Review Article

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Advances in MASLD Management: From Lifestyle Intervention to Pharmacotherapy

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Abstract

Metabolic dysfunction–associated steatotic liver disease (MASLD), previously called nonalcoholic fatty liver disease, is the most prevalent chronic liver disease worldwide. MASLD is strongly associated with obesity, type 2 diabetes and metabolic syndrome and is not only a liver disease but also a multisystem condition that affects other organs, particularly the heart and kidneys. Despite its growing burden, treatment options are still limited. Till date, Resmetirom (in 2024) and semaglutide (in 2025) are conditionally FDA-approved medications for the treatment of adults with MASH and moderate to advanced fibrosis. Therefore, lifestyle changes-such as healthy diet, regular exercise and behavior modification-remain the main and first-line treatment. Recently, there has been progress in drug development. New medicines are targeting different disease mechanisms like insulin resistance, fat toxicity, bile acid pathways, inflammation, and fibrosis. Among these, GLP-1 receptor agonists, SGLT2 inhibitors and PPAR agonists have shown promising results. This review summarizes the current management of MASLD, focusing mainly on drug therapy and lifestyle changes and advanced treatments. It also highlights important clinical trials, guidelines and future treatment strategies.

Keywords: MASLD, Lifestyle intervention, Pharmacotherapy

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Introduction:

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the updated term to describe non-alcoholic fatty liver disease (NAFLD). In December 2023, an expert consensus was made to change the term NAFLD to MASLD after 4 rounds of the Delphi survey[1]. The disease is closely linked to metabolic syndrome components, including obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension, which collectively contribute to its pathogenesis and progression. MASLD is defined as the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor, such as obesity, type 2 diabetes (T2D) or any component of metabolic syndrome. NAFLD was a diagnosis of exclusion because it was diagnosed only when the use of excessive alcohol and other liver diseases were excluded. In contrast, the MASLD is a diagnosis of inclusion which is defined as the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor, such as obesity, type 2 diabetes (T2D), or any component of metabolic syndrome[2]. The new definition of MASLD differs importantly from that of NAFLD in being a positive diagnosis, which emphasizes metabolic dysfunction as its cause, distinct from NAFLD that only emphasized what the condition was not (i.e. non-alcoholic). This positive MASLD definition also allows for the dual aetiology of MASLD with other causes of liver steatosis or liver disease (e.g. MASLD plus drug-induced steatosis or MASLD plus autoimmune hepatitis). MASLD sits within the new broad grouping of steatotic liver disease and along with metabolic and alcohol-related steatotic liver disease (MetALD) and alcohol-related liver disease (ALD), forms part of a continuum of conditions differentiated by alcohol intake[3].

It is important to note that, whilst the NAFLD and MASLD definitions are similar, updated studies will be required into aspects of MASLD, including its prevalence, progression and treatment to fully understand how this may differ from NAFLD. However, early evidence suggests significant overlap and in this article, studies undertaken using the NAFLD criteria will be considered to apply to MASLD[4]. In addition, for clarity the term MASLD will be used throughout this article, even when describing studies that took place using the previous NAFLD criteria.

Due to the spread of metabolic syndrome, MASLD has become a significant global health burden. Currently, 38% of all adults and 7-14% of children and adolescents have MASLD. The global prevalence of MASLD is expected to grow 55.4% by 2040[5]. About 75% of people with obesity have concomitant MASLD[6]. Among patients with T2DM, the prevalence of MASLD reaches 50-75%, with approximately 17% developing advanced liver fibrosis[7]. Approximately 10-30% of patients with hepatic steatosis if untreated progress to metabolic dysfunction-associated steatohepatitis (MASH), a more advanced stage of MASLD that is formerly known as nonalcoholic steatohepatitis (NASH). MASH can further progress to fibrosis, cirrhosis and eventually hepatocellular carcinoma (HCC)[2,8]. Patients with MASLD, are confronted with an excess risk developing type 2 diabetes mellitus (T2DM), cardiovascular disease, chronic kidney disease and extrahepatic malignancies[6]. Cardiovascular disease is the leading cause of death in this patient group.

