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Review

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Prevention and control of risk factors in metabolic and alcohol-associated steatotic liver disease

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Abstract

Steatotic liver disease (SLD), including metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD), is the primary cause of illness and mortality. In particular, MASLD affects more than 30% of the global population, while ALD accounts for 5.1% of all diseases and injuries worldwide. The SLD spectrum includes a variety of clinical conditions, from mild fatty liver and inflammation to different stages of liver fibrosis. Additionally, both conditions (MASLD and ALD) can be complicated by hepatocellular carcinoma (HCC), while around one-third of ALD patients can also develop at least one alcohol associated hepatitis (AH) episode. Both of these diseases are also associated with multiple extrahepatic complications, such as cardiovascular disease, chronic kidney disease, and malignancies. In MASLD, the rapid rise in global obesity and

type 2 diabetes mellitus (T2DM) prevalence due to Westernized lifestyles has led to an increase in the prevalence of MASLD. Thus, the prevention and control of cardiometabolic risk factors (CMRFs) are the cornerstone of its treatment. Hypertension and atherogenic dyslipidemia are also important CMRFs associated with MASLD. Susceptible individuals with MASLD are adversely affected by even a small amount of alcohol consumption (though there is no agreed definition of a small amount), increasing the risk of severe outcomes and a faster progression of liver disease. This review explores factors that play a role in the development of SLD, especially focusing on the management of CMRFs and levels of alcohol use to prevent liver disease progression.

Keywords: Alcohol, alcohol use disorder, metabolic dysfunction-associated steatotic liver disease, alcohol-associated liver disease (ALD)

INTRODUCTION

Steatotic liver disease (SLD) represents the leading cause of chronic liver disease worldwide, especially in Western countries[1]. SLD encompasses several conditions, including metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD with increased alcohol intake (MetALD), alcohol-associated liver disease (ALD), etiology-specific entities [i.e., drug-induced liver injury (DILI) or monogenic diseases], and finally cryptogenic steatotic liver disease[2,3]. The common feature of these conditions is the presence of liver steatosis due to the identification of triglyceride deposits within the liver[4]. Liver steatosis is classically defined as the pathological identification of intrahepatic fat, which accounts for at least 5% of the liver weight and is graded based on the percentage of the fat fraction within the hepatocytes. Grade 0 represents a healthy state (< 5%), grade 1 indicates mild steatosis (5%-33%), grade 2 represents moderate steatosis (34%-66%), and grade 3 represents severe steatosis (> 66%)[5].

MASLD is extremely common in adults, affecting up to 30% of the global population, and is closely linked to the rising prevalence of obesity worldwide[6]. The previous terminology non-alcohol-associated fatty liver disease (NAFLD) was replaced by this new MASLD definition to avoid stigmatization. According to the latest 2023 criteria, MASLD is characterized by the presence of liver steatosis +/- one of five cardiometabolic risk factors[3]: (1) Increase in body mass index (BMI) or waist circumference; (2) Impaired glucose metabolism; (3) High blood pressure; (4) Elevated triglyceride levels; and (5) Low high-density lipoprotein (HDL) cholesterol levels. This new definition excludes other specific etiologies and acknowledges an average alcohol use lower than 140 and 210 grams in women and men, respectively. Therefore, the prevention and management of MASLD requires the identification of these cardiometabolic risk factors (CMRFs), which are essential for its diagnosis. The occurrence of obesity and type 2 diabetes mellitus (T2DM) is predicted to increase rapidly due to Westernized lifestyles, leading to a greater burden of MASLD. Hypertension and atherogenic dyslipidemia are also important cardiovascular risk factors often associated with MASLD[7]. Individuals who are susceptible to MASLD may also experience additional negative effects even from low amounts of alcohol consumption.

ALD accounts for 5.1% of all diseases and injuries worldwide, which is probably an underestimation. In 2016, it contributed to 50% of the estimated liver disease deaths for age groups above 15 years, making it the leading cause of cirrhosis in Western countries[8]. Due to increased alcohol and substance use during the COVID-19 pandemic, the rates of ALD are expected to rise[9]. If an individual consumes an excessive amount of alcohol, specifically more than 60 grams per day for two weeks, over 90% of patients will likely be diagnosed with steatosis[10]. Alcohol is known to worsen the effects of MASLD strongly and further increases the risk of poor liver-related outcomes[11]. Recognizing this association, MetALD is a newly coined term for individuals who consume high amounts of alcohol per week (140 g/week in females and 210 g/week in males) and also meet the MASLD criteria. This combination of alcohol and metabolic risk factors exacerbates the progression of SLD[12].

Efforts in disease prevention for SLD are fundamentally grounded in identifying their risk factors and implementing corresponding control measures. However, the complexity lies in the diverse array of global risk factors associated with MASLD and ALD, posing a challenge to solicit uniform recommendations. Effective mitigation of these risk factors requires a multidisciplinary team, including hepatologists, gastroenterologists, psychologists, addiction specialists, behavioral therapists, and nutritionists. It is recommended that these professionals have expertise in metabolic syndromes and associated complications. Additionally, the engagement of public health experts, patient groups, advocacy organizations, and policymakers is indispensable for advancing progress in this field.

