Review Article

Metabolic dysfunction-associated steatotic liver disease: Beyond the fatty liver

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a significant global health challenge. Changing lifestyles, over-nutrition, and physical inactivity have promoted its development. Closely linked to obesity and metabolic syndrome, MASLD represents a shift in terminology from non-alcoholic fatty liver disease (NAFLD), reflecting a more precise understanding of its pathogenesis. Beyond liver-related complications, MASLD is associated with an increased risk of cardiovascular disease, chronic kidney disease, and certain extrahepatic cancers. The disease exhibits heterogeneity in its clinical manifestations due to complex molecular pathways involved in its pathogenesis. The expanding role of noninvasive techniques, such as serum biomarkers and advanced imaging modalities, have improved risk stratification and identification of individuals at high risk for fibrosis progression. This comprehensive narrative review summarizes the global incidence and prevalence rates of MASLD and its related adverse hepatic and extrahepatic outcomes. We also highlight recent nomenclature changes, the clinical relevance of early intervention and emerging pharmacological therapies.

Keywords: Metabolic dysfunction-associated steatotic liver disease, Non-alcoholic fatty liver disease, Cardio-metabolic risk factor, Fatty liver.

Introduction:

Nonalcoholic fatty liver disease (NAFLD) has emerged as a prominent cause of chronic liver disease globally.[1] Since June 2023, NAFLD nomenclature has been changed to metabolic dysfunction-associated steatotic liver disease (MASLD). It is commonly associated with cardiometabolic risk factors. Due to worldwide epidemics of metabolic syndrome, obesity, and type 2 diabetes, the prevalence of MASLD has been increasing over time. Recent meta-analysis estimating that more than one-third of the adult population are afflicted by MASLD.[2] About 75% of people with obesity[2] and 69% of people with type 2 diabetes[3] have concomitant MASLD.

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MASLD consists of two clinical entities: metabolic dysfunction- associated steatotic liver (MASL, previously NAFL) and metabolic dysfunction-associated steatohepatitis (MASH, previously called NASH). While simple steatosis does not often progress, patients with MASH are at risk of progressive liver injury that can advance to cirrhosis and the development of hepatocellular carcinoma. Progressive MASH is characterized histologically by steatosis, lobular inflammation, and hepatocyte ballooning with varying degrees of fibrosis.[4,5]

MASLD is mostly asymptomatic, although a proportion of patients report fatigue and right upper quadrant abdominal pain. MASLD is suspected by identifying commonly associated risk factors, finding steatosis on imaging and excluding other causes of chronic liver disease. Early diagnosis and management of MASLD are essential in preventing the progression to severe forms of liver diseases.[6]

This review will focus on the most recent data on MASLD epidemiology, pathogenesis, risk prediction, diagnostic strategies, and current and emerging management approaches.

Epidemiology of MASLD:

Eestimated global incidence of NAFLD is 47 cases per 1,000 populations.[7] The global prevalence of MASLD has increased over time, from 26.0% in 1990-2006 to 38.0% in 2016-2019.[8,9] The prevalence varies by race and ethnicity.

The highest prevalence observed in Latin America 44.37%, then Middle East and North Africa 36.53%, South Asia

33.83%, South-East Asia 33.07%, North America 31.20%, East Asia 29.71%, Asia Pacific 28.02%, and Western Europe 25.10%.[10] These trends are expected to grow as the global prevalence of MASLD is forecasted to reach 55.4% by 2040.[11] The prevalence is higher among males (40%) compared to females (26%).[8] Although there is limited data on the prevalence of MASLD in Bangladesh, it is also experiencing an increasing trend of MASLD due to changing dietary patterns and sedentary lifestyles. A study conducted in 2018, showed that the overall prevalence of MASLD was 33.86% in Bangladesh.[12]

Background of new nomenclature:

Since the introduction of non-alcoholic fatty liver disease (NAFLD) in 1980, numerous efforts have been made to redefine the disease terminology.[13] In 2020, an international panel of experts proposed the term metabolic dysfunction–associated fatty liver disease (MAFLD) to better reflect its metabolic origins.[14] Following a four-round Delphi process, in June 2023, an international panel of 225 participants, led by three multinational liver associations, officially renamed NAFLD as MASLD.[14,15] This change also introduced steatotic liver disease (SLD) as an umbrella term, encompassing MASLD, MASLD with moderate alcohol intake (MetALD), alcohol-related liver disease (ALD), specific etiologies (e.g., drug-induced or monogenic causes), and cryptogenic SLD.

