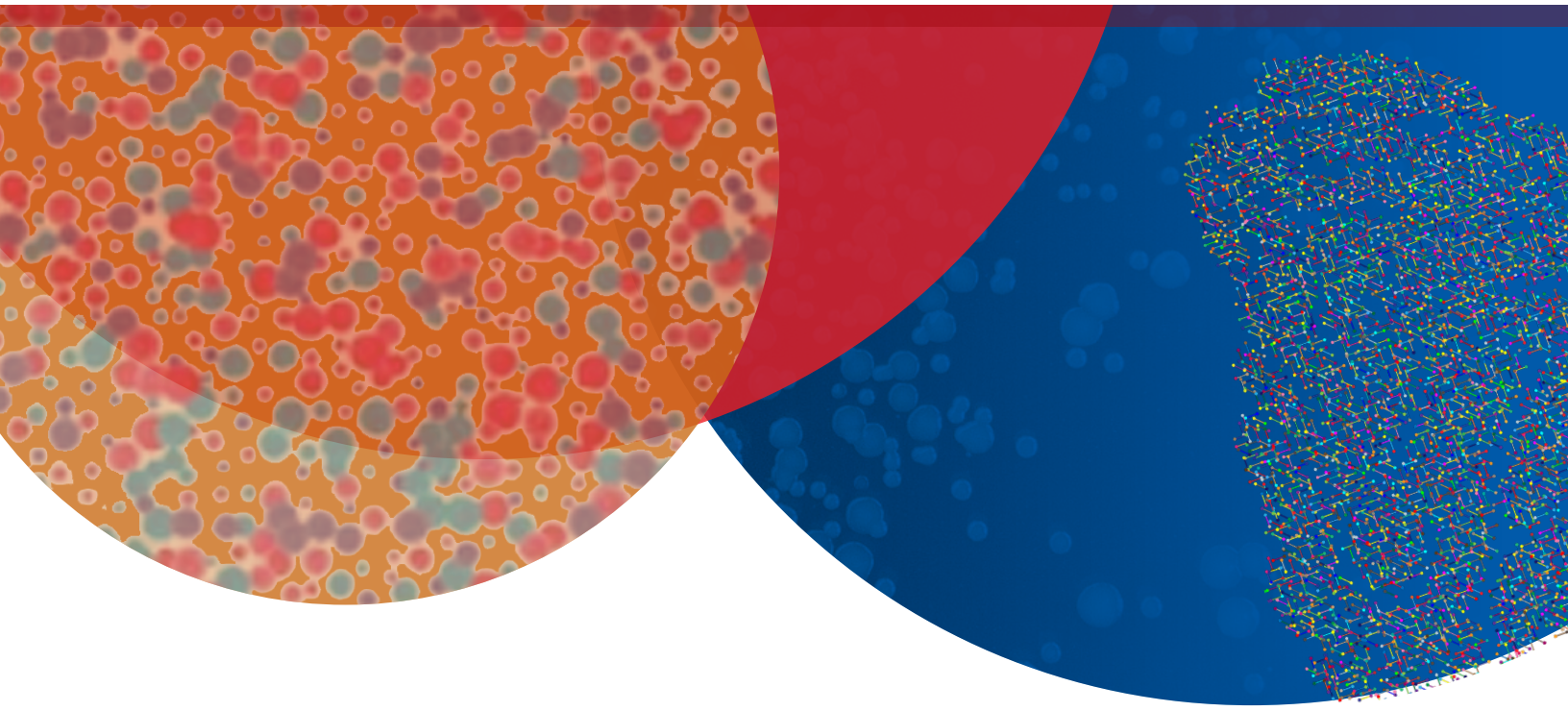
International Journal of

ATHEROGENIC DIABETIC DYSLIPIDEMIA



THIS ISSUE

Editor-in-Chief
Dr. Prof. Subhankar Chowdhury

VOLUME 5
ISSUE 1

Salubris

International Journal of

ATHEROGENIC DIABETIC DYSLIPIDEMIA

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VOLUME 5
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International Journal of ATHEROGENIC DIABETIC DYSLIPIDEMIA

Project Manager- Anirban Mukherjee

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About the Journal

Atherogenic dyslipidemia, characterized by elevated triglycerides (TGs), raised small dense LDL (low-density lipoprotein) levels and decreased HDL (high-density lipoprotein) cholesterol levels, is the most common pattern of dyslipidemia in type 2 diabetic patients. It is characteristically seen in patients with obesity, metabolic syndrome, insulin resistance, and T2DM and has emerged as an essential marker for the increased CVD risk observed in these populations. In fact, the combined presence of dyslipidemia and diabetes escalates the CV risk by 3–4 times.

Dyslipidemia, diabetes and hypertension are all a part of the cluster that includes nonalcoholic fatty liver disease (NAFLD) too, another major CVD risk factor. As diabetic dyslipidemia is characterized by hypertriglyceridemia, the risk of pancreatitis is also high in these patients.