As our understanding of the contributory role of alcohol and metabolic risk factors in progressive liver disease evolves, it becomes imperative for clinicians to promptly identify SLD and administer appropriate treatment to avert severe health consequences for patients. This review aims to shed light on MALSD, ALD, and MetALD, while also exploring strategies for preventing and managing risk factors, all with the overarching objective of alleviating the burden of liver disease.

EPIDEMIOLOGY OF STEATOTIC LIVER DISEASE

Metabolic dysfunction-associated steatotic liver disease

The prevalence of MASLD worldwide has significantly increased over time, with an overall prevalence estimated at 32.4%, higher in men (39.7%) than in women (25.6%), and an overall incidence of 46.9 cases per 1000 person-years, markedly higher in men compared to women[13]. Globally, the highest prevalence is noted in countries within the Middle East and South America[14]. The prevalence of MASLD is increasing concurrently with the global obesity epidemic. Among patients with T2DM, the prevalence of MASLD is notably elevated, surpassing 55%[15]. Among patients with MASLD, approximately 21% will have metabolic-associated steatohepatitis (MASH), which represents an inflammatory and progressive phenotype of MASLD.

Alcohol-associated liver disease

Alcohol-associated Liver Disease is a significant factor in liver-related health risks that result in morbidity, disability, and death on a global scale. It is prevalent in populations with high alcohol consumption rates. This disease encompasses a range of liver impairments, with studies indicating that more than 90% of individuals who consume alcohol heavily develop fatty liver, 10%-35% experience alcoholic hepatitis, and 8%-20% ultimately progress to cirrhosis[16]. Between 2005 and 2016, global alcohol per-capita consumption increased from 5.5 to 6.4 liters, with further projections to reach 7.6 liters by 2030. In 2019, approximately 25% of global cirrhosis deaths were linked to alcohol, and alcohol was associated with about one-fifth of global hepatocellular carcinoma-related deaths[17].

MetALD

Metabolic and Alcohol-associated Liver Disease refers to the presence of both alcohol-induced liver damage and metabolic syndrome (MetS). MetS is characterized by obesity, diabetes, hypertension, and dyslipidemia. This combination of factors can accelerate the progression of liver disease. This recently termed condition currently lacks a known global prevalence. Recently, a study that made use of the NHANES database suggested a potential population-level prevalence of 2.56% in the United States. Further research on the epidemiology, prevalence, and incidence of MetALD liver disease is warranted[12].

STEATOTIC LIVER DISEASE - PATHOPHYSIOLOGY

Various factors contribute to the pathogenesis and development of steatotic liver disease, collectively driving disease progression to different extents. The factors include free fatty acids (FFAs) and their oxidation, reactive oxygen species, genetics, epigenetics, the innate immune system, gut-derived endotoxins, intestinal dysbiosis, and small intestinal bacterial overgrowth (SIBO) [Figure 1][8].

It is relevant to mention the role of environmental pollutants, including microplastics, and also the misuse of antibiotics, which are emerging as significant risk factors for liver diseases such as MASLD, ALD, and MetALD. Microplastics, which are found in human tissues, can induce liver inflammation and oxidative stress, potentially leading to fibrosis and liver disease[18]. Antibiotic overuse disrupts the gut microbiome, increasing gut permeability and promoting liver inflammation and metabolic dysfunction, which are precursors to fatty liver diseases[19]. Collectively, all of these factors contribute to the risk of liver disease, highlighting the importance of rigorous monitoring, prevention, and mitigation strategies.

MASLD

The pathophysiology of MASLD is complex and multifactorial. It involves insulin resistance, dysregulated lipid metabolism, oxidative stress, inflammation, and genetic factors. Insulin resistance results in increased breakdown of fat in adipose tissue, which leads to a rise in the levels of free fatty acids (FFAs) in the liver. Elevated FFAs, impaired β-oxidation, and increased spontaneous lipogenesis can result in hepatic steatosis. Hyperinsulinemia also stimulates the expression of lipogenic enzymes, further enhancing lipid synthesis in the liver. The accumulation of FFAs in hepatocytes increases oxidative stress, which generates reactive oxygen species (ROS). These ROS contribute to mitochondrial dysfunction, exacerbating liver injury and promoting inflammation and fibrosis[20]. Pro-inflammatory cytokines from activated Kupffer cells and hormones from adipose tissue, such as adiponectin and leptin, also play a role in modulating liver inflammation and fibrosis. It is worth noting that the changes in gut microbiota contents (dysbiosis) can increase intestinal permeability, allowing endotoxins (e.g., lipopolysaccharides, methanol) to translocate to the liver and further contribute to hepatic inflammation and fibrosis. Genes are key factors in the predisposition and development of MASLD. Currently, gene variants PNPLA3 148M, TM6SF2 E167K, and MBOAT7 are major factors of differences in liver steatosis and susceptibility to progressive MASLD among individuals. PNPLA3 also directly affects hepatic stellate cells and retinol metabolism. These novel findings suggest that the accumulation of neutral lipids in hepatocytes is deleterious to the liver[21]. Genetic factors play a role in the development, worsening, and disease consequences of ALD. Epidemiological analysis completed among a genetic component is strongly supported by evidence within families and between twins[22]. Therefore, counseling family members could potentially play a role in preventing complications. Non-modifiable risk factors, such as being over the age of 40, male gender, and having genetic factors, are recognized as significant contributors that can enhance the likelihood or severity of MASLD/ALD. It is recommended that individuals with multiple metabolic risk factors undergo family screening. To mitigate the progression and complications of this disease, it is crucial to implement comprehensive management strategies that focus on both metabolic control and liver health.

