J Lipid Atheroscler. 2025 Jan;14(1):5-29
https://doi.org/10.12997/jla.2025.14.1.5
pISSN 2287-2892·eISSN 2288-2561

JLA Journal of Lipid and Atherosclerosis

Review

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Practical Approaches to Managing Dyslipidemia in Patients With Metabolic Dysfunction-Associated Steatotic Liver Disease

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OPEN ACCESS

Received: Dec 25, 2023
Revised: Feb 15, 2024
Accepted: Mar 10, 2024
Published online: Jun 26, 2024

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Funding
None.

ABSTRACT

Dyslipidemia is a major risk factor for cardiovascular disease, and its impact may be exacerbated when accompanied by metabolic dysfunction-associated steatotic liver disease (MASLD). The simultaneous management of these conditions poses multiple challenges for healthcare providers. Insulin resistance has been implicated in the pathogenesis of both dyslipidemia and MASLD, necessitating a holistic approach to managing dyslipidemia, glucose levels, body weight, and MASLD. This review explores the intricate pathophysiological relationship between MASLD and dyslipidemia. It also examines current guidance regarding the use of lipid-lowering agents (including statins, ezetimibe, fibrates, omega-3 polyunsaturated fatty acids, and proprotein convertase subtilisin/kexin type 9 inhibitors) as well as glucose-lowering medications (such as pioglitazone, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter 2 inhibitors) in patients with MASLD, with or without metabolic dysfunction-associated steatohepatitis (MASH), and dyslipidemia. Additionally, the review addresses the potential of emerging drugs to concurrently target both MASLD/MASH and dyslipidemia. Our hope is that a deeper understanding of the mechanisms underlying MASLD and dyslipidemia may assist clinicians in the management of these complex cases.

Keywords: NAFLD; NASH; VLDL; Insulin resistance; Type 2 diabetes

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), recently renamed metabolic dysfunction-associated steatotic liver disease (MASLD), is characterized by the ectopic accumulation of triglycerides (TG) and other lipids in hepatocytes, accompanied by at least one cardiometabolic risk factor.[1] MASLD can range from isolated steatosis to more severe liver disease, including lobular inflammation and hepatocyte ballooning (necrosis); this latter condition is known as metabolic dysfunction-associated steatohepatitis (MASH) and may even progress to MASH-related

Conflict of Interest

Fernando Bril is a consultant for NovoNordisk. Juan Patricio Nogueira is an editor of *Journal of Lipid and Atherosclerosis*; however, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Data Availability Statement

No data was generated in the current work.

Author Contributions

Conceptualization: Bril F, Nogueira JP; Writing – original draft: Bril F, Berg G, Barchuk M, Nogueira JP; Writing – review & editing: Bril F, Nogueira JP.

cirrhosis or hepatocellular carcinoma. The term "steatotic liver disease" has also been recently introduced to describe not only MASLD but other forms of hepatic steatosis, such as alcoholic liver disease, viral hepatitis, et cetera. Additionally, a new entity termed metabolic and alcohol-associated liver disease (MetALD) has been defined for patients who meet the criteria for MASLD but consume moderate amounts of alcohol.[1] As the overlap between NAFLD and MASLD has been demonstrated to be close to 99%,[2] we have adopted the new nomenclature throughout this manuscript, despite most of the evidence being derived from studies on patients with NAFLD (the previous terminology).

Despite the elevated risk of liver-related mortality in patients with MASLD, atherosclerotic cardiovascular disease (CVD) is the predominant cause of death in this population.[3] Recent studies have consistently shown that all stages of MASLD—including isolated steatosis and MASH—can heighten the risk of cardiovascular (CV) events such as myocardial infarction, stroke, revascularization, or CV death.[3,4] However, the exact cause of the increased CV risk remains uncertain; it is not clear whether the liver disease itself or the accompanying cluster of metabolic abnormalities is primarily responsible. Additionally, the role of clinically significant or advanced liver fibrosis in exacerbating CV risk is still under debate.[5]

Apart from the potential contribution of liver disease, metabolic disturbances are widely believed to be a key mediator of the increased CV risk observed in individuals with MASLD. MASLD is associated with increased visceral adiposity, insulin resistance (IR) with or without hyperglycemia, and atherogenic dyslipidemia, characterized by low high-density lipoprotein cholesterol (HDL-C), elevated TG, and high levels of remnant lipoprotein and small dense low-density lipoprotein (LDL-sd).[6] Both the American Association of Clinical Endocrinology and the American Association for the Study of Liver Diseases guidelines recommend that patients with MASLD be screened for CVD and that CV risk factors be aggressively managed in these patients.[1]

MASLD should be approached as a systemic disease, characterized by IR and the ectopic accumulation of lipids leading to lipotoxicity.[7] Within this context, key changes occur in the lipoprotein profile, impacting the concentration and size of very-low-density lipoprotein (VLDL), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) particles. Although the most pronounced changes in lipoproteins appear to be driven by IR and hepatic steatosis,[8] the severity of liver disease also plays a role, particularly when it begins to impair the liver's synthetic capabilities.[9] In this review, we explore the current understanding of the lipoprotein changes observed in patients with MASLD at different disease stages and address the appropriate management of patients with dyslipidemia and MASLD.

EPIDEMIOLOGY: THE FREQUENT COEXISTENCE OF DYSLIPIDEMIA AND MASLD

Recent meta-analyses have estimated that MASLD affects approximately 25% to 35% of the general population.[10,11] The prevalence rises to around 60% among patients with obesity or type 2 diabetes (T2D).[12,13] A significant proportion of these individuals also exhibit some form of dyslipidemia. For instance, in a study examining the global prevalence of MASLD, Younossi et al.[14] reported that dyslipidemia impacted 69% of patients with MASLD and 72% of those with MASH. However, the study did not provide a precise definition of dyslipidemia. In the same report, hypertriglyceridemia was observed in 41% of patients with MASLD and in 83%

of those with MASH.[14] The rates of MASLD and MASH are also higher among patients with hypercholesterolemia and/or hypertriglyceridemia. In the Dallas Heart Study, the prevalence of MASLD detected by proton magnetic resonance spectroscopy (^{1}H-MRS) was 50% in patients with only hypertriglyceridemia (TG≥150 mg/dL and total cholesterol [TC]<200 mg/dL) and 60% in those with mixed hyperlipidemia.[15] Similarly, a cross-sectional analysis of the Netherlands Epidemiology of Obesity study found that the prevalence of MASLD, as assessed by ^{1}H-MRS, was 57% in participants with hypertriglyceridemia. This prevalence was even higher among those with concurrent obesity and hypertriglyceridemia (81%) or T2D and hypertriglyceridemia (86%).[16] In a cohort of 993 participants in Argentina, the prevalence of MASLD diagnosed by ultrasound was 59% in patients with hypertriglyceridemia.[17]

Longitudinal studies have demonstrated that patients with MASLD are at relatively high risk of both fatal and non-fatal CV events.[18] A meta-analysis, including 5,802,226 individuals with a median follow-up period of 6.5 years, observed an approximate 45% increase in fatal and non-fatal CV events among patients with MASLD after adjusting for confounding factors. Furthermore, the severity of liver fibrosis, as assessed by histology, was also associated with the incidence of fatal and non-fatal CV events. At least a portion of this heightened CV risk can likely be attributed to abnormalities in the lipoprotein profile.

