Manual of Lipidology

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CHAPTER 16

Metabolic Dysfunction-associated Steatotic Liver Disease: Lipid Disease of Liver and Effect of Lipid-lowering Drugs

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is growing at pandemic proportions worldwide, following closely on the heels of the rising prevalence of obesity and type 2 diabetes mellitus (T2DM). It has an intricate association with metabolic risk factors and thus control of these metabolic risk factors remains the mainstay of the treatment. Dyslipidemia is commonly associated with MASLD, warranting the use of drugs such as statins. However, the role of antilipid agents for treating MASLD/nonalcoholic steatohepatitis (NASH) per se is still controversial. Studies with statins, dual peroxisome proliferator-activated receptor (PPAR)-α and -γ agonists, ezetimibe, and omega-3-fatty acids have shown mixed results, wherein few studies showed promising data while others did not. PPAR-α agonists have not shown much benefit. Stearoyl-CoA desaturase-1 inhibitors are novel antilipid agents that are currently being evaluated for their role in MASLD.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), is the most prevalent chronic liver disease worldwide, affecting >30% of the global population.[1,2]

MASLD is not a single disease entity but represents a spectrum of liver disorders. This spectrum ranges from metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH), fibrosis, cirrhosis, and MASH-associated hepatocellular carcinoma (HCC).[3] MASLD is defined as the development of steatosis in >5% of hepatocytes identified either histologically or radiologically, after ruling out secondary causes such as viral hepatitis, alcohol, or hereditary liver diseases.[4]

Over the years, MASLD has emerged as the most common form of chronic liver disease in both the developed and developing countries, mirroring the exponential rise in the prevalence of obesity and type 2 diabetes mellitus (T2DM).[5] Moreover, MASH is not considered innocuous anymore. An increased risk of HCC has been documented in patients of MASH, with a worse prognosis.

EPIDEMIOLOGY AND RISK FACTORS

According to a very recent study, obesity prevalence increased in every country between 1975 and 2016.[6] The exact prevalence varies from country to country, ranging from 3.7% in Japan to 38.2% in the United States.[7] India has the dubious distinction of being one of the countries that have shown an accelerated increase in body mass index (BMI). The prevalence of MASLD is also highly variable, ranging from 25% in the general population to >90% in individuals with obesity.[8] Thus, obesity remains as one of the most important risk factors for MASLD. However, the true prevalence may be even higher as many patients of MASLD remain undiagnosed. Other than obesity, T2DM is another important risk factor for MASLD, and vice versa. The prevalence of MASLD and MASH in patients with T2DM is over 60%.[8] Older age, female sex, and Hispanic ethnicity have also been established as risk factors for MASLD.[8,9] MASLD has also been associated with other cardiovascular (CV) disease risk factors such as dyslipidemia, hypertension, and smoking.[10]

PATHOGENESIS

The pathogenesis of MASLD could perhaps be described aptly as the "dyslipidemia of the liver." There is an increase in intrahepatic lipid accumulation, which can be attributed to an interplay between various factors such as dyslipidemia, insulin resistance, and obesity. A specific pattern of "atherogenic" dyslipidemia has been observed in patients of MASLD, which is characterized by elevated triglycerides (TGs) and small dense low-density lipoprotein cholesterol (sdLDL-C) levels and by decreased high-density lipoprotein cholesterol (HDL-C) concentrations.[11] Insulin resistance in adipose tissue (due to increased visceral adiposity in individuals with obesity) impairs the ability of insulin to suppress lipolysis; as a result of which free fatty acids (FFAs) released from adipose tissue are transported into the liver. These FFAs contribute to ~60% of the hepatic lipid accumulation. Not only this, but the insulin resistance also leads to increased hepatic very-low-density lipoprotein (VLDL) production and enhanced hepatic gluconeogenesis. VLDL consists of almost all of the measurable TGs. Visceral adiposity also increases the drainage of FFAs into the liver via increased levels of portal blood FFAs. All of these mechanisms combine to culminate in unrestricted hepatic steatosis.[12] Hepatic steatosis leads to oxidative stress, mitochondrial dysfunction, and the generation of reactive oxygen species. All of this culminates in hepatic ballooning, inflammation, and cell death. It also triggers the activation of Kupffer cells and hepatic stellate cells, which are the main drivers of fibrosis and then cirrhosis, and proliferate in response to tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and other proinflammatory cytokines.