Lack of awareness of the risk of developing the disease, the initial absence of clinical signs or uncharacteristic symptoms means that MASLD is often diagnosed too late, at the stage of decompensated cirrhosis or after a first cardiovascular incident9. Early diagnosis and control of MASLD are crucial to preventing its complications and improving outcomes for affected individuals.

Despite its high prevalence and potential for serious complications, therapeutic options for MASLD remain limited. Current management strategies primarily focus on lifestyle modifications, including weight loss through diet and exercise. Lifestyle modifications have shown efficacy but adherence remains challenging, and many patients fail to achieve the weight loss thresholds required for histological improvement. Currently there is a robust therapeutic pipeline across a variety of new targets to resolve MASH or reverse fibrosis or both. While several pharmacotherapies have been investigated, until recently, only resmetirom had received regulatory approval specifically for MASLD treatment, being granted accelerated FDA approval in March 2024 for noncirrhotic MASH with moderate to advanced liver fibrosis[10].

In this review, we provide a comprehensive update on MASLD management, highlighting lifestyle, pharmacological, surgical and advanced interventions, with special emphasis on pharmacological strategies as the emerging backbone of therapy.

Screening and Risk Stratification:

Early detection of MASLD-related fibrosis is essential to prevent irreversible liver damage and to reduce long-term complications such as cirrhosis, HCC, and liver failure. Given the asymptomatic nature of MASLD in its early stages, many individuals remain undiagnosed until advanced disease has developed. This underscores the need for proactive screening, particularly in high-risk groups including individuals with obesity, type 2 diabetes (T2D), metabolic syndrome, or persistently elevated liver enzymes. Noninvasive tests now form the backbone of MASLD screening strategies. The fibrosis-4 (FIB-4) index and vibration-controlled transient elastography (VCTE; commonly performed using FibroScan) are widely recommended as first and second line tools, respectively. The FIB-4 score based on age, AST, ALT and platelet count is simple, inexpensive and easily applied in both primary and specialty care settings. It effectively categorizes patients into low intermediate or high risk groups for advanced fibrosis. When results are indeterminate or suggest high risk, VCTE can further assess liver stiffness, providing a reliable surrogate of fibrosis severity.

Patients with FIB-4 less than 1.3 are categorized as intermediate risk group and can be followed in the primary care setting and reassessed every 1-3 years. Patients with FIB-4 >2.67 (or >2.0 in individuals aged >65) are categorized as high-risk group and in these patients assess with alternative noninvasive test (e.g., VCTE) to clarify the stage of fibrosis. Patients with FIB-4 between 1.3 to 2.67 are categorized as intermediate risk group and can proceed to elastography or undergo a 1-year intervention of lifestyle change and intensified management of cardiometabolic risk factors. If the re-tested FIB-4 level is still elevated after 1 year, VCTE is recommended as the second step to clarify the stage of fibrosis.[3]

Importantly, MASLD screening should not be limited to hepatology practice. Primary care physicians, endocrinologists, cardiologists and diabetes care providers play a key role in early detection. Integrating noninvasive testing into routine care, supported by clear referral pathways and increased awareness is essential to reduce the burden of undiagnosed advanced fibrosis and improve long-term outcomes in MASLD.

Lifestyle interventions in MASLD:

Lifestyle interventions, including dietary adjustments, weight management, increased physical activity and exercise, are considered cornerstone of MASLD management. Lifestyle intervention can improve patient's pathological conditions and slow down disease progression. Lifestyle interventions through structured programs are recommended. The main barrier to lifestyle change is that the achievement as well as the maintenance across the years is challenging due to compliance, food accessibility and geographical restrictions.