As previously mentioned, the most common lipid findings observed in patients with MASLD are high TG and low HDL-C levels. However, the role of liver disease progression in lipoprotein changes remains poorly understood. Studies comparing lipid profiles in patients with isolated steatosis versus those with MASH found no significant differences in routine lipid profiles, lipoprotein size, or lipoprotein composition, provided that patients were well-matched for other clinical variables such as obesity and IR.[8,9] Nevertheless, the development of significant liver fibrosis, particularly at advanced stages in which the synthetic function of the organ is compromised, is associated with a paradoxical "improvement" in the lipid profile, characterized by lower levels of TG, TC, and LDL cholesterol (LDL-C).[9,19-21] Indeed, in patients with cirrhosis, reduced levels of LDL-C and HDL-C have been shown to possess meaningful prognostic value.[19,22]

PATHOPHYSIOLOGY: FROM ADIPOSE TISSUE (AT) TO MASLD AND FROM MASLD TO DYSLIPIDEMIA

1. From AT to the liver

The development and progression of MASLD involve complex and multifactorial mechanisms. Several theories have been proposed, leading initially to the "two-hit" hypothesis. According to this theory, hepatic lipid accumulation—resulting from nutrient excess, a sedentary lifestyle, obesity, and/or IR—functions as a "first hit" that sensitizes the liver to further damage. The "second hit" triggers inflammatory cascades and fibrogenesis.[23] However, this perspective was quickly deemed too simplistic, and as a result, the "multiple-hit" hypothesis has gained prominence. This updated hypothesis posits that multiple, parallel factors act in an insidious and synergistic manner in individuals with a genetic predisposition.[24]

MASLD and IR are closely linked. Even in the presence of genetic variants associated with liver fat accumulation (such as *PNPLA3*), IR seems to be a prerequisite for the development of MASLD.[25] In most cases, the presence of overweight or obesity represents a trigger associated with reduced insulin sensitivity in AT. The pathways from excessive AT accumulation to its

https://doi.org/10.12997/jla.2025.14.1.5

dysfunction are discussed in detail elsewhere.[26] However, once AT becomes dysfunctional, associated changes include increased rates of lipolysis (elevated plasma free fatty acids [FFAs]), decreased adiponectin levels, and overproduction of proinflammatory adipocytokines.[27]

The accumulation of intrahepatic TG is partially dependent on the supply of FFAs to hepatocytes, which occurs in a dose-dependent manner.[28] These FFAs are primarily derived from AT lipolysis and (to a lesser extent) from the hydrolysis of chylomicrons (Qm), the uptake of remnant-like lipoprotein particles (RLP) by specific receptors, and liver *de novo* lipogenesis (DNL).

In cases of IR within AT and heightened lipolysis, the liver receives an increased flux of FFAs.[29] Furthermore, IR differentially impacts metabolic pathways, leading to an increase in hepatic DNL in these patients in the presence of hyperinsulinemia. This also contributes to a high hepatic FFA burden.[30] Skeletal muscle IR further leads to reduced glucose uptake, resulting in glucose being rerouted to the liver, where it provides additional substrate for DNL.[31,32]

2. From the liver to dyslipidemia

Under physiological conditions, excess fat is stored in lipid droplets (LDs), which are the hallmark of hepatic steatosis. These droplets provide the majority of the TG for the synthesis and assembly of VLDL, a process regulated by microsomal transfer protein (MTP).[33] In patients with MASLD, the process of VLDL synthesis and secretion is complex. Rather than responding linearly to hepatic TG content, a plateau is often reached early on, resulting in a lowered capacity to export TG-VLDL.[34] The liver may produce large, TG-rich lipoproteins (TRL) as an alternative pathway for lipid secretion, primarily in MASLD cases without fibrosis.[35] However, as the degree of fibrosis progresses, VLDL tends to display a lower mass and TG content. This is likely due to reduced efficiency of lipoprotein synthesis,[36] and it is associated with the inhibitory effect of insulin on apolipoprotein (apo) B and MTP synthesis.[37]

However, the overproduction of TG-enriched particles accounts for only a small portion of the variation in triglyceridemia among patients with MASLD. The primary factor influencing hypertriglyceridemia in patients with obesity and IR concurrent with MASLD is the altered catabolism of TRL.[38] The activity of lipoprotein lipase (LPL), which acts on TRL to produce FFA and RLP, is regulated by insulin and several other factors. Studies have demonstrated that in the context of IR, the expression and activity of LPL are reduced, not only in the bloodstream,[39,40] but also in AT and the myocardium.[41] This contributes to the decreased catabolism of TRL, leading to hypertriglyceridemia and the accumulation of RLP.