ALD

ALD development and mortality are closely linked to alcohol consumption levels. Recent studies have shown that consuming over two standard drinks per day for females and over three for males significantly increases the chance of liver cirrhosis morbidity[23,24]. Chronic heavy drinking ushers to cellular injury through immediate and indirect harmful consequences of alcohol and its metabolite, acetaldehyde, resulting in immune responses and structural and functional alterations in proteins, phospholipids, and nucleic acids. Alcohol metabolism further contributes to oxidative stress, DNA damage, and inflammation, with factors such as daily consumption, fasting drinking, and binge drinking exacerbating the risk[25]. Moreover, genetic

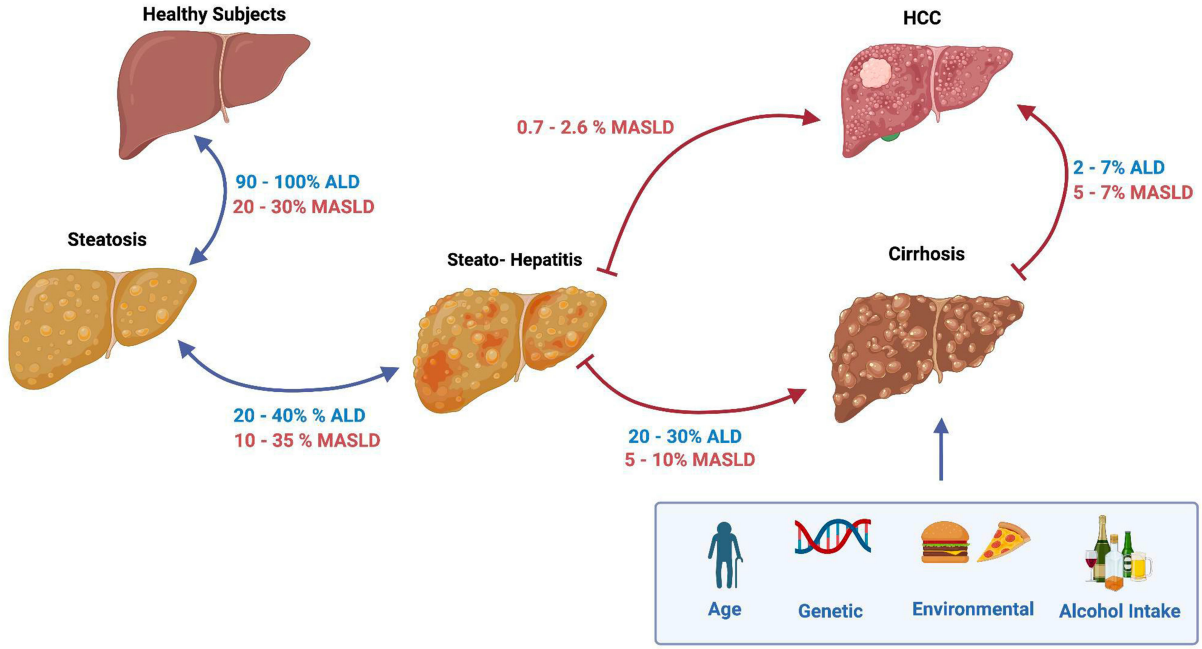

Figure 1. Pathogenesis spectrum of MASLD and ALD leading to HCC. The accumulation of fat in a healthy liver can cause steatosis. Most individuals who engage in heavy alcohol consumption develop fatty liver. Steatosis can be alcohol-associated or metabolic dysfunction-associated, depending on the cause. This condition can lead to inflammation and fibrosis in nearly one-third of patients with ALD/MASLD. Steatohepatitis can be reversed by abstaining from alcohol, making lifestyle changes, and adjusting one's diet. If fibrogenesis continues, it can lead to cirrhosis and eventually to HCC. The development of end-stage liver disease may be amplified at any stage by factors such as older age, genetic, and environmental factors, including alcohol intake. MASLD: Metabolic-associated steatotic liver disease; ALD: alcohol-associated liver disease; HCC: hepatocellular cancer.

ancestry and sex can modify the risk and severity of ALD, with certain polymorphisms identified as modifiers of ALD progression, although further research is needed for confirmation[26].

Additionally, cultural influences, environmental factors, and diet play roles in ALD development and severity. Despite the toxic effects of alcohol, only a minority of patients with continued excessive consumption develop alcohol-related liver cirrhosis, suggesting that further risk factors need to be elucidated[25]. The effect of smoking on the development and progression of MASLD has been controversial; a systematic review and meta-analysis of 20 observational studies demonstrated a significant association between smoking and MASLD[27], and recent animal studies have provided robust evidence supporting the notion that nicotine either promotes the development of MASLD or hastens its progression[28].

During pregnancy, physiological stress is marked by heightened accumulation of visceral adiposity and increased hepatic lipid accumulation. This combination significantly amplifies the risk of developing metabolic complications, including diabetes mellitus (DM) and hepatic insulin resistance[29].