Diet:

Diet is a key factor in the management of MASLD. Limiting overall calorie consumption and regulating food intake are essential components of dietary interventions. Patients with MASLD should consume 1,500-1,800 kcal calories per day for men and 1,200-1,500 kcal calories per day for women or reduce the total calorie intake of the current diet by 500-1,000 kcal per day.[11] The most widely studied dietary models are: the Mediterranean diet (MD), low-fat diets (LFD), low-carbohydrate diets (LCD), the ketogenic diet (KD), and intermittent fasting (IF). Among them most effective and widely accepted dietary model is the Mediterranean diet (MD).[12] The MD is basically a plant-based diet that emphasizes high consumption of fruits, vegetables, whole grains, nuts, and olive oil as the primary source of fat, with moderate intake of fish and poultry and minimal consumption of red meat and processed foods. Studies have shown that following a MD can reduce blood lipid levels, enhance insulin sensitivity and decrease liver fat, even in the absence of weight loss. The MD is also associated with a lower risk of T2DM, cardiovascular and cancer mortality, including from liver cancer.[13] The European Association for the Study of the Liver (EASL) has endorsed the MD as the primary dietary intervention for MASLD.[3]

Low-fat (LFD) or low-carbohydrate (LCD) diets offer alternative strategies, with evidence decreasing lower intrahepatic lipid accumulation, triglyceridemia, lipid oxidation, and insulin resistance.[12] LCD is as effective as LFD on weight loss and metabolic risk factors improvement. However, few large-scale and high-quality studies have analyzed the long-term effects of LCD and LFD on metabolic risk factors.[14]

Intermittent fasting allows an unlimited energy intake, but the consumption is limited to certain time intervals. By maintaining this type of diet, metabolic dysfunction is improved with better glycemia and blood pressure control and a better evolution in terms of steatosis and liver fibrosis.

Although there are different IF approaches, daily time-restricted feeding regimen (TRF) with an 18-h fasting period and a 6-h eating window (16/8) and alternate-day fasting (ADF), characterized by 24 h of fasting at 25% of baseline energy, have recently gained attention as potential interventions in improving the management of metabolic condition.[12] Although IF regimens can improve some markers of cardiometabolic and liver function, the available evidence to support the benefits of IF regimens is limited and derived from a small number of studies. Thus, further research is needed to clarify the impact of IF on the cardiometabolic health of MASLD patients.[15] IF has been compared to other dietary interventions such as that mediterranean diet, low-calorie diets and calorie restriction, however further research is needed to establish regime guidelines and to confirm any long-term benefits. While there has been evidence showing reduced liver fat content, inflammation and fibrosis with IF, the American Gastroenterological Association (AGA) recommends other dieting methods over IF.

The Ketogenic Diet (KD), characterized by high fat, moderate protein and very low carbohydrate intake. In KD, fat is used as the primary energy source significantly reducing glucose availability for de novo lipogenesis, a key driver of hepatic fat accumulation. Some studies suggest that the KD can lead to weight loss, reduced insulin resistance and decreased liver fat content.[12] However, the long-term safety and practicality of the KD remain areas of concern. Prolonged adherence may lead to hepatic lipid accumulation, inflammation and activation of fibrogenic genes, potentially exacerbating liver damage. Additionally, the high saturated fat content in many KD protocols raises cardiovascular risks, particularly for patients with metabolic syndrome.[16]

Regular coffee consumption has been associated with lower risk of MASLD and fibrosis compared to non-coffee drinkers.[17] Any coffee consumption was associated with a 29% lower risk of MASLD, a 30%- 39% lower risk of liver fibrosis and a 39% lower risk of cirrhosis in two meta- analyses.[18] Also, a dose dependent inverse relationship was evident in two different meta analyses for cirrhosis and liver related death[19]. A meta-analysis showed that intake of ≥3 cups of coffee per day (vs.<2 per day) was related to reduced risk of MASLD. In a nationally representative cross-sectional study, >3 cups of coffee daily were independently associated with lower liver stiffness but not steatosis as measured by CAP among US adult.[20]

Coffee consumption has also a protective effect against HCC. In a US multi-ethnic prospective cohort of 162,022 participants, those who drank 2-3 cups of coffee per day had a 38% risk reduction for HCC compared with non-coffee drinker. Those who drank ≥4 cups per day had a 41% reduction in HCC risk. Furthermore, compared with non-coffee drinkers, participants who consumed 2-3 cups of coffee per day had a 46% risk reduction of death from chronic liver disease and those who drank ≥4 cups per day had a 71% reduction.[21,22]