Among apolipoproteins, apoCII promotes LPL activity on VLDL and Qm, representing a necessary factor for enzymatic activity.[42] In contrast, apoCIII, which is primarily synthesized in the liver and to a lesser extent in the intestine, is a well-known inhibitor of LPL activity and is considered an emerging CV risk factor. ApoAV exhibits complex behavior; it interacts with the LPL activator glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1, facilitating the enzyme's hydrolysis of TRL.[43] Additionally, apoAV may be involved in the intracellular lipid metabolism of TG, contributing to the assembly and stability of LDs as well as the storage and secretion of hepatocyte TG.[44]

Angiopoietin-like proteins (ANGPTL1–8) are a family of secretory glycoproteins that exhibit a tissue-specific expression pattern[45] and influence TG metabolism and LPL function to varying degrees. For instance, ANGPTL3, 4, and 8 inhibit LPL in addition to performing additional functions in various tissues.[46]

https://doi.org/10.12997/jla.2025.14.1.5

With the changes in TRL described above, significant fluctuations are also observed in HDL-C and LDL-C. Cholesteryl ester transfer protein (CETP) is an enzyme that facilitates the exchange of cholesterol esters and TGs between lipoproteins.[47] When there is an increase in VLDL particles that contain more TGs, CETP preferentially transfers TGs to HDL and LDL particles.[48] Subsequent hydrolysis of these TGs by various lipases leads to the formation of smaller HDL and LDL particles. The small HDL particles can pass through the glomerular filtration barrier, after which apoAI is reabsorbed in the proximal tubule and degraded.[49] The resulting LDL-sd is highly atherogenic and represents an excellent predictor of CV risk in patients with IR.[50]

3. Role of diet and the intestine in dyslipidemia

Dysregulated pathways in other tissues, such as the intestine, could also play a key role in the development of dyslipidemia and MASLD. Dysbiosis, or altered intestinal flora, is associated with increased gut inflammation, bacterial translocation into the portal circulation, and endotoxemia. These conditions contribute to increased liver steatosis, inflammation, and fibrosis. Accompanying these phenomena is a disruption of the gut barrier, which leads to increased absorption of FFAs and elevated circulating levels of proinflammatory cytokines. Concurrently, alterations in intestinal bile acid metabolism may result in decreased levels of glucagon-like peptide-1 (GLP-1), impacting glucose metabolism and potentially exacerbating liver steatosis and fibrosis.[51]

The overproduction of Qm has been demonstrated in patients with IR and is associated with a decrease in TRL clearance.[28,52] Insulin acutely suppresses the secretion of apoB-48 from the intestine as Qm particles through both direct and indirect pathways.[53] However, in patients with MASLD, Qm production does not respond to the normal acute suppressive effects of insulin.[54] In MASLD, approximately 15% of the FFA that contributes to TG synthesis in the liver comes from dietary FFA flux to hepatocytes.[55] In cases of MASH with advanced fibrosis, higher serum apoB-48 levels have been observed,[56] suggesting an increase in palmitic acid transport via Qm in these patients. Furthermore, dietary changes have been linked to the onset and progression of MASH.[56]

DIAGNOSIS: DO WE NEED ADVANCED LIPID TESTING IN PATIENTS WITH MASLD?

The risk of developing atherogenic dyslipidemia, characterized by a higher presence of atherogenic lipoprotein subfractions,[9,35] is about twice as high in patients with MASLD compared to those without hepatic metabolic compromise.[8,57] We previously mentioned a higher rate of LDL-sd particles in patients with MASLD, which corresponds to a higher apoB content relative to LDL-C levels. Furthermore, the role of TRL and RLP in the development of CVDs has garnered significant interest, especially regarding patients with elevated IR.[36] In this context, it has been suggested that the standard lipid profile—which includes TC, TG, HDL-C, and LDL-C—should be supplemented with additional measurements. These may include the assessment of lipoprotein subfractions and sizes or the quantification of other lipid-related markers, such as apoB, apoA1, or Lp(a). The rationale behind these so-called advanced lipid profiles is that they may better enable prediction of residual atherogenic risk in patients with T2D and MASLD.[58] This is particularly relevant given that elevated levels of these lipoproteins persist even after LDL-C has been successfully lowered through pharmacological interventions.[59]

https://doi.org/10.12997/jla.2025.14.1.5

In addition to TC, TG, HDL-C, and LDL-C, the standard lipid profile can also be used to estimate non-HDL-C. This is calculated by subtracting HDL-C from TC (non-HDL-C=TC−HDL-C), representing the cholesterol content in all atherogenic particles, including LDL, VLDL, intermediate-density lipoprotein, and Lp(a). When measured in a nonfasting state, this calculation also encompasses RLP cholesterol (RLP-C).[60] Furthermore, RLP-C can be estimated from the standard lipid profile using the formula (RLP-C=TC–HDL-C–LDL-C). This includes cholesterol in TRL and, if measured nonfasting, cholesterol in Qm remnants as well. Although RLP-C is a component of non-HDL-C, the latter does not distinguish between LDL-C and RLP-C.[60]

The debate continues over whether additional testing for apoB, apoA1, or Lp(a) provides meaningfully more information in a clinical setting. The 2018 American Heart Association (AHA) guideline on the management of blood cholesterol[61] suggests that apoB, the structural protein for all non-HDL lipoproteins, may be useful for the prediction of CVD, particularly in patients with hypertriglyceridemia—a condition common among individuals with MASLD. While apoB has been shown to predict CVD more effectively than LDL-C,[62] studies comparing apoB to non-HDL-C have yielded conflicting results.[62,63] However, even in those studies where apoB demonstrated statistical differences from non-HDL-C in predicting CV risk, the differences were minimal and likely of very low clinical significance.[62] This, along with the additional costs associated with apoB testing, may limit its utility in clinical practice.

Regarding Lp(a), the 2018 AHA guideline[61] considers it a risk-enhancing factor and suggests that it may be measured in patients with a family history of premature CVD. The primary limitation of this measure, however, is that it often does not alter management, as there are currently no effective tools to reduce Lp(a) levels. Nevertheless, as we will explore in the treatment section, emerging pharmacological options for MASLD include medications that can concurrently lower Lp(a) by approximately 30% (e.g., resmetirom).[64] As such, as more pharmacological options to decrease Lp(a) become available, its measurement may become a standard part of our clinical diagnostic work-up. Until that time, a routine lipid profile provides most of the necessary information for clinical decisions, with additional tests requiring a case-by-case discussion with patients.

TREATMENT: HOW SHOULD WE APPROACH PATIENTS WITH MASLD AND DYSLIPIDEMIA?