The new nomenclature emphasizes the role of metabolic dysfunction in fatty liver disease and aligns more closely with its underlying pathophysiology. MASLD is defined as hepatic steatosis in the presence of one or more cardiometabolic risk factor(s) (Table 1) and the absence of harmful alcohol intake.

Table 1. Cardiometabolic risk factors and cut off values

Metabolic risk factor	Adult criteria
Overweight or obesity	Body Mass Index ≥25 Kg/m^2 (≥23 Kg/m^2 for Asians) Waist circumference • ≥94 cm in men and ≥80 cm in women (Europeans) • ≥90 cm in men and ≥80 cm in women (South Asians and Chinese) • ≥85 cm in men and ≥90 cm in women (Japanese)
Dysglycaemia or type 2 diabetes	Prediabetes: HbA1c 39-47 mmol/mol (5.7-6.4%) or fasting plasma glucose 5.6-6.9 mmol/L (100-125 mg/dl) or 2-h plasma glucose during OGTT 7.8-11 mmol/L (140-199 mg/dl) or Type 2 diabetes: HbA1c ≥48 mmol/mol (≥6.5%) or fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dl) or 2-h plasma glucose during OGTT ≥11 mmol/L (≥200 mg/dl) or On treatment for type 2 diabetes
Plasma triglycerides	Plasma triglycerides ≥150 mg/dl (≥1.70 mmol/L) or lipid- lowering treatment
HDL-cholesterol	Plasma HDL-cholesterol <40 mg/dl (<1.0 mmol/L) for men and <50 mg/dl (<1.3 mmol/L) for women or lipid- lowering treatment
Blood pressure	Blood pressure ≥130/85 mmHg or on treatment for hypertension

HbA1c (glycated hemoglobin); HDL (high-density lipoprotein); OGTT (oral glucose tolerance test).

The updated terms MASLD and MASH (metabolic dysfunction–associated steatohepatitis) replace the previous NAFLD and NASH terminology, addressing key limitations such as exclusionary definitions and potentially stigmatizing language. The previous nomenclature also failed to reflect the disease's multisystem involvement and metabolic origins.[15]

Additionally, the new classification introduces MetALD, a category for individuals with hepatic steatosis, cardiometabolic risk factors, and moderate alcohol consumption (20–50 g/day for females and 30-60 g/day for males), differentiating them from MASLD and heavy alcohol-related liver disease. Individuals with steatosis but no identified cardiometabolic risk factors fall under "possible MASLD", requiring further evaluation for insulin resistance or cryptogenic SLD.[15]

The pathogenesis of MASLD:

The two-hit hypothesis was initially proposed to explain the pathogenesis of MASLD. In this model, hepatic fat accumulation promotes insulin resistance (the "first hit"), which subsequently triggers inflammatory mechanisms and fibrosis (the "second hit"). However, this hypothesis is being reconsidered as new theories emerge. Research suggests that MASLD results from a complex interplay of genetic, dietary, metabolic, and environmental factors.[16]

Certain genetic polymorphisms have been linked to advanced liver disease and the development of hepatocellular carcinoma (HCC) in MASH.[17] The most significant genetic variants influencing MASLD susceptibility and progression include: PNPLA3 (patatin-like phospholipase domain-containing protein 3)[18] and TM6SF2 (transmembrane 6 superfamily member 2).[19] PNPLA3– mutations in this gene are associated with increased hepatic lipid content. TM6SF2– mutations lead to loss of function in hepatic VLDL secretion, increasing susceptibility to liver damage.[20]