There is an association between added sugars and NAFLD. Added sugar refers to refined sugars (sucrose, fructose and high fructose corn syrup) added to sugared sweetened beverages (SSB) and incorporated into food, fruit drinks and other beverages.[23] Adults with MASLD are recommended to avoid deeply processed foods, fast foods and snacks and replace them with fiber-rich unprocessed foods (such as whole grains, vegetables, fruits, legumes, nuts and seeds. It is recommended that adults with MASLD limit excessive fructose intake and avoid processed foods and beverages with added fructose. It is recommended that industrial fructose intake should be limited to less than 5% of total daily carbohydrate intake.[24] Alcohol consumption should be limited in adults with MASLD and abstinence from alcohol is recommended for adults with MASLD who have steatohepatitis or fibrosis[11]. Research advocates that a mild-moderate intake of alcohol is associated with an elevated risk of liver outcomes. Therefore, healthcare professionals need to ban alcohol consumption for those with MASLD to benefit from optimal liver functioning.[25]

Weight Loss:

Weight loss interventions have been significantly associated with improved liver parameters, including alanine aminotransaminase levels, steatosis, histologic MASLD activity score and steatohepatitis. Research shows that achieving a weight loss of 7-10% is generally necessary to bring about meaningful improvements in the MASLD Activity Score (MAS).[26] Patients with MASLD maybe benefited differently depending on the ratio of weight loss to the initial body weight. For instance, a weight loss of ≥5% can reduce hepatic steatosis, weight loss of ≥7% can contribute to the regression of steatohepatitis and weight loss of ≥10% can lead to the regression or stabilization of liver fibrosis.[27,28] Weight reduction also results in marked improvement in MASLD risk factors, particularly T2D, obesity and cardiovascular disease. Weight loss is difficult to achieve and harder to maintain and patients should be aided with individualized weight-loss targets (aiming for gradual, sustained loss of 7-10%) and referral to assisted weight-loss programmes where available.

Physical Activity and exercise:

Physical activity refers to any movement that increases energy expenditure, while exercise is a subset of physical activity that is planned, structured and repetitive, with a specific goal in mind.[29] Exercise independently improves hepatic fat content even in the absence of weight loss. Both aerobic and resistance exercise are effective in decreasing liver fat content. Aerobic exercises, also known as cardiovascular exercises, are great for individuals with MASLD. Activities like walking, jogging, cycling, swimming and aerobic dance can be excellent choices to help improve cardiovascular health and are effective in burning calories, which can aid in weight management. It is recommended that individuals aim for at least 150 min of moderate-intensity aerobic activity each week.[25] Resistance exercise is recommended for adults with MASLD who have poor cardiorespiratory function or are unable to tolerate aerobic exercise.

Behavioral and psychological interventions:

Some studies focus on the role of behavioral therapy, employing psychological and behavioral approaches to help patients establish healthy lifestyle habits. This includes changing unhealthy dietary and exercise behaviors, enhancing patients' self-management skills and lifestyle changes correlating with a greater degree of weight loss and improvement in MASH histological features. Psychosocial factors are crucial for patients' lifestyle changes. Promoting social support and psychological health contributes to increased treatment compliance and the alteration of unhealthy behavior patterns.[30]

Pharmacological therapy in MASLD:

Thyroid hormone receptor-b agonist: Resmetirom

Resmetirom, a selective thyroid hormone receptor (THR), became the first agent to be approved by the FDA for the treatment of MASH on 14 March 2024. Thyroid hormones exert their effects by binding to 2 receptor isoforms, THR-α and THR-β. While THR-α is linked to negative effects on the heart and bones, THR-β, which is predominantly expressed in the liver, plays a critical role in lowering cholesterol levels and enhancing liver metabolism.When THR-b is stimulated by agonists (ie, resmetirom), it improves liver health by initiating a cascade of processes that are commonly dysregulated in patients with MASH. THR-β activation enhances mitochondrial fatty-acid oxidation, reduces lipogenesis and promotes cholesterol efflux.[31] Unlike THR-α, which influences cardiac and skeletal muscle function, THR-β activation is hepatoselective, minimizing systemic side effects such as tachycardia or bone loss. The U.S. Food and Drug Administration approved Resmetirom based on a phase III trial of 966 patients with Metabolic dysfunction–associated steatohepatitis. MASH resolution without fibrosis worsening occurred in 25.9-29.9% of treated patients vs 9.7% with placebo. Fibrosis improved by ≥1 stage without worsening MSH in 24-26% of treated patients vs 14.3% with placebo.[32] Resmetirom should be avoided in patients with decompensated cirrhosis because impaired liver function can increase drug levels in the body, raising the risk of side effects.[33] It is mainly metabolized by the CYP2C8 enzyme, so caution is needed when using it with drugs that inhibit this enzyme-such as repaglinide, clopidogrel and some statins-as these can increase resmetirom levels and the risk of adverse effects.[34]