1. Lifestyle intervention

Lifestyle intervention is the cornerstone of treatment for all patients with MASLD.[65] Several randomized controlled trials have demonstrated that lifestyle interventions leading to weight loss result in a decrease in intrahepatic TG content.[66] Studies assessing different interventions, such as hypocaloric diet, exercise, a combination of diet and exercise, and intermittent fasting, and their effects on weight and intrahepatic TG content are summarized in **Fig. 1**. A strong correlation was observed between the amount of weight loss and the reduction of intrahepatic TG content ($r=-0.70$; $p<0.0001$), indicating that weight loss is the primary factor driving improvements in hepatic steatosis. Importantly, various dietary strategies, including low-carbohydrate, low-fat, and Mediterranean diets, have all been associated with reductions in intrahepatic TG content that are proportional to the extent of weight loss.[67] Longitudinal studies[68] and randomized control trials[69] that have used liver biopsy as an endpoint demonstrate that weight loss through lifestyle intervention also leads

https://doi.org/10.12997/jla.2025.14.1.5

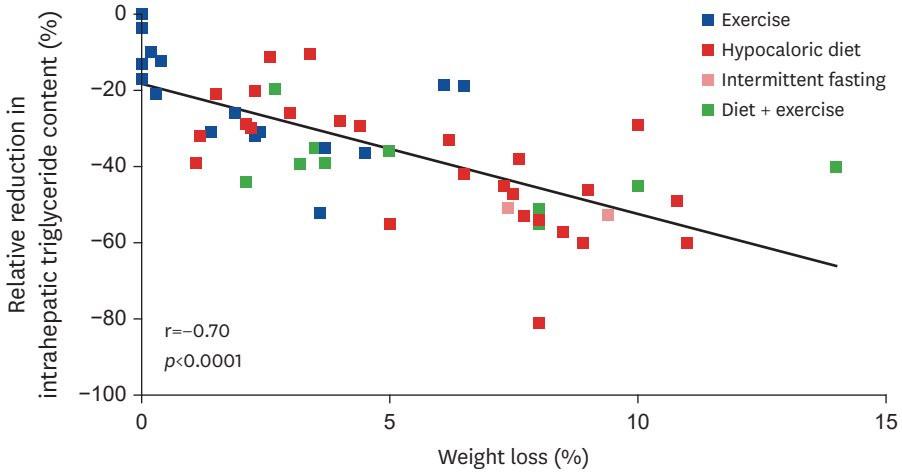

Fig. 1. Magnetic resonance imaging demonstrates that the reduction in intrahepatic triglyceride content due to lifestyle interventions is proportional to the extent of weight loss, regardless of the strategy employed. Adapted with modifications from Bril et al.[66]

to improvements in lobular inflammation, hepatocyte ballooning, and even liver fibrosis. Histological improvements in MASH appear dependent on the degree of weight loss, with reductions in steatosis and inflammation associated with more than 5% weight loss, resolution of MASH with more than 7% weight loss, and regression of liver fibrosis with more than 10% weight loss.[68] Despite the key role of weight loss in managing MASLD, several studies have also indicated that exercise alone and changes in macronutrient composition (even when isocaloric) can influence intrahepatic TG accumulation without significant weight loss.[70]

A well-recognized advantage of lifestyle intervention and weight loss is its holistic approach, with benefits extending beyond liver health to include improvements in hypertension, diabetes control, sleep apnea, and other conditions.[71] In this context, dyslipidemia is also likely to improve with weight loss, particularly through reductions in plasma TG and increases in HDL-C.[72] The effects of weight loss on LDL-C are less straightforward.[72] Nonetheless, certain foods, especially those high in unsaturated fats and low in saturated and trans fats, have been shown to contribute to reductions in LDL-C levels.[73]

2. Bariatric surgery

In 1991, the National Institutes of Health Consensus Statement set the criteria for bariatric surgery eligibility at a body mass index (BMI) of ≥40 kg/m^2 or ≥35 kg/m^2 with accompanying comorbidities.[74] More recently, the American Society for Metabolic and Bariatric Surgery updated its guidelines in 2022, recommending bariatric surgery for patients with a BMI of ≥35 kg/m^2 regardless of comorbidities. It also suggested that patients with a BMI between 30–34.9 kg/m^2 who have obesity-related comorbidities and have not achieved significant weight loss through non-surgical methods could benefit from the procedure.[75] Patients with MASLD or MASH would be included in this latter category. Furthermore, bariatric surgery has been linked to a decrease in the number of CV deaths and a lower incidence of CV events among adults with obesity.[76] A meta-analysis that evaluated lipid level changes up to 4 years after bariatric surgery found improvements in dyslipidemia. However, the timing of improvements varied among different lipid fractions, indicating that multiple concomitant mechanisms may play a role.[77] While changes in TG and HDL-C are only observed after weight loss has been achieved (at 3 months and 1 month post-surgery, respectively), persistent changes in TC

https://doi.org/10.12997/jla.2025.14.1.5

and LDL-C begin immediately after Roux-en-Y gastric bypass (RYGB), suggesting a weight-independent mechanism.[77]

According to a 2019 meta-analysis, bariatric surgery leads to the resolution of MASH in nearly 80% of patients after 1 year of follow-up, and approximately 40% of patients experience significant improvements in fibrosis stage.[78] The weight loss associated with bariatric surgery corresponds with a marked reduction in the hepatic expression of various proinflammatory adipocytokines and mediators of fibrogenesis.[79] Sleeve gastrectomy (SG) and RYGB, the two primary bariatric surgical techniques, result in comparable weight loss and increases in GLP-1 levels.[80] A recent study that compared these surgical approaches to lifestyle intervention in patients with biopsy-proven MASH found that, among 288 patients, those assigned to RYGB and SG had higher rates of MASH resolution without worsening fibrosis (56% and 57%, respectively) compared to those undergoing lifestyle intervention (16%, both $p<0.001$) after 1 year of follow-up.[81] This study also suggests that, at least in the short term, the outcomes for RYGB and SG are similar.

3. Optimizing diabetes control in patients with MASLD and dyslipidemia

The close link between T2D and MASLD is undeniable.[82] Patients with T2D exhibit a higher prevalence of MASLD and experience a more rapid progression to liver fibrosis and cirrhosis.[83] Furthermore, individuals with MASLD are at an increased risk of developing T2D. However, it remains incompletely understood whether hyperglycemia itself contributes to the development and progression of MASLD, or if IR, a common factor in both conditions, is the primary driver of the progression of T2D and MASLD. In children with T2D, the initiation of glucose-lowering medications that do not have known effects on the liver, such as metformin and/or insulin, has led to improvements in hemoglobin A1c (HbA1c) levels without significant changes in aspartate transaminase (AST) or alanine transaminase (ALT) levels.[84] While the debate continues, most medications for T2D that are known to affect the liver either improve insulin sensitivity (e.g., pioglitazone) or induce weight loss (GLP-1 agonists and sodium-glucose cotransporter 2 [SGLT-2] inhibitors). These medications not only lower glucose levels but also exert significant impacts on MASLD and lipid profiles (**Table 1**).