With the increasing burden of these conditions in the world, clinicians can struggle to keep themselves updated in the advances in research and therapy.

With this journal, we aim to keep doctors updated in the current understanding, trends in therapy and new modalities of care. Our objective is:

- To be the knowledge partner for healthcare professionals by presenting contemporary research and novel treatment options in the field of atherogenic diabetic dyslipidemia.
- To raise awareness about the latest clinical practices, for better management of the condition, thus improving on the standards of overall disease management
- To provide researchers of the field with a medium to elicit like thought processes in their peers working on similar innovations or experiments
- To provide clinicians with a platform to showcase their case studies

International Journal of Atherogenic Diabetic Dyslipidemia will contain literature encompassing all the scientific and clinical aspects that address the cause and management of atherogenic dyslipidemia. The content of the journal shall include, but not limited to subject areas like atherogenic dyslipidemia, obesity, NAFLD, acute pancreatitis, hypertriglyceridemia, pharmacological management/therapeutic options for atherogenic dyslipidemia in type 2 diabetes and new strategies for management.

We hope to provide a platform to publish interesting and informative articles on topics connected with the management of atherogenic diabetic dyslipidemia as well as encourage correspondence and participation from our readers.

Editorial Board

Contents

Review

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Review

Non-Pharmacological Interventions for Management of NAFLD/MASLD

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Abstract

The prevalence of steatotic liver disease linked to metabolic dysfunction (MASLD) is rising at a startling rate. Research has shown that over 40% of middle-aged men and women who are overweight and have liver enzymes within the normal range also have MASLD. Although liver fat score (LFS) had the best accuracy in identifying MASLD, biomarker scores often did not perform well. The main indicator of MASLD risk was the existence of metabolic syndrome.

MASLD, formerly NAFLD, affects almost 30% of the world's population. Between 25% and 60% of the general population and high-risk groups, such as those who are obese or have type 2 diabetes, are affected by MASLD. The prevalence rises with advancing age, obesity, and inactivity.

This review will provide an overview of the non-pharmacological management of non-alcoholic fatty liver disease (NAFLD) or MASLD.

Keywords: MASLD, insulin resistance, non-pharmacological therapy, diet, physical activity, Mediterranean diet, weight loss

Introduction

Metabolic dysfunction-associated liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), is a growing condition that has been related to metabolic, cardiovascular, and neoplastic complications.[1] It affects almost 30% of the world's population.[2] It is described as hepatic steatosis combined with metabolic risk factors, the most common of which are type 2 diabetes and obesity.[1]

MASLD is regarded as more than one entity because it encompasses a variety of phenotypes, ranging from isolated steatosis, in which lipid accumulation in hepatocytes is the predominant histological feature, to metabolic dysfunction-associated steatohepatitis, which includes hepatic inflammation and/or fibrosis, as well as metabolic dysfunction-associated steatohepatitis-related cirrhosis and hepatocellular carcinoma.[1]

Abdominal obesity, particularly visceral obesity, which causes insulin resistance, is closely linked to MASLD, both through increased transport of free fatty acids to the liver and through enhanced hepatic lipogenesis, both of which are related to hyperglycemia and hyperinsulinemia. As a result, MASLD is classified as the hepatic manifestation of metabolic syndrome.[1]

Metabolic syndrome is a collection of metabolic disorders that raises the risk of cardiovascular disease and type 2 diabetes (T2DM). It is commonly diagnosed when an individual meets at least three of the five criteria: abdominal obesity, hypertension, raised fasting glucose, and high or low high-density lipoprotein cholesterol.[1]

The prevalence of MASLD ranges from 25% in the general population to 60% in high-risk groups, such as those with obesity and/or type 2 diabetes. The prevalence increases with age, obesity, and a lack of physical activity. When detected early, MASLD can be reversed by implementing lifestyle changes and correcting the underlying causes. However, advancement

to the fibrotic stages of MASLD is highly correlated with liver-related and overall mortality. Thus, rapid identification of MASLD is undoubtedly recommended.[1]