GLP-1 receptor agonists (GLP1 RAs)

GLP-1 is released by enteroendocrine cells in the gastrointestinal tract to play a crucial role in regulating postmeal blood sugar levels by by stimulating insulin secretion and increasing peripheral insulin sensitivity. It also decreases appetite, delays gastric emptying, reduces body weight. Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is approved for the treatment of type 2 diabetes and overweight or obesity, with reports of improvements in cardiovascular and renal outcomes in these populations.[34] In preclinical studies, these agonists could alleviate MASH by mitigating hepatic steatosis, inflammation and injury, whereas these effects were suggested to be secondary to the weight loss induced by GLP-1 receptor agonists.[35] Once daily subcutaneous semaglutide 0.4 mg demonstrated superiority over placebo for MASH resolution without worsening fibrosis, with 59% response in the treatment group versus 17% in placebo. Fibrosis improvement occurred in 43% of treated patients versus 33% with placebo. Mean weight loss was 13% vs. 1%.[36] The ongoing ESSENCE phase 3 trial evaluating weekly semaglutide 2.4 mg in adults with MASH and moderate to advanced liver fibrosis showed significant improvements. At 72 weeks, 37.0% achieved improved liver fibrosis without worsening steatohepatitis versus 22.5% on placebo. Additionally, 62.9% achieved steatohepatitis resolution without worsening fibrosis versus 34.1% on placebo.[37] The FDA has granted accelerated approval to semaglutide (Wegovy; Novo Nordisk) injection 2.4 mg for the treatment of adults with metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis, making it the first glucagon-like peptide-1 (GLP-1) receptor agonist approved for this indication.[38]

GLP-1 and GIP receptor co-agonists (GLP1- GIPRAs)

Tirzepatide is the first dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide-1(GLP-1) receptor agonist that has been approved for the treatment of T2DM and obesity.[39] Clinical studies reported that a weekly dose of 5 mg, 10 mg or 15 mg of tirzepatide for 72 weeks leads to significant and sustained reduction of body weight in obese individuals.[40] The phase 2, double-blind, dose-finding trial of tirzepatide included 190 participants with biopsy-proven MASH and fibrosis stage F2-F3 Participants were randomly assigned to receive once-weekly subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo. for 52 weeks. The primary endpoint of resolution of MASH without worsening of fibrosis was achieved in 44%, 56%, and 62% of participants in the 5, 10 and 15 mg groups, respectively, compared to 10% of those in the placebo group. The secondary endpoint of ≥ 1 stage improvement in fibrosis with no worsening of MASH was achieved in 55%, 51% and 51% of participants in the 5, 10 and 15 mg groups, respectively, compared to 30% of those in the placebo group.[41]

Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

Sodium-glucose cotransporter-2 inhibitors are a class of antidiabetic drugs that lower blood glucose levels by promoting urinary glucose excretion, thereby preventing renal glucose reabsorption. In addition to urinary glucose excretion, SGLT2i promote natriuresis and diuresis, leading to reductions in blood pressure and plasma volume, which may contribute to their cardioprotective effects in MASLD patients at high risk of CVD. Initially developed for T2DM, SGLT2i have demonstrated broad cardiovascular and renal protective benefits, leading to their expanded use beyond glycemic control. Emerging evidence suggests that SGLT2i may also have hepatoprotective effects in MASLD/MASH by improving hepatic steatosis, inflammation, and hepatic

