flux of free fatty acid into liver, thereby activating stress and inflammatory pathways. This promotes cell death, fibrinogenesis, and carcinogenesis.^{1,13}

De novo lipogenesis (DNL) is markedly elevated in patients with MASLD/MASH.¹⁴ Obesity and insulin resistance disrupt signals from the gastrointestinal tract and adipose tissue that normally regulate carbohydrate, lipid, and amino acid metabolism. In MASLD/MASH, increased glucose flux via DNL leads to higher conversion of glucose into blood lactate, which is released into portal circulation and taken up by hepatocytes and hepatic stellate cells, contributing to fibrosis. Fructose that is metabolized into acetyl-CoA also serves as a key substrate for DNL and induces gastrointestinal inflammation in gut macrophages.

On a cellular level, MASLD/MASH is associated with mitochondrial structural abnormalities, such as swollen mitochondria, fragmented cristae, and decreased mitochondrial

density.^{14,15} These mitochondrial damages reduce hepatic fatty acid oxidation. While this initially stimulates pathways for mitochondrial biogenesis, there is poor reserve to do this in MASH.¹⁵ Furthermore, in high concentrations of glucose substrates in MASLD/MASH, the flux of lactate is higher, which has important implications for the liver. Hepatic stellate cells utilize lactate, which is a key cellular contributor to liver fibrosis. As such, this may explain higher risk of MASH in patients with T2DM.^{14,15}

Genetic variants also contribute to MASLD/MASH pathophysiology. The PNPLA3 I148M variant, which encodes liver and adipose expressed membrane-bound lipid droplet-associated protein, results in increased lipid droplet stability and accumulation.¹⁶ This variant has been found associated with increased MASLD risk and higher rates of fibrosis, cirrhosis, and HCC.¹⁷

Insulin regulation, which physiologically insulin would inhibit adipose tissue lipolysis, is defective in MASLD/MASH. Insulin resistance increases more fatty acid delivery to the liver even in the postprandial state, driving both increased DNL flux, impaired adipose tissue lipolysis, and steatosis.¹⁷

Some basic science research has suggested leveraging other biochemical pathways in the liver and the futile lipid cycle to help systemic metabolic homeostasis. One of which is the glycerol/fatty acid cycle, which involves repetitive hydrolysis of glycerides and re-esterification of fatty acids into glycerides in the liver. This allows fatty acids to be sequestered as glycerol in the liver instead, reducing fatty acid stores in liver. Moreover, this cycle requires ATP consumption and may help reduce metabolic burden in MASLD/MASH.¹⁸

SCREENING AND DIAGNOSIS

Risk factors for MASLD include T2DM, multiple metabolic risk factors (i.e., atherogenic dyslipidemia [elevated triglycerides and apolipoprotein B, small LDL particles, and low HDL cholesterol concentrations], elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state), and elevated liver enzymes.¹⁹

Fibrosis-4 index (FIB-4) is a widely used screening methods for MASLD/MASH in primary care clinics and uses noninvasive blood-based fibrosis biomarkers calculated from age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count.¹ FIB-4 stratifies patients into low, indeterminate, and high-risk for MASLD. Low-risk patients can be managed by primary care providers with re-evaluation every one to three years. Indeterminate-risk patients should be referred for additional testing based on liver-specific biomarkers, vibration-controlled transient elastography (VCTE), Enhanced Liver Fibrosis (ELF) test, or histology. High-risk patients should also have a VCTE and be referred to a hepatologist.¹

MANAGEMENT FOR MASLD, MASH, AND MASH CIRRHOSIS

Lifestyle Modifications

Lifestyle modification remains the cornerstone of MASLD management and is indicated for all patients at risk, including those with low-risk FIB-4.^{1,20} Weight loss targets are stratified by therapeutic goal: 1) at least 5% to reduce liver steatosis; 2) 7–10% to reduce liver inflammation; and 3) at least 10% to reduce liver fibrosis.²⁰ However, less than 20% of individuals achieve and maintain requisite levels of weight loss over sustained periods.¹ The Mediterranean diet, physical exercise (ideally >150 minutes per week of moderate or 75 min/week of vigorous intensity), and alcohol and smoking abstinence are recommended. Alcohol is the strongest modifiable risk factor with increased risk for liver-related mortality in overweight or obese males starting at 15 drinks per week. Overall, there is no quantifiable recommended safe level of alcohol consumption. Per the European Association for the Study of Liver (EASL) Practice Guidelines, avoidance of alcohol for individuals with or at risk for MASLD is generally recommended.²⁰ Vitamin E supplementation may also help reduce liver inflammation, specifically reduction in aminotransferases, steatosis, and cellular ballooning on biopsy.²¹ However, vitamin E has not been shown to have an antifibrotic benefit. As such, recent guidelines do not widely recommend vitamin E supplementation but can be considered in select individuals without diabetes to improve steatosis.²²