DIAGNOSIS

The diagnosis of MASLD requires the following.[13]

Hepatic steatosis detected by imaging or biopsy, plus at least one of the following five criteria:

1. BMI ≥ 25 kg/m^2 (≥23 kg/m^2 in Asian) or waist circumference > 94 cm in men, >80 cm in women, or ethnicity-adjusted waist circumference thresholds
2. Fasting serum glucose ≥ 100 mg/dL (≥5.6 mmol/L) or 2-hour postload glucose level ≥ 140 mg/dL (≥7.8 mmol/L) or hemoglobin A1c (HbA1c) ≥ 5.7% or on specific drug treatment

3. Blood pressure ≥ 130/85 mm Hg or specific drug treatment
4. Plasma TGs ≥ 150 mg/dL (≥1.70 mmol/L) or specific drug treatment
5. Plasma HDL cholesterol < 40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment

Fibrosis-4 (FIB-4) index, vibration-controlled transient elastography (VCTE), magnetic resonance elastography (MRE), shear wave elastography (SWE), and enhanced liver fibrosis (ELF) can be used as noninvasive methods to diagnose hepatic fibrosis. FIB-4 is the most widely used scoring system.[3]

MANAGEMENT

Since obesity and insulin resistance are the main factors behind MASLD, lifestyle modifications remain the mainstay of the treatment of MASLD. A weight loss of 7–10% for overweight and individuals with obesity is optimal, which can be achieved via dietary restriction and aerobic exercise along with resistance training. Diet should be devoid of processed foods and fructose-containing food items.

Pharmacotherapy is primarily recommended for progressive MASH, though it can be tried in early-stage MASH too. While there is no robust data, existing guidelines say that pioglitazone, vitamin E, or their combination can be tried for MASH. Resmetirom and glucagon-like peptide-1 (GLP-1)-based semaglutide have been recently approved for the treatment of MASH. The role of the various antilipid agents in MASLD/MASH has been elaborated here.

Statins

Many of the patients with MASLD are on statin therapy, not because of the disease per se, but because of the associated comorbidities such as dyslipidemia, T2DM, and coronary artery disease (CAD). At the same time, many physicians are wary of initiating patients with MASLD on statins, fearing the worsening of transaminitis. Management of atherogenic dyslipidemia in MASLD is warranted and should be done as per the standard guidelines for the general population. Statins are safe even in patients with baseline elevated liver enzymes and have low hepatotoxicity; in fact, they can lead to an improvement in liver function tests.[14] As per the available literature, the incidence of acute liver failure in patients on statin therapy is not any different from that seen in the general population (1:130,000 vs. 1:114,000).[15]

All of the existing guidelines agree on the safety of statins in MASLD, even in cirrhosis. Decompensated cirrhosis and acute liver failure are the only contraindications to its use.

Patients may experience an elevation in alanine aminotransferase (ALT) levels with statin therapy, but this increase is not synonymous with liver injury and remains asymptomatic in most cases. Meta-analyses[16] have shown that treatment with low-moderate intensity statins is safe but high-intensity statin treatment may lead to hepatotoxicity, particularly lipophilic statins (such as atorvastatin). It is usually recommended that if ALT <3× ULN (upper limit of normal), statin therapy can be continued with annual monitoring of liver enzymes. If values rise ≥3× ULN, therapy should be withheld or the dose should be reduced and liver enzymes should be rechecked after 4–6 weeks. Though all statins are equally efficacious in lowering cholesterol levels in MASLD patients, the experience is richer with atorvastatin, and it is the only statin that has shown a reduction in CV events in these patients.