fibrosis through weight loss, insulin sensitization and reduction of oxidative stress. Additionally, SGLT2i enhance lipid metabolism by promoting lipolysis, ketogenesis and reducing hepatic DNL, which collectively mitigate liver injury and hepatic fibrosis progression.[42,43,44] SGLT2 inhibitors consistently improve liver-related outcomes in patients with T2DM and MASLD. Recent systematic reviews and meta-analyses demonstrated that SGLT2 inhibitors consistently decrease liver fat content (measured by MRI-PDFF), improvements in liver enzyme levels, better glycemic control and reductions in body weight and BMI.[45,46,47,48,49,50] Evidence for direct, biopsy-proven fibrosis regression remains limited,[50,51] though some studies show improvement in non-invasive fibrosis markers. Current guidelines now recommend SGLT2 inhibitors for patients with diabetic MASLD/MASH, and based on emerging evidence, they may soon be considered for non-diabetic MASH as well.[52]

Peroxisome proliferator-activator receptors (PPAR) agonists

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear receptors that regulate lipid metabolism, glucose homeostasis, inflammation, and liver fibrosis, making them key therapeutic targets in MASLD/MASH. PPAR-α (fibrates) boosts fatty acid oxidation, PPAR-γ (TZDs, e.g., pioglitazone) enhances insulin sensitivity & adipogenesis and PPAR-δ modulates glucose metabolism, inflammation and mitochondrial function.

Pioglitazone (PPAR-γ agonist)

Pioglitazone, a PPAR-γ agonist, improves insulin sensitivity, reduces hepatic fat and modulates inflammation in MASLD/MASH. In the PIVENS trial, 30 mg/day in non-diabetic MASH patients led to histologic improvement, with MASH resolution in 47% versus 21% with placebo ($p < 0.001$), though effects on fibrosis were not significant.

Saroglitazar (PPAR-α/γ agonist)

Saroglitazar, a dual PPAR-α/γ agonist approved by the Drug Controller General of India (DCGI) for MASLD.[53] Saroglitazar is a dual PPAR agonist with strong PPAR-α and moderate PPAR-γ activity. It helps lower triglyceride levels, raise HDL-cholesterol and improve insulin sensitivity and glucose metabolism. The drug also increases adiponectin and reduces inflammatory markers such as hs-CRP, TNF-α and IL-6, contributing to metabolic and vascular benefits. Clinical studies have shown that it can reduce liver enzymes (ALT, AST) and decrease hepatic fat in patients with NAFLD/NASH. Unlike many other metabolic drugs-such as statins, thiazolidinediones, fibrates and SGLT2 inhibitors-saroglitazar acts on lipid metabolism, glucose regulation, and inflammation at the same time. A phase 2 RCT in 106 NAFLD/MASH patients with elevated ALT showed that saroglitazar 4 mg led to a 45.8% ALT reduction versus a 3.4% increase with placebo ($p < 0.001$) and decreased liver fat by 19.7% compared to a 4.1% rise with placebo. Saroglitazar also improved insulin resistance (HOMA-IR) and lowered triglycerides ($p < 0.05$), was well tolerated, and caused modest weight gain (1.5 kg). These results highlight its potential in MASLD/MASH, especially in patients with metabolic dysfunction and dyslipidemia.[54]

Lanifibranor (Pan-PPAR agonist: α/γ/δ)

Lanifibranor is a pan-PPAR agonist that targets all three PPAR isoforms. Activation of PPAR-α helps reduce hepatic fat accumulation, PPAR-δ activity decreases inflammatory responses, and PPAR-γ activation limits hepatic stellate cell activation and slows the progression of liver fibrosis. Lanifibranor, can suppress the progression of MASH by influencing key metabolic, inflammatory and fibrogenic pathways. It promotes fatty-acid oxidation and suppresses inflammatory signaling through inhibition of the NF-κB pathway. In a phase II trial including 247 patients with active, non-cirrhotic MASH, treatment with lanifibranor 1200 mg daily for 24 weeks resulted in significant improvement in hepatic steatosis, ballooning and inflammation compared with placebo.[55] Improvement of MASH without worsening of fibrosis was observed with both 800 mg and 1200 mg doses. However, treatment was associated with several adverse effects, including diarrhea, nausea, anemia & weight gain and a few patients developed serious complications that required discontinuation of therapy. To further evaluate its efficacy and safety, a phase III clinical trial is currently underway in adults with NASH and F2–F3 fibrosis.