Metformin

General consensus supports the concept that metformin, despite its insulin-sensitizing effect in the liver, does not substantially impact liver histology in patients with MASLD.[1] Consequently, it is not recommended solely for treating MASLD in patients with T2D. Although its use has been linked to some minor improvements in hepatocyte ballooning in a randomized controlled trial[85] and to significant resolution of MASH in an uncontrolled, open-

Table 1. Effects of glucose-lowering medications approved for type 2 diabetes in the treatment of MASLD and their impact on lipid profiles in randomized placebo-controlled clinical trials

Drugs	Improves steatosis	Improves MASH	Delays progression of fibrosis	Reduces CV outcomes	TG	LDL	HDL
Metformin	-	-	-	-	↓	↓	↑
DPP-IV-I	-	-	-	-	↓	↓	↔
Pioglitazone	+	+	+	+	↓	↔	↑
GLP-1RAs	+	+	+	+	↓	↓	↔
SGLT-2is	+	?*	?*	+	↓	↑	↑

MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; CV, cardiovascular; LDL, low-density lipoprotein; HDL, high-density lipoprotein; DPP-IV-I, Dipeptidyl peptidase 4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT-2is, sodium-glucose cotransporter-2 inhibitors.
*Conflicting data.

https://doi.org/10.12997/jla.2025.14.1.5

label study,[86] the overall results have been inconsistent. It is possible that the minor effects of metformin could be partly attributable to weight loss.[86] In terms of its impacts on the lipid profile, metformin may slightly reduce LDL-C levels, a finding observed in patients with T2D, as well as in those with T1D and individuals without diabetes.[87-89] However, this reduction is modest, and its clinical implications remain uncertain.

Pioglitazone

Pioglitazone is a thiazolidinedione that primarily acts as a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, with some additional PPAR-alpha agonistic activity.[90] Its main function is to promote insulin sensitivity in AT through its PPAR-gamma effects. However, it also appears to exert various pleiotropic effects on the liver, such as improving mitochondrial function, which may account for its benefits in patients with MASH.[91] In contrast to another PPAR-gamma agonist, rosiglitazone,[92] pioglitazone has demonstrated a significant impact on liver histology, indicating a mechanism of action that extends beyond PPAR-gamma agonism. Furthermore, PXL065, a deuterium-stabilized (R)-enantiomer of pioglitazone that lacks PPAR-gamma activity yet retains non-genomic effects, has recently been shown to ameliorate hepatic steatosis, necroinflammation, and fibrosis in patients with MASH.[93] This suggests that many of the hepatic actions of pioglitazone may not be mediated by PPAR-gamma agonism.

Regardless of the specific mechanism, pioglitazone has been demonstrated in multiple clinical trials to significantly reduce liver fat, improve metabolic variables such as HbA1c and IR, and resolve MASH along with other histological improvements.[94,95] Consequently, it has been recommended in all current guidelines for the management of patients with T2D and MASH.[1,96] Debate has continued over whether pioglitazone possesses antifibrotic effects. Results from individual randomized controlled trials have been mixed, with some indicating no improvement in fibrosis[94] and others showing a modest benefit.[95,97] A meta-analysis of all randomized controlled trials that assessed histological changes following pioglitazone treatment reported a significant improvement in liver fibrosis, regardless of the stage of fibrosis at baseline.[98]

In addition to its benefits for diabetes control and MASH, pioglitazone has also been shown to improve the lipid panel, an effect not observed with rosiglitazone.[99] This improvement may be attributed to pioglitazone's partial PPAR-alpha agonist effect. Specifically, pioglitazone leads to a significant decrease in TG (−40 mg/dL; 95% confidence interval [CI], −53, −26 mg/dL) and an increase in HDL-C (4.6 mg/dL; 95% CI, 3.6, 5.5 mg/dL), with no significant impact on LDL-C levels.[99] However, it does reduce LDL particle size and number.[100] Furthermore, several studies have demonstrated that pioglitazone reduces CVD and CV events in patients, with or without diabetes.[101,102]

GLP-1 agonists with or without GIP agonism

Initially considered for the management of T2D, GLP-1 agonists—with or without GIP agonism—have become a cornerstone in the pharmacological treatment of obesity.[103] Liraglutide and semaglutide, both GLP-1 agonists, as well as the more recently approved tirzepatide (a GLP-1 and GIP agonist), have been authorized for obesity management due to the significant and sustainable weight loss observed in clinical trials. Beyond their impressive metabolic profile, which includes weight loss and significant HbA1c reduction, these agents have consistently demonstrated improvements in CV outcomes in patients with T2D.[104,105] More recently, semaglutide has even been shown to improve CV outcomes in patients

without diabetes.[106] Given these findings, GLP-1 agonists should be considered early in the treatment of patients with T2D, particularly those with obesity or with a history of CVD. Since a significant proportion of the patients with or without diabetes in these trials likely had MASLD, it is reasonable to infer that the CV benefits may extend to patients with MASLD.

These compounds have also been shown to produce hepatic improvements in patients with MASLD and MASH.[57] Because hepatocytes exhibit no apparent expression of GLP-1 or GIP receptors, it is widely accepted that the hepatic effects of GLP-1/GIP agonists are primarily mediated indirectly through weight loss. Liraglutide and semaglutide have been evaluated in randomized controlled trials for their effects on histological changes compared to placebo,[107,108] while until recently, tirzepatide had only been assessed using imaging as the primary outcome in patients with MASLD.[109] However, a recent study by Loomba et al, showed that among 190 patients followed for 52 weeks, all doses of tirzepatide were associated with significant MASH resolution and improvement in fibrosis stages.[110] In the largest randomized controlled trial involving a GLP-1 agonist to date,[108] a daily dose of semaglutide successfully led to the resolution of MASH. However, no significant improvements in liver fibrosis were observed compared to placebo, although the progression of fibrosis was delayed. Another study administering the standard weekly dose to patients with MASH and advanced fibrosis at baseline also did not demonstrate significant changes in liver fibrosis compared to placebo.[111] The lack of improvement in liver fibrosis in these trials may be attributed to the relatively short duration of therapy or the advanced stage of liver fibrosis at baseline.[112]

Regarding their effects on the lipid profile, the changes are relatively minor and are likely driven primarily by weight loss, although some specific effects on lipids have been suggested.[113] Overall, GLP-1 agonists are associated with modest reductions in LDL-C and TG, while having a neutral effect on HDL-C. More pronounced effects have been noted on postprandial TG, although the underlying mechanism remains unclear.[113]

Dipeptidyl peptidase 4 (DPP-IV) inhibitors

Unlike GLP-1 agonists, and perhaps due to their neutral effect on weight, DPP-IV inhibitors have not demonstrated positive outcomes in MASLD or MASH,[114,115] nor have they shown any CV protection.[116,117] Given that the combination of DPP-IV inhibitors and GLP-1 agonists is not recommended because of the lack of additional benefits[118] and the potential for increased side effects,[119] the use of DPP-IV inhibitors in T2D is generally reserved for patients who cannot tolerate GLP-1 agonists, or when GLP-1 agonists are unavailable or contraindicated. Several meta-analyses have reported on the effects of DPP-IV inhibitors on lipid profiles,[120,121] revealing associations with statistically significant reductions in TC, LDL, and TG, with decreases of 5%–18%, 4%–16%, and 7%–20%, respectively.