Though there is a plethora of data on the safety of statins in MASLD, the same cannot be said for their beneficial effects in MASLD/MASH. Owing to the pleiotropic effects of statins, which include anti-inflammatory and antioxidant effects, they have been proposed for the treatment of MASLD/MASH. In a recent meta-analysis that included two trials, an improvement in liver enzymes and ultrasound findings was seen in patients with MASLD with statin therapy, but there was no data on histology. These trials included a small number of patients and had a high risk of bias.[17]

In a study by Hyogo et al.,[18] the role of pitavastatin in MASH was evaluated. About 20 patients with biopsy-proven MASH received pitavastatin (2 mg/day) for 12 months. Liver enzymes improved at the end of 12 months but there was no significant improvement in the MASLD activity score or fibrosis stage. Similar results were seen in another study by Nakahara et al.[19] wherein 19 patients of biopsy-proven MASH received rosuvastatin (2.5 mg/day) for 24 months.

However, few studies have shown improvement in liver histology with statins. In a study from Italy and Finland with biopsy-proven MASH (n = 107), statin therapy was associated with protection from steatosis, MASH, and advancement of fibrosis stage.[20] Similar results were reported in a study from Italy and France which analyzed 346 diabetics with biopsy-proven MASLD.[21] The retrospective nature of both the studies, however, makes it difficult to draw a causal association between statin therapy and liver histology. Also, in the former study, the proportion of patients with fibrosis was small, which is again a limitation. The post hoc analysis of two large studies [GREACE (Greek Atorvastatin and Coronary Heart Disease Evaluation) study[22] and IDEAL (Identification of the Determinants of the Efficacy of Arterial Blood Pressure Lowering Drugs) study[23]] investigated the efficacy and safety of statins in CAD patients with MASH/MASLD (total number of participants combined >10,000). Apart from a significant reduction in secondary CV events with atorvastatin, a significant improvement in liver enzymes was seen with atorvastatin. Interestingly, the statin-related relative risk reduction in CV events was greater in patients with deranged liver enzymes than in those with normal liver tests. However, neither of the studies had data on histopathology, which was a major drawback.

In a retrospective analysis of 18,080 patients with MASLD, the use of statins was seen as an independent factor associated with a decreased risk of HCC development. However, the study had several limitations such as lack of prospective data and lack of histopathological data.[24]

Based on all the available literature, we can conclude that the safety of statins in MASLD, even with deranged liver enzymes, is unquestionable. The data on efficacy in amelioration of MASLD, on the other hand, is controversial, with different studies showing varied results. Not surprisingly, none of the guidelines (EASL/NICE/Asia-Pacific/AISF/AASLD) have said that statins are beneficial for MASH per se. Large randomized-controlled trials (RCTs) with data on biopsy are needed to further study the same.

Peroxisome Proliferator-activated Receptor Agonists

Fibrates are agonists of the peroxisome proliferator-activated receptor alpha (PPAR-α), that is mainly expressed in the hepatocytes, and are commonly used for the treatment of hypertriglyceridemia. A protective role of PPAR-α against liver steatosis and inflammation in MASH has been suggested based on the enhanced vulnerability of PPAR knockout mice

to MASH. Their clinical role in MASLD/MASH has only been studied in small studies and has not shown promising results.