EXISTING FDA-APPROVED PHARMACEUTICAL THERAPY

Resmetirom

Resmetirom, a selective thyroid hormone receptor beta (THR-beta) agonist, was the first FDA-approved medication for treating noncirrhotic MASH with moderate to advanced fibrosis (F2-3) in March 2024.²³ The approval was based on the phase 3 MAESTRO-NASH trial, which randomized 966 patients with biopsy-proven MASH and F1-3 fibrosis to receive resmetirom 80 mg, 100 mg, or placebo daily for 52 weeks.²³ Both resmetirom doses achieved the primary endpoints (MASH resolution without worsening of fibrosis) in 25.9% (80 mg) and 29.9% (100 mg) versus 9.7% (placebo). There was fibrosis improvement by at least one stage without worsening of MASH in 24.2% (80 mg) and 25.9% (100 mg) versus 14.2% (placebo).

Resmetirom improves hepatocyte mitochondrial function, promotes mitochondrial biogenesis and mitophagy, increases hepatic fatty acid beta-oxidation, decreases lipotoxic burden, regulates bile acid synthesis, facilitates hepatic uptake of LDL, and thereby lowers triglyceride and cholesterol level. The most common adverse events are nausea and diarrhea.^{24,25}

Treatment initiation does not require liver biopsy. Per AASLD guidelines, noninvasive tests such as VCTE would

suffice to identify adults with MASH and F2-3 fibrosis. The recommended dosage is 100 mg daily for person over 100 kg or 80 mg for those less than 100 kg.²⁶ Main exclusion criteria include compensated or decompensated cirrhosis, active liver diseases, sub-optimally managed thyroid disease, or ongoing alcohol consumption (>20 g/day for women or >30 g/day for men).²⁷

Semaglutide

Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, received accelerated FDA approval in August 2025 for treating MASH with moderate to advanced fibrosis (F2-F3) based on interim results from the phase 3 ESSENCE trial.^{1,28} At 72 weeks, subcutaneous semaglutide 2.4 mg weekly achieved both primary histologic endpoints, which was resolution of MASH without worsening of fibrosis (62.9% vs 34.3% placebo) and fibrosis stage reduction without worsening of MASH (36.8% vs 22.4% placebo).²⁸ Semaglutide also achieved combined resolution of MASH and reduction in liver fibrosis in 32.7% vs 16.1% with placebo with mean body weight reduction of 10.5% vs 2% with placebo.²⁸ The most common adverse events were diarrhea, nausea, constipation, and vomiting. Per the AASLD guidelines from November 2025, semaglutide is not approved as an indication for patients with MASH cirrhosis. Those with compensated cirrhosis on semaglutide for another FDA-approved indication should be monitored carefully.²⁹

Other Emerging Pharmaceutical Therapy

Multiple therapeutic classes are under active investigation for MASH, with incretin-based agents showing the most promising results to date. GLP-1 receptor agonists and dual/triple incretin agonists, including tirzepatide, survodutide, and retatrutide, have demonstrated substantial rates of MASH resolution and reductions in liver fat, with tirzepatide achieving up to 62% resolution without fibrosis worsening in phase 2b trials.^{1,30,31} PPAR agonists (i.e., lanifibranor) and FGF21 analogues have also shown meaningful improvements in steatohepatitis and fibrosis in mid- to late-phase trials.^{1,27,32-42} Additional approaches, including SGLT2 inhibitors, genetic therapies targeting variants such as PNPLA3 and HSD17B13, and metabolic pathway modulators (i.e., DGAT2 and fatty acid synthase inhibitors), demonstrate varying degrees of efficacy, though some programs have been discontinued due to limited benefit.⁴³⁻⁴⁶ Emerging agents targeting inflammation and fibrosis pathways, such as phosphodiesterase inhibitors, adenosine receptor agonists, and glucocorticoid receptor modulators, are in earlier stages of development.^{44,47-59} While several therapies show encouraging results, no single agent has demonstrated universal efficacy, and combination strategies are increasingly being explored to address the multifactorial pathogenesis of MASLD.