Farnisoid X receptor (FXR) agonists

Obeticholic acid (OCA) is an agonist of FXR, which is a nuclear receptor that regulates glucose and lipid metabolism. In a phase III clinical study, treatment with obeticholic acid resulted in improvement of hepatic fibrosis in 18% of patients with MASLD receiving 10 mg and in 23% of those receiving 25 mg, compared with 12% in the placebo arm. Despite these findings, the therapy did not produce a statistically significant resolution of MASH at the primary study endpoint, as the proportion of patients achieving disease resolution in the treatment groups (11-12%) was similar to that observed in the placebo group (8%).[56] OCA treatment elevates total cholesterol and LDL cholesterol, accompanied by a reduction in high-density lipoprotein (HDL) levels. OCA treatment is Although obeticholic acid has shown potential in improving liver fibrosis, several obstacles have limited its acceptance by regulatory authorities. A randomized controlled trial demonstrated that treatment with obeticholic acid was associated with unfavorable alterations in serum lipid profiles, including an increase in small very-low-density lipoprotein (VLDL) particles as well as both large and small low-density lipoprotein (LDL) fractions, accompanied by a reduction in high-density lipoprotein (HDL) levels. OCA treatment also causes pruritus in a significant proportion of people with MASH[57]. Furthermore, the REVERSE trial in patients with cirrhosis demonstrated that obeticholic acid did not achieve its primary endpoint of MASH resolution. These results raised concerns among regulatory authorities regarding both efficacy and safety, particularly in light of reported signals of hepatotoxicity. As a result, the U.S. Food and Drug Administration declined conditional approval and requested additional data.

Subsequently, the sponsor, Intercept Pharmaceuticals, discontinued further development of obeticholic acid for this indication.[2]

Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs) have attracted interest for their lipid-lowering and anti-inflammatory effects, making them a potential therapeutic option in MASLD/MASH. Early clinical studies suggest that omega-3 supplementation may decrease liver fat and improve metabolic parameters; however, the optimal dose, duration and source remain to be clearly established. A meta-analysis of 22 RCTs (1,366 patients) showed that omega-3 PUFAs reduced steatosis and improved triglycerides, total cholesterol, HDL and BMI, indicating metabolic benefits.[58] Similarly, a meta-analysis of six RCTs evaluating plant-based omega-3 reported reductions in ALT and triglycerides, along with improvements in BMI, waist circumference and body weight, particularly when combined with lifestyle modification.[59]

Vitamin E

Vitamin E supplementation has been shown to significantly lower serum aminotransferase levels and improve histological features such as steatosis and hepatic inflammation. However, its impact on liver fibrosis remains unclear, reflecting a notable limitation in the current body of evidence. While vitamin E appears to improve liver function and reduce inflammatory processes in patients with NAFLD/MASLD, its effectiveness in reversing or halting fibrosis progression is yet to be definitively established. Therefore, further large-scale, long-term studies are necessary to clarify its role, particularly in individuals with advanced stages of liver disease.[60]

Role of metformin, dipeptidyl peptidase-4 inhibitors, sulfonylurea and insulin in diabetic MASLD