In an RCT of patients with MASLD ($n = 186$), with three arms (atorvastatin/fenofibrate/both), atorvastatin fared significantly better than fenofibrate in improving liver enzymes and ultrasonography features.[25] In yet another RCT on NASH patients, fibrates demonstrated no significant benefit on the biochemical, radiological, or histological outcome.[26] Saroglitazar is a dual PPAR-α and PPAR-γ agonist. PPAR-γ agonists are potent insulin sensitizers. In mouse studies, saroglitazar has shown biopsy-proven improvement in MASH.[27]

Saroglitazar is a predominant PPAR-α agonist with some PPAR-γ activity also. It has been found to be useful and is approved for use for managing hypertriglyceridemia in T2DM in India. Initial data has suggested some benefit of saroglitazar on MASLD. Clinical data from the Phase 2 EVIDENCES IV trial in the United States demonstrated a robust 44.39% reduction in ALT and significant improvements in hepatic fat content with a 4 mg dose of saroglitazar for 16 weeks.[28] In India, saroglitazar received the world's first regulatory approval for the treatment of MASH in 2020, based on biopsy-driven Phase 3 data (EVIDENCES II) demonstrating histological resolution. Real-world evidence continues to support its efficacy in improving liver stiffness and metabolic parameters in diverse patient populations. The pivotal Phase 2b NATIVE trial positioned lanifibranor (PPAR-α, PPAR-γ, and PPAR-δ agonist) as a potential breakthrough therapy, meeting its primary endpoint of reducing the SAF-A activity score (≥2) and achieving statistically significant fibrosis regression (≥1 stage improvement) with a 1,200 mg once daily dose for 24 weeks—a notoriously difficult endpoint in MASH trials.[29] The ongoing Phase 3 NATiV3 trial, which completed enrollment in April 2025, is poised to provide definitive data on long-term histological outcomes by the second half of 2026. LEGEND trial is currently ongoing to evaluate the combination of lanifibranor with empagliflozin in patients with MASH and T2DM.

Elafibranor is a dual PPAR agonist that targets the PPAR-α and PPAR-δ isoforms. Unlike saroglitazar (PPAR-α and -γ) and lanifibranor (pan-PPAR agonist), elafibranor lacks PPAR-γ activity, which is the receptor primarily associated with insulin sensitization and adipose tissue modulation. Clinical development for MASH has been discontinued for elafibranor. Although elafibranor showed promise in early Phase 2b studies (GOLDEN-505) through post hoc analyses, it ultimately failed in its Phase 3 trial for MASH (RESOLVE-IT trial).

Ezetimibe

Ezetimibe, which is a potent inhibitor of cholesterol absorption, has been used as a treatment for MASLD/MASH, but the results have been highly variable. In a study of 10 patients with MASH, ezetimibe was given at a dose of 10 mg daily for 6 months.[30] At the end of 6 months, a significant improvement was seen in the liver enzymes. Also, the histological features of steatohepatitis were reduced, though there was no significant improvement in the fibrosis stage. However, the small sample size and the lack of a control group in the aforementioned study somewhat abrogated the impact of the findings.

Similar findings were observed in yet another study wherein 45 patients of MASH were treated with ezetimibe (10 mg OD) for 24 months, though this study too lacked a control arm.[31] Various possible mechanisms of action of ezetimibe have been postulated. These include inhibition of absorption of biliary cholesterol in the liver [via inhibition of the

transporter Niemann–Pick C1-like 1 (NPC1L1)], improvement in insulin resistance, and increased sterol regulatory element-binding protein-1c (SREBP-1c) mRNA expression in the liver. The recent MOZART trial was a randomized, double-blind, placebo-controlled trial wherein 50 patients with biopsy-proven MASH were randomized to either ezetimibe 10 mg OD or placebo for 24 weeks.[32] The primary outcome was a change in liver fat as measured by magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF). Ezetimibe did not fare better than the placebo in achieving the primary outcome.

As per a meta-analysis[33] which included three other studies apart from the three aforementioned ones, it was concluded that though ezetimibe improved hepatic steatosis, it did not improve hepatic fibrosis and inflammation. The meta-analysis itself had many limitations, including the fact that the duration of therapy was highly variable between the studies. Also, it included only two RCTs. The only positive change observed in these RCTs was an amelioration of hepatocyte ballooning.