Accumulating evidence suggests that mitochondrial dysfunction plays a significant role in steatosis and steatohepatitis. Impaired β-oxidation of lipids leads to the overproduction of reactive oxygen species (ROS) in hepatocytes.[21] Excessive ROS triggers lipid peroxidation, protein damage, and DNA injury, creating a pro-inflammatory environment.[22,23] The resulting oxidative stress sensitizes hepatocytes to injury and apoptosis, exacerbating liver inflammation.[24]

Emerging evidence suggests that changes in the gut dysbiosis might play a vital role in the development and progression of MASLD from simple steatosis to steatohepatitis and even HCC. Changes in the gut microbiome can alter the production of short-chain fatty acids and increase intestinal permeability, allowing bacterial endotoxins to enter the portal circulation.[25,26] These endotoxins activate hepatic Toll-like receptors (TLRs), particularly TLR4, triggering inflammation and fibrosis.[27]

Chronic liver injury and inflammation activate hepatic stellate cells (HSCs), which produce extracellular matrix proteins, leading to scar tissue formation (fibrosis). As fibrosis progresses, it causes architectural distortion of the liver, significantly increasing the risk of cirrhosis and HCC.[28]

Diagnosis and Diagnostic Modalities:

The diagnosis is made by combining clinical assessment, along with laboratory tests and imaging. Most of the patients are asymptomatic, and the disease is often overlooked. Some patients may present with non-specific symptoms, such as fatigue, right upper quadrant discomfort, or epigastric fullness. In early disease stages, hepatomegaly may be the only physical finding. In advanced disease (cirrhosis), signs such as splenomegaly, spider angiomata, palmar erythema, or ascites may be present. MASLD is often suspected with the finding of hepatomegaly on physical examination, or incidentally on abnormal liver function tests (elevated liver enzymes) or on abdominal imaging.[17,29]

Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are common but not specific for MASLD. Fasting glucose, HbA1c, lipid profile, and serum triglycerides aid in identifying metabolic dysfunction. Assessment of insulin resistance (e.g., using the Homeostasis model assessment of insulin resistance [HOMA-IR] or estimates derived from the oral glucose tolerance test) may be considered to clarify metabolic dysfunction in adults with suspected MASLD and without an established diagnosis of type 2 diabetes mellitus (T2DM). Additional tests (e.g., autoimmune markers, viral hepatitis panels, serum ceruloplasmin) may be required to exclude other liver diseases.[17,30]

In clinical practice, ultrasonography (USG) is the first-line imaging exam used for the diagnosis of hepatic steatosis because of its wide availability and lower cost. The sensitivity and specificity of the USG are 89% & 93%, respectively. The grading of liver steatosis is usually obtained using some USG features that include liver brightness, contrast between the liver and the kidney, USG appearance of the intrahepatic vessels, liver parenchyma and diaphragm. However, accuracy is reduced in morbid obesity.[31] Vibration-controlled transient elastography (VCTE), commonly known as FibroScan, is a noninvasive technique with higher sensitivity and specificity. It measures controlled attenuation parameter (CAP) and liver stiffness to assess liver steatosis and fibrosis, respectively.[31] Magnetic resonance proton density fat fraction (MRI-PDFF) is considered the gold standard for quantifying hepatic fat, but it is not yet widely available, and it is also very costly.[32] CT scan is not considered the best modality for MASLD due to higher cost, potential radiation exposure, and limited sensitivity in detecting mild steatosis.[17] Liver biopsy is the gold standard for assessing fibrosis stage and distinguishing MASH from simple steatosis. However, due to its invasive nature and risk of sampling error, it is reserved for unclear cases or suspected advanced disease.[33]

Risk Assessment of Patients with MASLD:

Liver enzymes may be a first-step to assess and monitor patients with liver diseases. However, serum liver enzyme concentrations can be normal in more than half of patients with MASLD, and correlate poorly with the histological severity. Traditionally, liver biopsy was used to characterize and quantify histological features of steatosis, inflammation, hepatocyte ballooning, and fibrosis but it has several limitations. Several noninvasive tests composed of demographic, clinical, and routine laboratory parameters have been developed and can be applied easily in the community. Available tools are NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) index and AST-to-platelet ratio index (APRI), Enhanced Liver Fibrosis (ELF) panel, Fibrometer, FibroTest.[34] Among these tools, FIB-4 is the most well validated and recognized by most guidelines as a useful tool in identifying patients with higher likelihood of advanced liver fibrosis (F3 or F4).[17,30]

Although the overall sensitivity of FIB-4 is assumed not to be high, it has high negative predictive values to exclude advanced liver fibrosis. Patients with low FIB-4 score are also at a low risk of developing liver-related complications. Patients with high FIB-4 score should undergo a second noninvasive test of higher sensitivity.[35] Vibration-controlled transient elastography (VCTE) or MR elastography (MRE) are commonly used due to its availability and can estimate both hepatic steatosis and liver stiffness more accurately.[36] The noninvasive tests are used to identify individuals at high risk of progressive fibrosis who may benefit from more comprehensive management. Patients with T2DM or abdominal obesity and ≥1 additional metabolic risk factor(s) or persistently elevated liver enzymes should be screened for advanced fibrosis. Usually, a multi-step process is used. First, an inexpensive simple fibrosis score (e.g., FIB-4) is used to categorize patients according to their risks. Then individuals with a relevant risk profile should follow different pathways depending on the result of this test.[17,30]

Patients with FIB-4 less than 1.3 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.[30]

Management of MASLD:

The cornerstone of MASLD management are lifestyle modifications, including weight loss, a healthy diet, and regular exercise. In addition to lifestyle changes, the management of MASLD also focuses on addressing underlying metabolic risk factors, preventing disease progression, and mitigating complications.

- **Lifestyle Modification**
  Lifestyle intervention should be emphasized at all levels of patient care with the goal of improvements in both MASLD and the cardiometabolic and overall health of the individual patient. Evidence suggests that comprehensive changes in diet and physical activity can significantly improve liver histology, reduce hepatic fat, and address associated metabolic conditions such as obesity and T2DM.[37] Lifestyle interventions are effective even in advanced stages of MASLD, including non-alcoholic steatohepatitis (MASH) and fibrosis.

Diet

The Mediterranean diet (MD) is widely recognized as a leading dietary approach for managing MASLD. Several studies consistently demonstrated that the Mediterranean diet offers significant benefits for liver and cardiovascular health.[38,39] This dietary pattern has been shown to reduce liver fat accumulation and improve insulin sensitivity in individuals with MASLD and insulin resistance, even without weight loss.[38] This diet emphasizes whole grains, fish, monounsaturated fats, antioxidants, polyphenols, vitamins, fiber and olive oil, while maintaining a low intake of sugars and refined carbohydrates, saturated fat, ultra-processed foods, and red and processed meat.[39]

Regular coffee consumption has been found to offer protective effects against MASLD and liver fibrosis. It is also significantly associated with decreased risk of liver fibrosis development in already diagnosed MASLD patients. A meta-analysis encompassing diverse observational studies revealed that individuals who consumed coffee had a lower risk of MASLD and fibrosis compared to non-coffee drinkers.[30,40] The findings indicated a more robust and consistent protective effect against fibrosis than steatosis. Similarly, an earlier 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.[41]

A comprehensive meta-analysis performed in 2023 investigated the impact of intermittent fasting (IF) on cardiometabolic and hepatic indicators in individuals with MASLD. 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.[39]

Physical exercise

Exercise, independent of weight loss, has hepatic and cardiometabolic benefits and should be routinely recommended and tailored to the patient's preferences and physical abilities. Aerobic and/or resistance training (30 mins/day, 5 days/week, 150min/week) with the goal of 400 kcl loss per day can prevent or improve MASLD.[17,42-45]