MANAGEMENT OF COMORBID CONDITIONS

Cardiovascular Risk Factors

Statins should be used when indicated for cardiovascular risk reduction. The side effect of elevated transaminases is not associated with clinically significant liver disease and typically resolves spontaneously without medication interruption.⁶⁰

Diabetes Management

GLP-1 receptor agonists are preferred for T2DM management in patients with MASLD given their dual benefits for glycemic control and liver histology.^{61,62} Pioglitazone is an alternative, but it causes dose-dependent weight gain that can be mitigated when combined with SGLT2 inhibitors or GLP-1 receptor agonists.⁶¹ Combination therapy with pioglitazone and GLP-1 receptor agonists has shown to reduce hepatic steatosis.²⁷

Bariatric Surgery

Bariatric surgery is indicated for treatment of obesity and T2DM when inadequately controlled by lifestyle modification, particularly in patients with BMI >35 and MASLD.⁶³ Sleeve gastrectomy is preferred over Roux-en-Y gastric bypass after liver transplantation due to fewer malabsorption issues.

LIVER TRANSPLANTATION

Per the United States Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR) (2022), MASLD was second most common indication for liver transplantation in non-HCC patients and is the most common in HCC pts.^{64,65} Similar trends are observed in Europe, Latin America, and the Middle East.⁶⁶⁻⁷³ Liver transplantation is indicated for patients with MASLD who develop decompensated cirrhosis or HCC.²⁰

Patients with MASLD awaiting transplantation are typically older, have higher BMI, and have greater prevalence of metabolic comorbidities including diabetes, hypertension, dyslipidemia, coronary artery disease, and chronic kidney disease.⁷⁴ Per AASLD guidelines, BMI >40 is a relative contraindication for liver transplantation.⁷⁵ The EASL guidelines recommend BMI <35 for optimal outcomes.²⁰ Pre-transplant optimization includes comprehensive cardiovascular risk assessment, diabetes optimization, weight reduction with consideration of bariatric surgery if BMI >35, nutritional assessment to minimize sarcopenia risk, and regular HCC surveillance.²⁰ Management of post-transplant MASLD continues to be a multidisciplinary, multifaceted approach including lifestyle modification, metabolic comorbidity management, regular surveillance for fibrosis progression, and immunosuppression.²⁰

MASLD liver transplant recipients demonstrate favorable outcomes comparable to non-MASLD patients. Per the

California Liver Network Study, MASLD patient post-transplant survival at five years was at least 83%.⁷⁴ Other studies found that five-year survival for patients with MASLD in addition to other liver diseases were comparable to patients without MASLD.^{76,77} However, recurrent MASLD occurs in almost all recipients by five years post-transplantation. Recurrent MASLD and MASH was found to occur in frequencies of 35–49% and 11–24%, respectively.⁷⁸ Fibrosis occurred in 4–25%.⁷⁸ This is likely driven multifactorially, including metabolic comorbidities, immunosuppressive medication and steroids, donor-related factors, and chronic inflammation. Adverse outcomes such as disease-related cirrhosis (0–2%), graft failure (3–9%), re-transplant (0–1%), HCC (0%), and mortality (0%) were fortunately infrequent five years post-transplant.⁷⁸

CLINICAL SCENARIOS

Case 1: When to consider liver transplant?

A 60-year-old female with T2DM, obesity (BMI 38), and MASH cirrhosis presents with new-onset ascites requiring large-volume paracentesis and a MELD-Na score of 18.

Liver transplantation should be considered when patients with MASLD develop decompensated cirrhosis (i.e., ascites, hepatic encephalopathy, variceal bleeding) or HCC.²⁰ When the MELD-Na score is greater than 10, referral to hepatology should be made. When the MELD-Na score is greater than 14, consideration for liver transplantation is recommended.⁷⁹ The median survival from first hepatic decompensation to death or transplantation in MASLD is approximately two years with ascites being the most common initial liver-related event (69.5%).⁸⁰ Pre-transplant evaluation should include comprehensive cardiovascular risk assessment given the high prevalence of coronary artery disease in MASLD patients, diabetes optimization preferably with GLP-1 receptor agonists, and weight reduction strategies. Per above, BMI >40 is a relative contraindication as stated in the AASLD guidelines, and EASL recommends BMI <35 for optimal outcomes.²⁰ Despite higher comorbidity burden, MASLD patients demonstrate favorable post-transplant outcomes comparable to non-MASLD recipients with five-year survival of 83–88%.

Case 2: How to assess for response to resmetirom or semaglutide?

A 60-year-old male with T2DM, BMI 35, MASH and F2 fibrosis has been on resmetirom 100 mg daily for 12 months. His liver stiffness by VCTE has decreased from 13 kPa to 9 kPa. He asks whether he should continue therapy or consider switching to semaglutide.