MetALD

Initial studies yielded controversial findings, with some suggesting that light to moderate alcohol intake might confer protection against the development of progressive liver disease[30,31]. However, all completed studies were retrospective. Recently, the effect of moderate alcohol consumption on MASLD has been further studied. Individuals with significant fibrosis progression were found to have higher alcohol consumption levels via biomarker PEth evaluation[31]. These findings underscore the potential risk of fibrosis progression in MASLD patients consuming moderate amounts of alcohol and highlight the importance of PEth as a biomarker for assessing and identifying harmful alcohol consumption in MASLD.

In the MetALD spectrum, there exists a spectrum where the contribution of MASLD and ALD will alter across it. An important point to remark is the gut microbiota. The microbiota of the gut is a complex collection of microorganisms residing in the gastrointestinal tract and has been increasingly incriminated in the evolution and progression of liver diseases such as MASLD and ALD. One of the significant mechanisms by which the gut microbiota influences liver health is through the production of endogenous ethanol. This can take place when gut dysbiosis, or the imbalance of gut microbiota, can lead to raised intestinal permeability. This allows endotoxins and other microbial metabolites, including ethanol, to enter the bloodstream and reach the liver, where they can cause inflammation and liver damage. Studies have shown that dysfunctional gut microbiota activates multiple pathways in the liver, sustaining hepatic inflammation and contributing to the pathogenesis of MASLD[32]. Specific gut bacteria such as Limosilactobacillus fermentum, Enterocloster bolteae, and Streptococcus mutans have been identified as ethanol producers. Increased fecal ethanol concentrations have been observed in patients with MASH[33]. These findings suggest that the gut microbiota's capacity to produce ethanol plays a prominent role in the advancement of liver illness[34]. In MASLD, the interplay between gut microbiota and liver metabolism is pivotal. Endogenous ethanol exacerbates liver inflammation and steatosis, similar to the effects observed in ALD due to external alcohol consumption[35]. Thus, targeting gut microbiota and reducing endogenous ethanol production could be a therapeutic strategy for managing MASLD and preventing its progression to more severe forms like MASH[34].

MANAGEMENT OF STEATOTIC LIVER DISEASE

It is crucial to consider the overlap between MASLD and ALD, as both diseases can coexist and progress to hepatic outcomes in a related fashion. Age, genetic predisposition, and exposure to environmental factors (such as diet, sedentary lifestyle, and alcohol use) can lead to more advanced liver disease [Figure 1] through the activation of inflammatory and fibrogenic signals[2]. Along with prioritizing the diagnosis and treatment of patients in clinical settings, community-level interventions should also be implemented. This includes raising awareness, improving screening practices, and advocating for early diagnosis and treatment. Our approach encompasses both non-pharmacological and pharmacological methods to effectively control the development and advancement of MASLD and ALD.

Management: lifestyle and behavioral management

MASLD

Lifestyle modifications - weight loss

One method to reduce liver steatosis in patients with MASLD is through weight loss. It is recommended to create an energy deficit of 500-1,000 kcal per day, resulting in a loss of approximately 1 kg/week. It is important to note that individuals in a weight loss program should consume an adequate amount of protein and engage in resistance exercise to prevent muscle loss[7]. Most studies support a Mediterranean-style diet with high protein intake, while avoiding beverages containing fructose and foods with saturated fatty acids[6]. People should be encouraged to consume fruits, vegetables, whole grains, beans, and legumes throughout the day, along with omega-3 fatty acids such as extra virgin olive oil, nuts, and seeds. Excessive sugar and refined carbohydrates should be limited, as they can worsen steatosis. In cases where weight loss is difficult to achieve, other options such as bariatric surgery and intragastric balloons demonstrated promise in improving liver fat content[36]. A systematic review found that bariatric surgery resolves fibrosis in 40% of patients with morbid obesity who have not responded to conventional approaches through lifestyle modifications and medications[37].

Coffee consumption

Regularly drinking two to three cups of coffee daily has been shown to decrease the risk of hepatic fibrosis. Studies indicate that people with existing liver conditions who drink > 2 coffee cups per day have a lower incidence of fibrosis and cirrhosis. They also have reduced rates of hepatocellular carcinoma and lower mortality rates[8]. This evidence applies to different causes of liver disease, including viral hepatitis and metabolic liver disease. A strong positive association was found between consuming ≥ 2 cups of coffee per day and a lower chance of advanced liver fibrosis in patients with MASLD[9].

Physical activity

Engaging in moderate-intensity aerobic physical activities, such as brisk walking and stationary cycling for a weekly total of 150-200 min in 3-5 sessions, along with 45 min of resistance training three times a week, is beneficial. Additionally, incorporating 75 min of vigorous-intensity aerobic exercise per week can help improve hepatic steatosis and reduce the predisposition to heart outcomes[38]. Losing weight and exercise have been found to be associated with long-term improvements in liver enzymes, histology, serum insulin levels, and overall quality of life in patients with MASLD. In patients with MASLD who are overweight or obese, reducing their body weight by 3% to 5% can help decrease steatosis, while a weight loss of 7% and 10%, respectively, can lead to regression of MASH and fibrosis[39]. Additionally, adopting these lifestyle changes can also help reduce the risk of developing other health conditions that are associated with metabolic syndrome, including cardiovascular disease (CVD).