Metformin remains the first-line therapy for T2DM and should be continued in all diabetic MASLD patients unless contraindicated. As an insulin sensitizer, it improves metabolic parameters, reduces insulin resistance and offers cardiovascular protection-key factors in MASLD pathogenesis. However, it has no significant effect on liver histology or fibrosis. Evidence from trials such as the TONIC study and meta-analyses shows improvement in liver enzymes (ALT, AST) without meaningful histological benefit.[61,62] Observational data suggest a potential reduction in hepatocellular carcinoma (HCC) risk among metformin users with T2DM.[61] Despite these advantages, current guidelines do not recommend metformin as a targeted therapy for MASLD. Therefore, in diabetic patients with MASLD, additional agents-such as GLP-1 receptor agonists (e.g., semaglutide), SGLT2 inhibitors, pioglitazone, or saroglitazar-should be considered based on fibrosis severity to address both metabolic dysfunction and liver-related outcomes. Dipeptidyl peptidase-4 (DPP-4) inhibitors have been explored for their potential metabolic and anti-inflammatory effects in MASLD/MASH. Although preclinical data suggested possible benefits in reducing steatosis and fibrosis, clinical evidence has not confirmed meaningful histological improvement. Meta-analyses of randomized trials indicate that these agents may produce modest reductions in liver enzyme levels, but they do not significantly improve fibrosis or overall liver histology.[63] In view of more effective therapies such as GLP-1 receptor agonists and SGLT2 inhibitors, DPP-4 inhibitors are not currently recommended as a treatment for MASLD. The role of sulfonylureas in MASLD is not well defined. These agents do not target key pathogenic mechanisms such as insulin resistance, hepatic steatosis, or fibrosis. Moreover, sulfonylurea induced hyperinsulinemia may promote hepatic lipogenesis and fat accumulation, potentially accelerating disease progression. Despite their common use in diabetes care, current evidence does not support their use for MASLD management.[64] Therefore, in patients with T2DM and MASLD, sulfonylureas should be used cautiously and preference should be given to agents with proven metabolic and hepatic benefits, such as GLP-1 receptor agonists or SGLT2 inhibitors. Insulin therapy lowers hepatic glucose output and improves insulin resistance, which may indirectly reduce hepatic steatosis. However, available evidence does not demonstrate meaningful improvement in MASH or liver fibrosis with insulin treatment. Comparative studies, including trials evaluating insulin glargine versus liraglutide in patients with diabetic MASLD, have shown similar reductions in MRI-assessed liver fat, suggesting that insulin alone does not significantly modify liver histology.[65] Therefore, although insulin remains essential for glycemic control, its use in MASLD should be individualized, with preference for agents that provide both metabolic and hepatic benefits whenever feasible.

Statin drugs

MASLD frequently coexists with hyperlipidemia and cardiovascular disease, making lipid-lowering therapy an important component of management. Statins are commonly prescribed in patients with dyslipidemia and have demonstrated additional benefits in this population.In a study of 437 patients with Metabolic dysfunction-associated steatotic liver disease and mildly abnormal liver tests, treatment with Atorvastatin (≈24 mg/day) significantly improved liver enzymes, whereas untreated patients showed worsening levels.[66] Similarly, therapy with Ezetimibe plus Simvastatin or simvastatin alone was found to be safe and effective, with significant reductions in liver enzymes.[67] Furthermore, long-term follow-up data suggest that treatment with atorvastatin in combination with Vitamin E and Vitamin C significantly lowers the likelihood of MASLD and reduces the risk of hepatic steatosis.[67] Overall, statins are considered safe in MASLD and may improve liver biochemistry while also reducing cardiovascular morbidity. However, larger population-based studies and well-designed trials are still required to better define their role in patients with MASLD and Metabolic dysfunction-associated steatohepatitis.

Ursodeoxycholic Acid

Ursodeoxycholic acid is a hydrophilic bile acid known for its cytoprotective, anti-apoptotic and anti-inflammatory effects. It helps stabilize hepatocyte membranes, lowers serum transaminase levels and shields liver cells from oxidative injury. Although it is widely utilized in cholestatic liver disorders, its role in Metabolic dysfunction-associated steatotic liver disease remains uncertain.[68] Some smaller clinical studies have shown improvements in liver enzyme levels and hepatic steatosis with UDCA therapy; however, consistent histological benefits have not been clearly demonstrated. Furthermore, much of the available evidence is derived from patients with Nonalcoholic steatohepatitis or cholestatic conditions, limiting its generalizability to the broader MASLD population.

Conclusion:

MASLD represents a shift from Nonalcoholic Fatty Liver Disease toward a positive, metabolism-centered diagnosis that better reflects disease pathogenesis and clinical complexity. With its rising global burden and strong links to cardiometabolic disorders, MASLD requires early recognition and comprehensive management. Lifestyle modification remains the cornerstone but is often limited by poor long-term adherence. The emergence of targeted therapies, including Resmetirom, along with promising agents such as Semaglutide and Tirzepatide, marks a new era in treatment. A combined approach integrating lifestyle, pharmacotherapy and metabolic risk control is essential, while future advances in combination and precision therapies are expected to further improve outcomes.

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