Weight loss

In all adults with MASLD and overweight or obesity, dietary and behavioral therapy-induced weight loss should aim at a sustained reduction of ≥5% to reduce liver lipid content, 7-10% to improve liver inflammation, and ≥10% to improve fibrosis.[17,27,38] In people with lean MASLD, weight loss is still beneficial, the recommended targeted weight loss is 3-5%. A study on patients with biopsy-proven MASH demonstrated that this could result in the resolution of MASH and improvement in liver fibrosis in up to 90% and 45% of patients, respectively.[38] A 5-10% bodyweight loss could be a challenging goal for many patients if they only do exercise or follow a diet. Therefore, bariatric surgery is an option for some patients who cannot achieve the goal of losing 0.5-1 kg/week.[46]

- **Pharmacological therapy**
  In some cases, diet and lifestyle measures cannot be successfully or sustainably implemented. Pharmacological treatment is an option when non-pharmacological treatment fails, or when the patients already have advanced disease. The majority of drugs are

used to control CV risk factors and to help people to lose weight. Liver-targeted therapy, especially for NAFLD, is limited.

MASLD/MASH directed therapy

Thyroid Hormone Receptor Beta (TR-β) Agonists

Resmetirom is a thyroid hormone receptor beta (THR-β) agonist. Activation of THR-β in the liver improves liver enzymes, LDL-C, triglyceride, and lipoproteins by modulating hepatic lipid metabolism and this signaling pathway has been identified as a promising target to treat MASLD and hypercholesterolaemia.[47] Individuals receiving resmetirom should be monitored for gastrointestinal side effects and thyroid hormone function.

Vitamin E

Vitamin E has antioxidant, anti-inflammatory, and anti-apoptotic properties. It reduces liver lipid content by inhibiting de novo lipogenesis. Broad population-level analyses indicate that higher consumption of dietary vitamin E may lower the risk of metabolic dysfunction-associated steatotic liver disease (MASLD), based on both clinical assessments and imaging findings, especially in people with T2DM.[48] In the PIVENS randomized controlled trial, treatment with 800 IU of natural vitamin E (α-tocopherol) daily for 96 weeks led to significant histological improvement—defined as a reduction of at least 2 points in the NAFLD Activity Score-compared to placebo in nondiabetic individuals with NASH.[49] Case-control studies suggest that prolonged use of vitamin E may lower the chances of mortality, liver transplantation, and liver function decline in people with MASH who also have bridging fibrosis or cirrhosis.[50] Although some smaller studies have indicated that vitamin E may help lower liver enzyme levels, there is still no conclusive evidence that it improves fibrosis, and a large-scale phase III clinical trial has yet to be carried out.[30]

Targeting MASH through glycemic and body weight control

Patients with MASLD have 2-3-fold increased risk of subsequent diabetes.[51] There is a bidirectional relationship between NAFLD and T2DM i.e. the possible involvement of fatty liver disease in patients with T2DM, and, in turn, the possibility of these T2DM in patients with MASLD.[52] Patients with MASH should be screened for T2DM and vice versa. The insulin resistance may result in development of both MASLD and T2DM, thus, the same management principle can be applied for both. Several antidiabetic medications have a role not only treating hyperglycemia per se but also reduce hepatic steatosis, liver enzyme levels, and inflammation, with some potential role in fibrosis.