Pharmacological therapies for the prevention of MASLD progression

Several drugs targeting different pathways in disease development are currently being investigated, although only a few have confirmed their effectiveness so far. There is no currently licensed therapy for MASLD[30] despite numerous clinical trials. The successful intake of glucose-lowering drugs in patients with MASLD and T2DM has provided some understanding of their effectiveness in resolving steatosis, improving inflammation, impacting fibrosis, and providing additional cardiac benefits. In this review article, we have chosen a few medications that may have potential benefits in treating MASLD.

In meta-analyses, it was found that patients with T2DM who took metformin experienced a significant 62% reduction in the risk of developing liver cancer[40]. The other drugs with a benefit in reducing cancer risk are statins. Observational studies have shown that statins reduce the risk of HCC, with an odds ratio of 0.63[41]. Statins are considered to have hepatoprotective effects in addition to lipid-lowering benefits. Multiple studies have shown that statins can also be given safely in patients with cirrhosis. A large UK-based study has shown that statins have a notable effect on reducing the incidence of hepatocellular carcinoma and liver-related mortality. The effect was significant in the prevention of fatty liver disease. Hence, statins should be provided to individuals with clinical indications to prevent CVD outcomes, irrespective of the stage of liver disease[42].

Vitamin E 800 IU/day has shown benefits in improving steatosis in patients with MASH (biopsy proven) who do not have type 2 diabetes or cirrhosis (Not recommended in type 2 DM due to lack of evidence). However, its effect on resolving MASH and improving fibrosis has yet to be proven[43]. Pioglitazone, on the other hand, is a class of drugs approved for T2DM and can be used in patients with biopsy-proven MASH, with or without T2DM. It has been shown to improve steatosis, activity, and resolution of MASH, but its impact on fibrosis remains uncertain[44]. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors improve the serum levels of liver enzymes, decrease liver fat and fibrosis, and have additional beneficial effects on various metabolic parameters such as obesity, insulin resistance, glycemia, and lipid parameters in type 2 diabetes patients with MASLD. They also reduce the deposition of collagen and the expression of

inflammatory cytokines in the liver. However, caution should be exercised when prescribing such drugs, as 17% of patients taking SGLT-2 inhibitors develop adverse events such as ketoacidosis, dizziness, and acute kidney injury, and more than 40% of them experience genitourinary tract infections. No serious adverse effects were reported[45]. SGLT-2 inhibitors help improve liver steatosis by stimulating glucagon secretion from the pancreatic α cells, which, in turn, stimulates gluconeogenesis and β-oxidation of fatty acids in the liver through the activation of peroxisome proliferator-activated receptor alpha and carnitine palmitoyl transferase-1[46].

The incretin hormone known as glucagon-like peptide (GLP-1) plays a role in controlling satiety, gastric emptying, and blood sugar levels. GLP-1 receptor agonists (GLP-1RAs) have been approved for managing diabetes and obesity. In a small trial with liraglutide[54] and a larger Phase 2 trial with semaglutide[47], both drugs demonstrated positive effects in resolving MASH. Liraglutide is administered at a dose of 1.8 mg subcutaneously daily for T2DM and 0.6-3 mg subcutaneously daily for obesity[48]. Semaglutide, on the other hand, is given at a dose of 0.4 mg subcutaneously daily or 0.25-2.4 mg subcutaneously weekly. Both drugs can also be used in MASH patients without cirrhosis. They have shown improvement in steatosis and resolution of inflammation, but their effect on fibrosis has not been established, although Semaglutide may slow down fibrosis regression[47]. Additionally, Pioglitazone[44], Liraglutide, and Semaglutide have the added benefit of cardiac protection[49].

Another potential benefit of pharmacological therapies is improving intestinal permeability. Administration of 24 μg of Lubiprostone orally twice daily for 48 weeks has shown a greater reduction in fat quantity by MRI-PDFF, and it was well tolerated; however, no improvement in liver stiffness was detected[50].

Aspirin exerts anti-inflammatory and antitumor effects on the liver. Even though larger, longer-term trials are important, in a 6-month trial, daily intake of 81 mg of aspirin significantly decreased hepatic steatosis as well as markers associated with hepatic inflammation and fibrosis. This is an additional potential benefit in individuals who are already taking low-dose ASA for CVD protection[51].

Treatment with SGLT-2i drugs, like empagliflozin, appears to cause slight weight loss, and significant reductions in liver fat content (a decrease of over 20% relative). Additionally, it may reduce the risk of fibrosis progression[52]. Importantly, SGLT-2i possess significant cardiorenal protective effects, as they are strongly associated with decreased overall mortality rates, as well as reduced cardiovascular mortality rates[53].

PPARs are nuclear receptors acting as lipid sensors, naturally activated by fatty acids or derivatives. PPARs exert pleiotropic effects on metabolism and immunomodulation. Lanifibranor, a pan-PPAR agonist, has demonstrated efficacy in various preclinical models of MASH. Specifically, it has exhibited the ability to ameliorate liver histology, including fibrosis, as well as facilitate weight loss and enhance glucose and lipid profile[54]. Saroglitazar is a dual agonist for PPAR-α/γ, which both promotes insulin resistance and protects against atherogenic dyslipidemia. This action leads to a decrease in small dense LDL and triglycerides[55].