SGLT-2 inhibitors

Like GLP-1 agonists, SGLT-2 inhibitors have gained popularity in the treatment of patients with T2D because of their favorable CV outcomes.[122,123] Additionally, they offer other key benefits such as nephroprotection and a reduction in hospital admissions due to heart failure.[124,125] However, their impact on liver health has not been as extensively studied as that of GLP-1 agonists.

Most of the current evidence for SGLT-2 inhibitors in patients with MASLD is derived from studies that assess changes in liver fat using imaging techniques.[126-128] Collectively, these

https://doi.org/10.12997/jla.2025.14.1.5

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studies indicate that SGLT-2 inhibitors lead to an approximate 25% reduction in liver fat in patients with T2D and MASLD. A more recent study has demonstrated that this effect is consistent in patients without T2D,[129] suggesting that the reduction in liver fat is not solely dependent on glucose control. However, this level of liver fat reduction is somewhat less than that observed with pioglitazone or the more potent GLP-1 agonists. Consequently, it remains uncertain whether the degree of liver fat reduction achieved with SGLT-2 inhibitors is sufficient to produce histological improvements. Information on histological changes following treatment with SGLT-2 inhibitors is primarily sourced from small open-label studies.[130,131] Although the histological improvements reported in these studies are significant, more robust research is required to draw definitive conclusions about the specific role of SGLT-2 inhibitors in the management of MASH.

Several meta-analyses have been published that demonstrate the effects of SGLT-2 inhibitors on lipid profiles.[132,133] Although these inhibitors are associated with significant increases in total, LDL, and HDL cholesterol, the relative changes are modest (0%–3%, 2%–4%, and 5%–9%, respectively). Additionally, plasma TG levels are reduced by approximately 2%–11% following treatment with SGLT-2 inhibitors.[133]

In summary, several medications currently used for managing T2D have been shown to benefit patients with MASLD, including those with more severe liver disease, namely MASH (**Table 1**). While SGLT-2 inhibitors may reduce liver fat, their effects on liver histology remain unclear. Consequently, for patients with T2D and MASH, particularly those with clinically significant fibrosis (stage ≥2 on liver biopsy) or at risk for liver fibrosis based on imaging or noninvasive scores, pioglitazone and potent weekly GLP-1 agonists (i.e., semaglutide or tirzepatide) should be considered the preferred treatment options.

We recommend semaglutide or tirzepatide over GLP-1 agonists in general because the largest randomized controlled trials with positive histological outcomes have utilized these drugs.[108,110,111] However, as previously noted, the benefits are primarily associated with weight loss, suggesting a class effect, with more pronounced benefits from the more potent GLP-1 agonists. Consequently, patients with higher BMI are likely to experience greater hepatic benefits. The efficacy of these medications in lean individuals with MASLD has yet to be established. For patients with a lower BMI and advanced liver disease, pioglitazone may be a preferable alternative. Lastly, similar to the management of T2D and hypertension, treating MASLD and/or MASH may necessitate a combination of multiple drugs, as monotherapy may be insufficient.

4. Addressing dyslipidemia: can we also help the liver?

The use of lipid-lowering medications is recommended for patients with MASLD due to their increased CV risk. The approach to treating dyslipidemia in these individuals should align with the standard care for any patient at elevated CV risk. Accordingly, the prescription of statins should be based on the patient's previous history of CVD, their calculated 10-year CV risk, and/or LDL-C levels.[61] For patients with high-risk atherosclerotic CVD and LDL-C levels of 70 mg/dL or higher, the addition of other therapies to statin treatment should be considered.[61] In the context of hypertriglyceridemia, which is common in patients with MASLD, the use of TG-lowering medications, such as fibrates, is advisable only for those at risk of pancreatitis with TG levels exceeding 500 mg/dL. Prior to using these drugs, secondary causes should have been excluded and lifestyle modifications attempted.

https://doi.org/10.12997/jla.2025.14.1.5

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Table 2. Effects of lipid-lowering medications in the treatment of MASLD and their impact on lipid profiles in randomized placebo-controlled clinical trials

Drugs	Improves steatosis	Improves MASH	Delays progression of fibrosis	Reduces CV outcomes	TG	LDL	HDL
Statins	?*	-	-	+	↓	↓↓	↑
Fibrates	-	-	-	-	↓↓	↓	↑
EPA-ethyl ester	?*	-	-	+	↓	↓	↑
Ezetimibe	-	-	-	+	↓	↓	↑
PCSK9-I	-	-	-	+	↓	↓↓	↑

CV, cardiovascular; EPA, Eicosapentaenoic acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitors; TG, triglycerides.
*Conflicting data.

The specific effects of these agents on the liver have been extensively studied. Although they are generally deemed safe for this population, they have not demonstrated consistent improvements in liver histology (**Table 2**).

Statins

Statins play a central role in both primary and secondary CV prevention due to their established efficacy and safety in patients with or without T2D.[61] As previously mentioned in this review, the presence of MASLD is linked to heightened risk of CVD and mortality.[134] Furthermore, CV mortality is the leading cause of death in patients with MASLD. Consequently, aggressive treatment of all CV risk factors, including dyslipidemia, is crucial in these patients.