Overall, validated stopping rules for MASH pharmacotherapy have not been established. For resmetirom, treatment response is suggested by reductions from baseline in ALT (>17 U/L or $\geq 20\%$), liver stiffness by VCTE ($\geq 30\%$),

MRE ($\geq 20\%$), or ELF score (≥ 0.5) at 72 weeks. Patients are recommended to continue therapy if these endpoints are met. Resmetirom should be discontinued if hepatotoxicity develops (AST or ALT >5x ULN on two occasions, total bilirubin >2.5 mg/dL with elevated transaminases, or INR >1.5 with elevated liver enzymes).²⁶

For semaglutide, similar response criteria apply (reductions in ALT (>17 U/L or $\geq 20\%$), CAP ($\geq 30\%$), VCTE LSM ($\geq 30\%$), MRE ($\geq 20\%$), or ELF (≥ 0.5)). Non-response may be suspected if ALT or noninvasive tests worsen.²⁹ For patients with T2DM or obesity requiring cardiometabolic benefits, semaglutide may be preferred given its established cardiovascular and renal protective effects. Semaglutide should be avoided if there is a history of medullary thyroid carcinoma, pancreatitis, or severe gastroparesis.

This patient is responding appropriately to resmetirom given the decrease in liver stiffness over 30% and does not prompt an urgent switch. Semaglutide can be considered if he is no longer meeting those endpoints and may help T2DM management.

Case 3: When to screen for HCC when patient has fibrosis?

A 60-year-old man with T2DM and MASLD with F3 fibrosis and FIB-4 >2.3 inquires about need for HCC surveillance. Guidelines typically target patients with F3 (advanced) fibrosis, cirrhosis (F4), or chronic hepatitis B for HCC screening. It is generally not routinely recommended for patients with F2 (moderate) fibrosis.^{37,81} AASLD specifically recommends against routine use of HCC surveillance in patients with MASLD who have advanced fibrosis (F3) but without cirrhosis (Level 3, Weak Recommendation). They note that while nearly one-fourth of MASLD-related HCC occurs in the absence of cirrhosis, these patients have a very low annual HCC incidence of 0.008 per 100 person-years, making surveillance not cost-effective.³⁷ However, surveillance may be considered on a case-by-case basis in select patients with clinical suspicion for under-staging of fibrosis by noninvasive markers or biopsy, evidence of fibrosis progression, or additional high-risk features such as diabetes.³⁷

For this patient with F3 fibrosis and T2DM, and elevated FIB-4, close monitoring with repeat noninvasive testing every one to two years is warranted to detect progression to cirrhosis. We also recommend formal HCC surveillance with VCTE and AFP every six months given additional risk factors.

GAPS IN THE FIELD AND FUTURE DIRECTIONS

There remain critical gaps in MASLD management. Despite a few approved therapies and multiple emerging trials, optimal treatment selection for individual patients remains unclear. Head-to-head clinical trials comparing current medications are lacking.⁸² No reliable predictors identify

patients likely to respond to resmetirom or semaglutide, and guidelines are needed to determine best practices for stopping ineffective medications. Combination therapy (i.e. resmetirom and semaglutide together for example) have also not been studied. There are also geographic and ethnic differences in MASLD prevalence, progression, and treatment response, which require further investigation. For example, large scale clinical trials on GLPs have limited representation from minority groups, which the authors of this review are actively studying. Furthermore, no liver-directed pharmacotherapies are yet available for MASLD-related cirrhosis, which is a major unmet need.²⁰ More research and real-world prospective cohort studies are needed to improve risk stratification, better identify patients at risk for progressive MASH, and consider potential applications in the advent of artificial intelligence.

CONCLUSION

In summary, MASLD is a leading cause of chronic liver disease worldwide, driven by the global epidemics of obesity and T2DM. It has substantial morbidity and mortality from both hepatic and extrahepatic complications. Resmetirom and semaglutide are major therapeutic advances as the first FDA-approved medications for noncirrhotic MASH with F2-F3 fibrosis. Effective MASLD management requires a multidisciplinary approach incorporating lifestyle modifications, optimization of other metabolic comorbidities, judicious use of pharmacotherapy, and consideration of liver transplantation among individuals with decompensated cirrhosis or HCC. This review highlights the areas that require additional work to address the growing clinical burden of MASLD, including cost-effective diagnostic and treatment strategies and collaborative care coordination to provide holistic patient care.

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[Editor's note: Email corresponding author for complete list of references]

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