One of the major advances in the management of MASLD/MASH is the approval of Resmetirom, the primary medication to get the U.S. Food and Drug Administration (FDA) approval in 2024[56]. Resmetirom selectively targets the thyroid hormone receptor-β in the liver, which enhances hepatic fatty acid oxidation, reduces lipogenesis, and improves lipid profiles. The drug is also well-tolerated with a favorable safety profile. However, it is not yet widely available, very expensive, and is a weight-neutral drug. Its clinical implementation of liver fibrosis assessment encounters challenges in patient selection and monitoring

treatment response. Non-invasive tests will play a crucial role in this process. Resmetirom has shown an acceptable safety profile, with only mild gastrointestinal adverse events being the most prevalent. However, long-term surveillance is necessary to monitor potential risks associated with thyroid, gonadal, or bone diseases[57]. We have included a table showing major advances in the field of MASLD [Table 1].

Alcohol

Alcohol is a main cause of preventable liver disease. Alcohol contributes to almost half of the morbidity and mortality observed in patients suffering from liver cirrhosis. Significant enhancement in health outcomes would be anticipated in the absence of alcohol[8]. The definition of low-risk drinking, according to WHO, is consumption of less than 40 grams per day for men and less than 20 grams per day for women. This is equivalent to consuming less than 280 grams per week for men and less than 140 grams per week for women[58]. However, even light (≤ 10 g/day) to moderate (≤ 30 g/day) alcohol intake may have a detrimental effect on the development of progressive fibrosis in MASLD[3,58]

Patients with concomitant MASLD and ALD (newly defined as MetALD) have a worse prognosis in terms of progression to cirrhosis and HCC. These patients also have a higher risk of CVD compared to patients with isolated MASLD. The synergistic impact of alcohol consumption in combination with cardiometabolic risk factors exacerbates the development of CVD and contributes to increased mortality rates associated with this condition[59].

The factor that worsens the progression of ALD is the development of untreated alcohol use disorder (AUD). In individuals who are otherwise healthy and have no metabolic factors linked to the disease, consuming more than 3 standard drinks per day for men and more than 2 drinks per day for women raises the chances of developing liver disease. It is important to understand that even small amounts of alcohol can pose a danger to individuals with underlying liver disease, metabolic risk factors, or who have undergone liver transplantation. In fact, mounting evidence suggests that no level of alcohol consumption can be considered entirely safe. Another often overlooked form of drinking is binge drinking, which also has negative effects on overall health and contributes to half of the yearly alcohol-related deaths[60].

In both patients with early and severe ALD, the most effective therapeutic measure to reduce long-term morbidity and mortality is prolonged abstinence. Abstinence is associated with improved life expectancy and a chance of recompensation has been documented in some studies[61]. A multidisciplinary team including hepatologists, gastroenterologists, nutritionists, psychologists, and addiction specialists is recommended to manage patients with AUD in patients with ALD.

Pharmacological therapies for AUD

There are three medications approved by FDA that can assist individuals in quitting or reducing their alcohol consumption and also prevent relapse. These medications are naltrexone (available in oral and long-acting injectable forms), acamprosate, and disulfiram. It is important to note that these medications are not addictive, habit-forming, or mood-altering. They do not develop tolerance with continued use, and there is no rebound effect when discontinued. They work by either restoring normal functioning in alcohol-altered neurophysiological processes or by reducing the rewarding effects of alcohol. Meta-analyses have shown a significant benefit in quitting in individuals who took a 6-month duration of therapy[62].

Naltrexone is an opioid antagonist that alters dopamine release following alcohol use. Hence, it is thought to help with craving and alcohol-associated euphoria[62]. Both oral and injectable forms of naltrexone decrease a return to any drinking and a return to heavy drinking outcomes. Naltrexone may also be helpful for binge

Table 1. Key Landmark studies and advances in the prevention and management of MASLD

1836	1980	2005	2007-2010	2010	2010-2015	2024
Addison was the first to describe fatty liver	The term NASH was coined by Ludwig	Genomic/proteomic analysis to obesity-related NAFLD	The first NAFLD guideline by the APASL 2008: PPARs as key role in regulating steatogenesis	PIVENS TRIAL	Role of the microbiome in the pathogenesis of fatty liver disease 2012, the first comprehensive guideline by AASLD, ACG, and AGA	MASLD. MASH, MetALD replacing the stigmatizing term NAFLD, and NASH
	NASH		2009: first evidence that NAFLD is associated with gut permeability	Fibrosis predicts outcome		Resmetirom: the first drug to receive FDA approval

MASLD: Metabolic-associated steatotic liver disease; NASH: non-alcoholic steatohepatitis; NAFLD: non-alcoholic fatty liver disease; APASL: Asian Pacific Association Study of the liver; PPARs; peroxisome proliferator-activated receptors; MASH: metabolic-associated steatohepatitis; MetALD: metabolic and alcohol-associated liver disease; FDA: the U.S. Food and Drug Administration.

drinkers, as taking the drug one hour prior to drinking decreases the reward of any cravings for alcohol, thereby improving drinking outcomes[63]. It can be taken as a 50-mg daily or a monthly injection (380 mg) or in a targeted fashion. It is contraindicated in patients who are on opioids. As naltrexone is metabolized in the liver, it is also not recommended in those with severe liver disease[64].