Patients with MASLD are typically excellent candidates for initiating statin therapy due to their abnormal cardiometabolic profile. Despite this, the overall rate of statin use among these patients remains relatively low.[135,136] This may be attributed to several factors, including healthcare providers' concerns about the potential for exacerbating liver disease. Nevertheless, it is well-established that the risk of hepatotoxicity associated with statins is quite low, making them safe for use in patients with MASLD and MASH.[137] Although large randomized controlled trials specifically evaluating the efficacy of statins in patients with biopsy-proven MASH are lacking, some prospective studies have indicated potential benefits in reducing steatosis and improving the NAFLD activity score, as summarized in a recent meta-analysis.[138] However, the meta-analysis did not report any effects on liver fibrosis. Furthermore, observational studies in the general population have shown that statin users experienced a 42% decrease in the incidence of hepatocellular carcinoma and a 28% reduction in liver-related mortality.[139] These findings are consistent with those observed in a separate cohort of patients diagnosed with MASLD.[140]

Thus, the initiation of statins in these patients should be encouraged when indicated.

Fibrates

Fibrates are activators of PPAR-α that serve as anti-hyperlipidemic agents, primarily reducing serum TG levels.[141] Large-scale clinical trials have demonstrated that fibrate treatment, which lowers TG levels and raises HDL-C levels, does not reduce atherosclerotic CVD risk in patients with T2D.[142,143] Recently, the PROMINENT study showed that pemafibrate did not reduce CV events despite the decrease in TG levels.[144]

In preclinical studies, pemafibrate was shown to reduce serum TG levels and increase HDL-C more effectively than fenofibrate. This was achieved by inhibiting VLDL secretion

https://doi.org/10.12997/jla.2025.14.1.5

and promoting TG clearance through the activation of LPL.[145] Furthermore, pemafibrate increased the expression of the VLDL receptor, leading to improved catabolism of VLDL and its remnants.[146] Pemafibrate also attenuated postprandial hyperlipidemia by inhibiting the expression of the intestinal cholesterol transporter Niemann-Pick C1-Like 1 (NPC1L1) mRNA in the small intestinal mucosa of mice fed a high-fat diet.[147] This attenuation may be due to the suppression of chylomicron synthesis and secretion by inhibiting NPC1L1-mediated cholesterol absorption, as well as the activation of PPARα in the small intestines. Clinically, pemafibrate significantly decreased RLP-C, non-HDL-C, and levels of apolipoproteins B, apoB-48, and apoC-III. From both a basic and clinical perspective, the effects of pemafibrate on MASLD/MASH included reduced liver function test values and improvements in fatty liver, ballooning, inflammation, and fibrosis.[148]

Despite demonstrating excellent results in mouse models of MASH,[149] the use of fibrates in humans with MASLD has been underwhelming due to their inability to reduce hepatic steatosis.[150,151] However, research conducted by Nakajima et al. revealed a reduction of liver stiffness, as measured by magnetic resonance elastography, that persisted for 72 weeks. Notably, this discrepancy between the impact on hepatic steatosis and the effects on liver inflammation/fibrosis has been similarly noted in a mouse model treated with pemafibrate.[152] Whether these findings will correspond to histological improvements in human biopsy studies is yet to be determined.

Omega-3 polyunsaturated fatty acids (omega-3 PUFAs)

Eicosapentaenoic acid (EPA) is the sole component of omega-3 PUFAs that is used clinically as a single-agent treatment for hypertriglyceridemia, and its serum TG-lowering effect has been clinically established.[153] A study evaluating the lipoprotein flux following 8 weeks of therapy with 1,080 mg of EPA and 720 mg of docosahexaenoic acid (DHA) in patients with T2D demonstrated that the reduction in TG levels was due to decreased production of VLDL apoB-100.[154]

Despite the TG reduction, several randomized controlled trials using a combination of EPA and DHA have failed to demonstrate CV benefits.[155] However, two distinct randomized controlled trials using isolated EPA indicated CV protection: the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) and the Japan EPA Lipid Intervention Study (JELIS).[156,157] In the REDUCE-IT trial, 8,179 patients on statins with established atherosclerotic CVD or with T2D and at least one other CV risk factor were randomized to receive either 4 g of icosapent ethyl (IPE, a highly purified EPA ethyl ester) or a placebo. The use of IPE was associated with a ≤20% reduction in TG levels and a significant 25% improvement in the composite CV outcome.[88] In the JELIS findings, the reduction in CV outcome against placebo was similar to the REDUCE-IT trial, at around 19%.[157]

Patients with MASH exhibit a higher liver ratio of omega-6 (n-6) to omega-3 (n-3) PUFAs compared to healthy controls. This suggests that either low n-3 PUFA or high n-6 PUFA content may play a role in the pathophysiology of the disease.[158] Kinetic studies have demonstrated that high doses of EPA can significantly reduce the production of apoB-48-containing lipoproteins from the intestine.[159] In animal models, omega-3 PUFAs have been shown to decrease hepatic lipogenesis and inflammation, downregulate sterol regulatory element-binding protein 1c, and activate PPAR-alpha, leading to fatty acid oxidation and a reduction in steatosis.[160] However, multiple meta-analyses evaluating the use of omega-3 in the treatment of MASH have concluded that, although some studies report decreases in ALT

and AST and even a small reduction in liver fat, histological outcomes remain unchanged after treatment.[161]

Treatment with omega-3 PUFAs for 6 months significantly improved hepatic proteomic and plasma lipidomic profiles, markers of lipogenesis, endoplasmic reticulum stress, and mitochondrial functions in patients with MASH.[162] However, histological data in these patients remained unchanged compared to the placebo group, complicating the interpretation of the true implications of these changes.[163]

Ezetimibe

Ezetimibe, a cholesterol absorption inhibitor, reduces LDL-C levels and has been associated with a decrease in CV events.[164]

Ezetimibe is used to treat patients with elevated cholesterol levels. In a mouse model of hepatic steatosis induced by a high-fat diet in C57BL/6J mice,[165] ezetimibe therapy prevented hepatic steatosis and decreased hepatic IR. However, in the MOZART trial, ezetimibe did not significantly reduce hepatic steatosis as assessed by magnetic resonance imaging-derived proton density fat fraction.[166] While meta-analyses have reported that ezetimibe improves histology and hepatic steatosis,[167,168] most of the included studies were small, open-label, or uncontrolled. It is currently accepted that ezetimibe does not provide any specific hepatic benefit in patients with MASLD, but it can be used safely in this population. When treating patients with MASLD, the potential side effects of ezetimibe on glucose metabolism should always be considered. Nevertheless, a recent meta-analysis reported that ezetimibe does not affect glucose or HbA1c levels, demonstrating the safety of ezetimibe treatment for patients with MASLD.[169,170]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