To summarize, in light of the conflicting evidence in support of ezetimibe for MASLD, its clinical use in this context remains controversial and has not found a place in any of the guidelines yet. Large-scale RCTs are needed to approve or disprove its benefits.

Omega-3 Polyunsaturated Fatty Acids

It has been postulated that omega-3 polyunsaturated fatty acids (ω-3 PUFAs) may ameliorate hepatic lipogenesis and inflammation and thus may have a role in the treatment of MASH. The results of the clinical trials examining the therapeutic benefit of ω-3 PUFAs in MASLD have been inconsistent. In a recent meta-analysis,[34] which included 18 RCTs (n = 1,424), an improvement in liver enzymes and reduction in liver fat was seen with ω-3 PUFAs. These RCTs included studies on pediatric MASLD as well. The postulated mechanism of action is via the downregulation of SREBP-1c and upregulation of PPAR-γ. Out of these 18 RCTs, only 5 had data on liver biopsy. Out of these five, three studies did not show any significant change in the histological parameters while two did. The rest of the studies evaluated liver fat radiologically.

Because of the varied results with ω-3 PUFAs, their role in MASLD is not established yet and is not endorsed by any of the guidelines. More large-scale RCTs are needed to study hard endpoints such as progression to cirrhosis and resolution of hepatic inflammation.

Stearoyl-CoA Desaturase-1 Inhibitors (Aramchol)

It is a novel inhibitor that inhibits the catalysis of the rate-limiting step in the synthesis of monounsaturated fatty acids, thereby leading to decreased liver injury in response to a high-fat diet and it also decreases insulin resistance. These results suggest that stearoyl-CoA desaturase (SCD)-1 inhibitor may be a promising agent for the treatment of MASH. It has shown attenuation of liver injury and inflammation in mouse models of MASH. Currently, there is a multicenter Phase 2b trial[35] ongoing to study its efficacy in MASH. The initial 3-month study demonstrated a reduction in hepatic steatosis on MRI.

CONCLUSION

While MASLD continues to grow as a pandemic, the need for good therapeutic agents is now greater than ever before. The various older and a few novel antilipid agents may have a promising role to play, but there is still a lot of scope for further research in this area which can help in expanding the therapeutic armamentarium for MASLD/MASH.

KEY POINTS

- The prevalence of MASLD is on the rise, mirroring the exponential increase in the prevalence of obesity and T2DM.
- Though MASLD and dyslipidemia are intricately connected, the role of lipid-lowering drugs in the treatment of MASLD per se is not yet well established.
- Certain lipid-lowering agents such as statins, PPAR-α agonists, cholesterol absorption inhibitors, and ω-3 fatty acids have shown benefits in MASLD in a few studies, but more robust data is needed to establish their usefulness.
- There are newer drugs such as stearoyl-CoA desaturase-1 inhibitors in the pipeline that may prove to be efficacious in MASLD in the coming future.

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Manual of Lipidology

The "Manual of Lipidology" (2026 Edition) provides a concise, clinically relevant, and evidence-based resource for understanding lipid metabolism and managing dyslipidemia in modern clinical practice. This updated edition bridges basic lipid science, clinical lipidology, and therapeutic decision-making, making it a practical reference for clinicians and trainees.

Key Highlights

- Comprehensive coverage of basic lipid metabolism, lipoprotein biology, and genetics of dyslipidemia
- Discussion on international lipid guidelines and their relevance to Indian patients
- Practical guidance on statins, nonstatin therapies, PCSK9 inhibitors, triglyceride-lowering agents, HDL-targeted therapies and lipoprotein apheresis
- Updated discussion on apolipoproteins, lipoprotein(a), HDL, and CV risk
- Chapters addressing statin intolerance, statin diabetogenicity, diabetic dyslipidemia and MASLD
- Special population focus including pregnancy
- By integrating recent clinical trial evidence, evolving therapeutic strategies, and guideline-based recommendations, the *Manual of Lipidology* serves as a reliable companion for clinicians involved in cardiovascular risk reduction.

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