Disulfiram is typically administered in a dosage of 500 mg daily during weeks 1-2, followed by a reduced dosage of 250 mg daily thereafter[62]. It should not be taken by individuals who are taking metronidazole, paraldehyde, or alcohol-containing preparations. It is important to note that disulfiram may cause various side effects, including neuropsychiatric manifestations, liver failure, and allergic dermatitis. Disulfiram inhibits the enzyme aldehyde dehydrogenase, and even small quantities of alcohol can lead to a rapid build-up of acetaldehyde, resulting in flushing, nausea, and vomiting. This acute physical distress helps decrease drinking and break the cycle of binge intoxication. Individuals should be advised to avoid consuming alcohol for a minimum of 12 h prior to taking disulfiram. This drug should be considered after discussion of the potential harms and in individuals who failed naltrexone or acamprosate therapies[65].

The third FDA-approved medication for AUD is acamprosate. Acamprosate is an oral medication that acts centrally and the recommended dosage is two 333 mg tablets taken three times a day. While generally safe, some patients may experience watery diarrhea as a side effect. It works by restoring homeostasis in N-methyl-D-aspartate (NMDA)-mediated glutamatergic neurotransmission. It takes approximately one week for acamprosate to reach steady-state levels in the nervous system. Studies have shown that its effects on drinking behavior can persist for up to one year after completing the treatment, which supports its role in restoring long-lasting homeostasis in brain glutamatergic activity. Acamprosate does not undergo liver metabolism and is not linked to liver damage[62].

Another important consideration is preventing relapse after liver transplantation (LT) for ALD. The definition of alcohol relapse after LT varies among different studies, and alcohol consumption is diagnosed based on information from family members, liver enzyme tests, carbohydrate-deficient transferrin[66], or urine alcohol measures. In a previous review, the authors discussed various measures used to assess AUD, including clinical history, serum, urine, or hair-based biomarkers[20]. Generally, direct measures of alcohol consumption have a higher specificity, reaching up to 100%, and a sensitivity of 62%-89%.

It is not uncommon for alcohol consumption to recur after LT, and 10% to 15% of those who have undergone LT return to heavy drinking, which can damage the new liver[67]. Most transplant centers no longer use the "6-month rule" to determine whether patients should undergo LT. This "6-mo rule" has simply never been shown to impact prognosis, sobriety, or survival. Studies have shown that individuals with ALD and those with other chronic causes of end-stage liver disease have similar survival rates after undergoing liver transplantation[66]. Relapse has been associated with unique histopathologic changes, graft loss, graft damage, and decreased survival. To resolve addiction issues and allow the liver to recover spontaneously, complete abstinence should be attempted[68]. Any drinking among post-LT patients is deleterious, and most international guidelines on ALD recommend complete abstinence[69].

On a global scale, different countries have shown that increased taxation and limitations on the hours of alcohol consumption can be effective in alcohol control. However, it is important to recognize that these measures may not be effective in countries where locally brewed alcohols are used as a measure of alcohol use. Therefore, country-level initiatives should consider cultural perspectives and be tailored to the specific policy measures that are proven to be effective in each country[70].

Pharmacological therapies for ALD

In patients with acute hepatitis, liver failure, or elevated liver enzymes ≥ 3 to 5 times normal, we suggest starting treatment with acamprosate. Baclofen is another option that has shown effectiveness in some trials, although not all, and is preferred by some practitioners[71]. Patients with decompensated liver disease should not take Naltrexone[49,72]. There has been limited progress in the management of ALD. Some drugs that have shown some success in AH treatment include corticosteroids, pentoxifylline, and N-acetylcysteine. These drugs have been administered to patients with AH and have been associated with short-term survival benefits. Currently, corticosteroids are the only known therapy that has been proven effective for patients with severe AH, with a survival benefit of 50%-60% of patients at 1 month[73].

In recent years, several studies have focused on liver regeneration, antioxidant effects, and modulation of the gut-liver axis in AH. These studies include the use of G-CSF, which has been shown to reduce the risk of death at 90 days compared to controls in a meta-analysis[74]. IL- 22 was associated with a significant decrease in MELD score, day-7 Lille score, cytokine inflammatory markers, and serum aminotransferases and an increase in regeneration markers at days 28 and 42 from baseline in a phase 2 clinical trial[75]. Another potential benefit for liver regeneration stimulants has been observed with Larsucosterol (DUR-928) in the AHFIRM study, where a phase 2 trial in moderate and severe AH patients showed an 89% overall response rate as measured by a Lille score of less than 0.45. All patients (n = 19) who have taken the drug have survived the 28-day study. A total of 14 subjects (74%), including 8 subjects (67%) with severe AH, were discharged within 72 h after receiving a single infusion[76].

MetALD

There is limited research on the management of MetALD. One study conducted in Japan showed a significant link between a decrease in BMI and the remission of MASLD/MetALD, regardless of gender. Therefore, weight loss seems to play a crucial role in managing MASLD/MetALD. Moreover, a significant association was confirmed between weight loss and MASLD/MetALD improvement in individuals having a BMI < 23 kg/m^2, suggesting that weight loss may be beneficial even for lean individuals[77]. Due to the limited available research, further investigation into the epidemiology of MetALD and the implementation of clinical trials to explore its management is recommended.