The discovery of PCSK9 has rapidly led to the development of PCSK9 inhibitors for the pharmacological management of hypercholesterolemia and CVDs. PCSK9 human monoclonal antibodies, which efficiently block the extracellular PCSK9 pathway, have significantly reduced major CV events in dedicated CV outcome trials when used in addition to statin therapy.[171] Some observational studies suggest a potential link between PCSK9 and hepatic steatosis. For instance, Ruscica et al.[172] found that circulating PCSK9 levels were positively associated with histological markers of MASH, such as steatosis severity, lobular inflammation, hepatocyte ballooning, and liver fibrosis. Conversely, Baragetti et al.[173] found that carriers of the R46L PCSK9 loss-of-function variant had a two-fold higher prevalence of hepatic steatosis. Recently, Wargny et al.,[174] in a multicentric observational study, showed that plasma concentrations of PCSK9 were not associated with the severity of liver steatosis or histological markers of MASH in a high-risk population. In a real-world study, a mean 6-month follow-up with PCSK9 inhibitors showed an increase in ALT and AST by 5.8 mg/dL (p=0.037) and 6.2 mg/dL (p=0.008), respectively, from baseline values, indicating that PCSK9 inhibitors should be used cautiously with follow-up liver function tests.[175] However, a large meta-analysis of randomized controlled trials did not find any significant elevation in AST or ALT levels.[176] Moreover, despite concerns that PCSK9 inhibitors may induce mild hyperglycemia, a meta-analysis including 163,688 patients without diabetes receiving either high or low intensity LDL reduction showed that neither LDL reduction nor PCSK9 inhibitor use was associated with new-onset diabetes.[177]

https://doi.org/10.12997/jla.2025.14.1.5

5. Future drugs for managing MASLD and MASH: can they concurrently improve lipid control?

Resmetirom

Resmetirom has recently become the first medication approved by the US Food and Drug Administration (FDA) for the management of MASH. This compound is a liver-specific thyroid hormone receptor-β agonist. It is believed that by selectively activating the hepatic thyroid receptor, resmetirom stimulates mitochondrial biogenesis and increases hepatic β-oxidation, thereby reducing the accumulation of lipotoxic intermediates. Additionally, it facilitates the uptake of LDL by the liver, which favorably impacts lipid profiles.[64]

In the MAESTRO-NASH trial (n=966),[178,179] resmetirom was associated with a significant resolution of MASH when compared to placebo. The resolution rates were 30% for the 100 mg daily dose and 26% for the 80 mg daily dose, versus 10% in the placebo group (p<0.001 for both). Additionally, the drug demonstrated a significant improvement in fibrosis stage (100 mg group, 26%; 80 mg group, 24%; placebo, 14%; p<0.001 for both comparisons with placebo). The most frequently reported side effects were diarrhea and nausea. Furthermore, in the MAESTRO-NAFLD-1 trial, a daily dose of 100 mg resmetirom led to a significant reduction in secondary outcomes related to dyslipidemia. Among participants with baseline TG greater than 150 mg/dL, the analysis revealed reductions of 13.9% in LDL-C, 16.5% in apoB, and 23.4% in TG.[64] For patients with LDL-C levels above 100 mg/dL, resmetirom treatment resulted in a 22% reduction in LDL-C, a 19.7% reduction in Lp(a), and a 17.6% reduction in apoCIII.

Due to its beneficial effects on liver function and lipid profiles, resmetirom could become an important therapeutic option for patients with MASH. It has the potential to simultaneously treat MASH and improve the lipid profiles of patients. Nevertheless, the CV safety and potential benefits of resmetirom need to be confirmed in larger randomized controlled trials.

Lanifibranor

Lanifibranor, a pan-PPAR agonist targeting alpha, delta, and gamma receptors, demonstrated promising results in a phase 2b randomized controlled trial by improving the resolution of MASH and liver fibrosis when compared to a placebo.[180] At a higher dose of 1,200 mg daily, 24 weeks of lanifibranor treatment led to the resolution of MASH without worsening fibrosis in 49% of patients, versus 22% in the placebo group. Additionally, 48% of patients experienced an improvement in fibrosis stage without MASH worsening, compared to 29% with placebo. In terms of lipid profile, the drug significantly reduced TG levels and increased HDL-C levels, showing a similar pattern to that observed with pioglitazone.

Obeticholic acid

Obeticholic acid is a synthetic farnesoid X receptor agonist approved for treating primary biliary cholangitis. Although initial results in patients with MASH were promising,[181] it remains uncertain whether the FDA will grant approval for its use in this patient population. The drug demonstrated significant improvement in liver fibrosis when compared to a placebo; however, the resolution of MASH did not differ significantly from the placebo group. Additionally, there are concerns regarding the tolerability and safety of obeticholic acid. Notably, pruritus is a common side effect that may persist throughout treatment. The drug also increases LDL-C levels while causing a slight decrease in HDL-C and TG concentrations. The implications of these lipid changes are not yet understood.[182] Furthermore, there have been instances of hepatic decompensation in patients with primary biliary cholangitis and

https://doi.org/10.12997/jla.2025.14.1.5

primary sclerosing cholangitis, which warrant further investigation before the medication can be recommended for broader use.

Efruxifermin

FGF-21 is a key regulator of glucose and lipid metabolism. Efruxifermin is composed of a human IgG1 Fc domain fused to a modified human FGF21, acting as an agonist for FGFR1c, FGFR2c, and FGFR3c. Unlike other FGF-21 agonists that have not demonstrated beneficial metabolic or hepatic effects, efruxifermin has shown improvements in lipid profiles. This includes reductions in LDL-C and TG levels, along with an elevation in HDL-C levels.[183] In a phase 2a randomized controlled trial involving patients with MASH, efruxifermin significantly reduced liver fat, as measured by magnetic resonance imaging-proton density fat fraction.[184]

CONCLUSION

Numerous existing medications have demonstrated promising results in improving liver histology and slowing the progression of liver fibrosis in affected patients. Additionally, some of these medications have displayed concomitant improvements in lipoprotein profiles. In contrast, lipid-lowering medications have not shown significant liver-specific benefits in MASLD; however, they are considered safe and, when indicated, should be recommended for patients with MASLD due to their elevated CV risk. Many drugs currently in development for MASLD also offer potential benefits to lipid profiles. Consequently, the approach to managing patients with MASLD and dyslipidemia may change substantially in the foreseeable future.

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