GLP-1 receptor agonists (GLP1 RAs)

Glucagon-like peptide 1 (GLP-1) is an endogenous gut hormone (incretin) that promotes insulin production and release, inhibits glucagon secretion indirectly. In addition to glycemic control, GLP-1 RAs also reduce appetite and have a weight loss effect.[53] A number of clinical studies documented beneficial effects of GLP- 1RAs in patients with MASLD, mainly in those with concomitant T2DM.[54-60] Given these robust benefits, GLP1 RAs have emerged as the key pillars for managing people with T2DM and/or obesity.[61] Although, several studies have reported positive effects of GLP-1 analogs on liver health, particularly in reducing hepatic steatosis and improving MASH, the impact on hepatic fibrosis appears to be less significant.[62]

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

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.[63] Tirzepatide was found superior to GLP-1 receptor agonists to decrease bodyweight, both in people with and without T2DM.[64] Tirzepatide, together with a marked improvement in glucose metabolism and cardiometabolic risk factors, is becoming an attractive therapeutic option for MASLD/MASH patients with coexisting T2D and obesity.[65]

Sodium-glucose cotransporter type 2 (SGLT2) inhibitors

SGLT2 inhibitors induce renal glucosuria and weight loss which could be beneficial in patients with MASLD. These agents have shown great advantages in patients with heart and kidney failure patients, even in patients with no diabetes. SGLT2i seem to be promising agents for MASLD treatment, since they could inhibit liver steatosis via a variety of mechanisms.[66,67,68,69] A recent study on the outcomes of various classes of oral antidiabetic drugs (OADs) on MASLD demonstrated that SGLT2 inhibitors might be preferred over other OADs (thiazolidinediones, DPP-4 inhibitors, and sulfonylureas) with respect to MASLD regression and composite liver-related outcomes using a well-established Korean nationwide cohort.[70] These findings also demonstrated more favorable outcomes associated with the use of SGLT2 inhibitors, including MASLD improvement, compared with thiazolidinediones.[71]

Peroxisome proliferator-activator receptor (PPAR) agonists

In several RCTs, pioglitazone, a thiazolidinedione which mainly activates PPAR- γ, has been shown to improve histological features of steatohepatitis,[72,73,74] without a clear effect on fibrosis regression even after prolonged (3-year) therapy with pioglitazone.[73] The clinical use of pioglitazone is limited due to availability of newer antidiabetic agents and side effects, such as the risk of fluid retention, heart failure, weight gain, risk of bladder cancer and a potential increase in bone fractures.[75,76,77]

Saroglitazar, a dual PPAR α/γ agonist, enhances β-oxidation of fatty acids, reduces triglyceride levels, improves insulin sensitivity and glucose uptake.[78,79] Saroglitazar was first approved in in 2013 for the management of diabetic dyslipidemia and in 2020, it received approval for MASLD and non-cirrhotic MASH by DCGI in India.[80] In patients with MASLD, saroglitazar has been shown positive benefits in glycemic control and lipid profile, along with reduction of liver fat, fibrosis and elevated liver enzymes in various studies.[81-84]

Metformin, dipeptidyl peptidase-4 inhibitors

Clinical studies demonstrated that metformin reduces liver enzymes and improves insulin sensitivity.[85-89] Currently, there is no actual evidence shows that the use of metformin shows that the use of metformin alone can improve histology in MASH.[30,89] Observational and case-control studies showed that, in people with T2D and MASLD-related advanced fibrosis or cirrhosis, metformin may improve transplant-free survival, and reduce the risk of primary liver and extrahepatic cancer.[90,91] Metformin contributes to intestinal barrier integrity and prevents bacteria translocation from the gut to the bloodstream, it may have a role in preventing hepatic encephalopathy.[89] Metformin can be used in adults with compensated cirrhosis and preserved renal function but should not be used in adults with decompensated cirrhosis, especially when there is concomitant renal impairment, because of the risk of lactic acidosis.[30]

Given the lack of efficacy data, dipeptidyl peptidase-4 inhibitors,[92] alpha-glucosidase inhibitors, and insulin are not recommended for the treatment of MASLD. However, these anti-hyperglycemic drugs can be tailored for hyperglycemia among people with T2DM and MASLD.[93]

Therapy targeting cardiovascular disease risk reduction:

Currently, CVD remains the leading cause of death in patients with MASLD. Due to the close association between MASLD and cardiovascular disease, regular evaluation of CVD risk factors is crucial. CVD risk factors should be screened for regularly and treated aggressively, focusing on lipid-lowering agents, smoking cessation, treatment of hypertension, glycemic control in patients with diabetes and weight loss through diet changes and exercise. SGLT2 is and GLP-1 RAs both offer cardiovascular benefits and support weight reduction, positioning them as encouraging therapeutic options for individuals with N2DM and cardiovascular disease risk.[94]

Lipid-lowering Drugs

Dyslipidemia affects approximately 60-70% of those with MASLD.[95] Moderate-intensity to high-intensity statins are the first line treatment of dyslipidemia in MASLD based on lipid risk levels and atherosclerotic CVD risk scores. Statins seem to be under-prescribed and several studies have shown a favorable safety profile for the use of statins in MASLD.[96-98] Moderately elevated transaminases should not preclude initiation of statins in MASLD. Except for decompensated cirrhosis, patients with all other stages of MASLD, including transplant, should be optimally treated. In the context of hypertriglyceridemia, the use of TG-lowering medications, such as fibrates, is advisable in cases of severe hypertriglyceridemia (fasting TG level ≥ 500 mg/dL).[99] There is a large but nevertheless inconsistent body of evidence supporting the use of omega-3 fatty acids in MASLD.[100] Non-statin medications are to be used as adjuncts when treatment goals are not achieved with statins, or in cases of statin intolerance.[101]

Anti-hypertensive drugs

A high prevalence of MASLD was observed among patients with hypertension and vice versa.[102-104] Lowering blood pressure is also vital to reduce CVD risk. The preferred agents with proven cardiovascular benefits are drugs that block the renin–angiotensin–aldosterone system (RAAS).[102] Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to exert protective effects against liver fibrosis.[105] Although several studies indicated the beneficial effects of these drugs, the current evidence is insufficient to support the efficacy of RAAS blockers in managing fibrosis in MASLD patients.

Management of MASLD: Bariatric surgery

Bariatric surgery has long-term beneficial effects on the liver and is associated with remission of T2DM and improvement of cardiometabolic risk factors. In the setting of obesity class III (BMI ≥40 kg/m2) or obesity class II (BMI ≥35 kg/m2) and comorbidities (T2DM or pre-DM, uncontrolled hypertension, osteoarthritis, polycystic ovarian syndrome, or sleep apnea), bariatric surgery should be considered, especially for patients at high or very high risk of CVD.[106]

Management of MASH-related cirrhosis

Once the patients develop cirrhosis, treatment should focus on preventing hepatic decompensation and managing complications of cirrhosis, including management of portal hypertension, sarcopenia and monitoring for hepatocellular carcinoma (HCC). Liver transplantation is the definitive treatment for end-stage MASH-related decompensated cirrhosis and/or HCC.[46] In adults with compensated advanced chronic liver disease but LSM ≥20 kPa and/or platelet count <150 × 109/L, an upper gastrointestinal endoscopy should be performed to screen for varices. may be considered for HCC surveillance. Surveillance with 6-monthly ultrasound examination of the liver with or without serum alpha-fetoprotein level is recommended in patients with advanced fibrosis or ≥F3 fibrosis with LSM-VCTE ≥16.1 kPa.[30]

Conclusion:

MASLD is one of the common liver diseases and is the leading cause of liver-related morbidity and mortality. It is commonly associated with metabolic syndrome such as obesity, dyslipidemia, and insulin resistance. Early diagnosis and management of comorbidities are essential to prevent disease progression. A multidisciplinary approach involving hepatologists, endocrinologists, cardiologists, and nutritionists is essential for better patient outcomes. The management of the underlying metabolic disorders by lifestyle modification and weight loss is the cornerstone of the treatment of MASLD/MASH. Despite the limited number of MASH-specific drugs, some drugs used to treat the comorbidities have some potential efficacy in slowing down disease progression. Several MASH-specific drugs are on the horizon and will likely change our management in the near future.

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