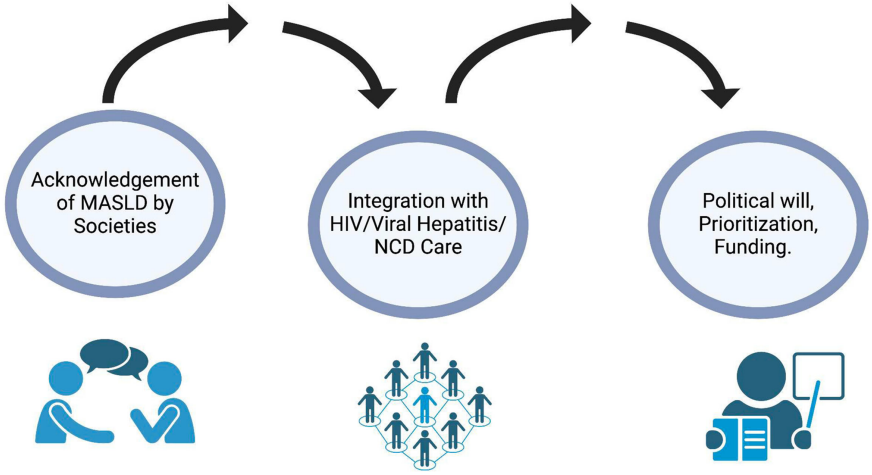

Figure 2. Strategic Roadmap for Prevention and Control of MASLD and ALD. Associations and international guidelines should acknowledge the definition of MASLD and recommend screening for patients with CMRFs. This screening should also integrate related conditions such as HIV, viral hepatitis, and other NCDs. Giving priority to active screening for ALD/AUD and MASLD is crucial, and advocating for their inclusion in the ICD is necessary. These efforts will hopefully generate political support, facilitate policy prioritization, and secure funding for prevention, control, and treatment trials. MASLD: Metabolic-associated steatotic liver disease; ALD: alcohol-associated liver disease; CMRFs: cardiometabolic risk factors; HIV: human immunodeficiency virus; NCDS: non-communicable diseases; AUD: alcohol use disorder; ICD: International Classification of Diseases.

CONCLUSION

Preventing and controlling risk factors for ALD and MASLD requires a comprehensive approach. It is important to recognize MASLD in societal guidelines, e.g., Diabetic associations, integration of care with viral hepatitis, human immunodeficiency virus (HIV), and other NCDs, and this could help push for political will, funding opportunities, and prioritization [Figure 2].

This approach should include implementing lifestyle changes, such as reducing alcohol consumption, maintaining a healthy diet, regularly monitoring health, and pharmacological interventions when necessary. By adopting these strategies, individuals can significantly lower their risk of developing ALD or MASLD and effectively manage any potential complications associated with these liver diseases. Public health campaigns and healthcare professionals play a crucial role in raising awareness, educating the public, and providing support to individuals who are working toward a healthier liver. It is important to establish specific policies that are tailored to the unique cultural practices and advertising regulations of each country regarding a healthy diet, alcohol abstinence, and the control of metabolic risk factors.

The management of ALD and MASLD presents significant challenges that require multifaceted strategies. Our comprehensive review underscores the critical need for an integrated approach that combines reducing alcohol consumption with lifestyle modifications, targeted pharmacological treatments, and robust public health campaigns to effectively mitigate these conditions.

Key strategies

Lifestyle modifications

The cornerstone of prevention for ALD and MASLD involves substantial lifestyle changes including dietary adjustments, increased physical activity, and a reduction in alcohol intake. These changes have proven effective in reducing the chances for progression to more severe stages.

Pharmacological interventions
Emerging treatments that target specific metabolic pathways offer promising prospects for managing MASLD and ALD. Continued research and development of these therapies are vital to improve outcomes for patients with these liver diseases.

Public health and policy
Strengthening public health campaigns that promote liver health and public education on the hazards of excessive alcohol consumption and unhealthy diets is imperative. Moreover, it is important to establish specific policies that are tailored to the unique cultural practices and advertising regulations of each country regarding a healthy diet, alcohol abstinence, and the control of metabolic risk factors.

Future research directions
There is a pressing need for ongoing research into the pathophysiological mechanisms of ALD and MASLD, as well as the development of more effective diagnostic tools and therapeutic options. Collaboration across disciplines and geographical boundaries will be essential to advance our understanding and treatment of these complex conditions.

By addressing these strategic imperatives, we can better equip healthcare providers, policymakers, and patients themselves with the tools and knowledge necessary to fight ALD and MASLD effectively. This holistic approach will not only reduce the prevalence of these liver diseases but also improve the quality of life for affected individuals across the globe.

DECLARATIONS

Authors' contributions
Conceptualization, investigation, writing - original draft, writing - review and editing: Desalegn H
Writing - review and editing: Farias R, Hudson D, Idalsoaga F, Cabrera D, Diaz LA
Conceptualization, writing - review, editing, and supervision: Arab JP

Availability of data and materials
The datasets generated and analyzed during the current study are not publicly available, but are available from the corresponding author upon reasonable request.

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All authors declared that there are no conflicts of interest.

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Not applicable.

Consent for publication
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