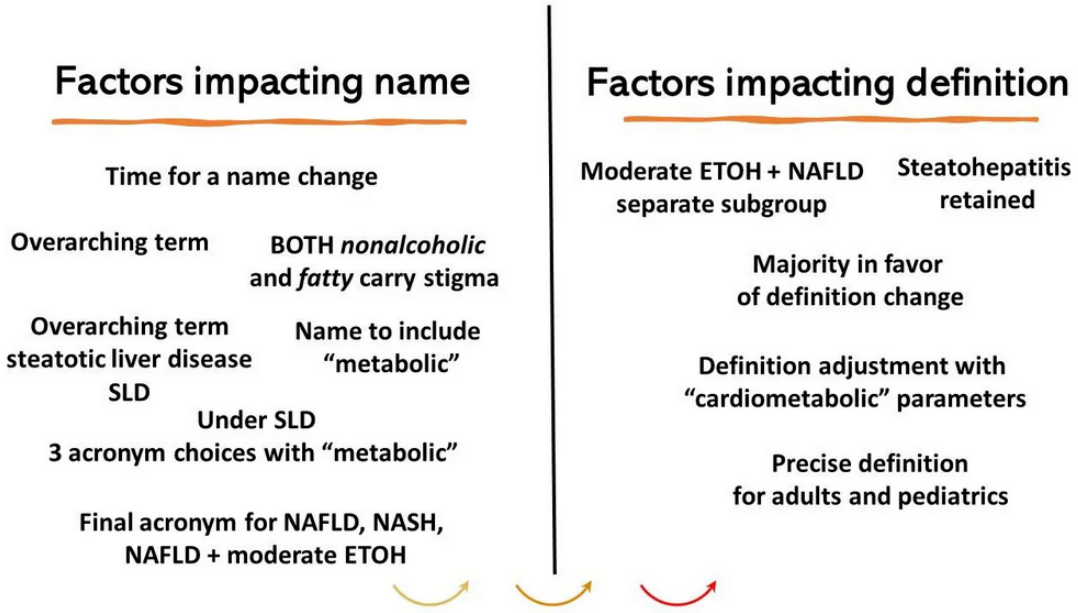

Fig 1. Difference in important predictors of NAFLD vs MASLD.[2]

MASLD: CAUSES, TREATMENT, AND MORTALITY

- MASLD is driven by obesity, adiposopathy, and metabolic disturbances like insulin resistance/T2DM, dyslipidemia, and hypertension.
- Treatment for MASLD is complex, with 90–95% of patients not progressing to liver cirrhosis.
- MASLD pathology is dynamic, with regress possible in steatosis and longer for fibrosis.
- Patients with MASLD have a two-fold increase in mortality compared to the general population, increasing with liver fibrosis prevalence and severity.
- The main causes of death are cancer, cardiovascular disease, and liver disease.
- Obesity-associated cancer risk is dependent on MASLD development.[3]

MASLD patients should be managed by multidisciplinary teams including hepatologists, endocrinologists, cardiologists, physical and rehabilitation doctors, dietitians, and psychologists. The treatment should target not only liver disease progression but also metabolic risk factors promoting cardiovascular disease and cancer. The most aspired endpoint is fibrosis reversal, as fibrosis severity is the main prognostic factor in MASLD. The ideal treatment should have a solid safety profile to prevent harm to asymptomatic patients who may continue morbid event-free for decades.[3]

MASLD prevalence is increasing as end-stage liver disease's leading cause, with weight loss being the most effective treatment, moving from lifestyle changes to bariatric surgery or endoscopy.[3]

NON-PHARMACOLOGICAL STRATEGY FOR TREATMENT OF MASLD

Non-pharmacological therapy options for MAFLD patients include diet and weight loss. Physical inactivity has been demonstrated to worsen the severity of liver disease. Cardiorespiratory fitness (CRF), muscle mass, and reduced body mass index (BMI) are health fitness indicators that characterize the risk of developing NAFLD/MASLD in healthy individuals. Aerobics, resistance training, rapid exercise training, and hybrid training have all been shown to improve weight, metabolic parameters, and CRF.

The Influence of Lifestyle Modifications

A. Dietary Modifications

Recent NHANES database studies indicated that a healthy diet and physical activity can protect against MASLD, with lower BMI and waist circumference largely explaining the protective effect. Physical activity also reduces all-cause and cardiovascular mortality in patients with MASLD. There is no lower threshold for mortality protection, and any increase in exercise can still positively impact survival.

General Dietary Guidelines for Weight Loss & Nutrition

- Adopt a hypocaloric diet with a 500–1,000 kcal deficit for weight loss.
- Limit consumption of animal proteins, especially red meat, due to insulin resistance and MASLD.
- Avoid added sugars, syrups, and sugar-sweetened beverages.
- Drink 3 or more cups of black coffee daily for hydration.
- Choose whole-grain, starchy carbohydrates over refined ones.
- Prioritize protein from animal or vegetable sources.
- Consume unsaturated fats from olive oil, fish, nuts, seeds, and avoid saturated fats and cholesterol.[4]

It is important to abstain from alcohol, adhere to a modified Mediterranean diet, and minimize consumption of red meat, processed foods, and junk food to maintain a healthy lifestyle.[4]

Mediterranean Diet Recommendations for NAFLD/MASLD

- High consumption of plant-based foods.
- Low consumption of sugars and refined carbohydrates.
- Favour fish over meat, especially red meat.
- Consume monounsaturated fatty acids-rich olive oil.[3]

Lifestyle Modifications in Non-Obese NAFLD/MASLD:

NAFLD/MASLD is influenced by unhealthy diets and sedentary lifestyles, and is influenced by host genetics, metabolism, endocrinology, and gut microbiota. It can lead to long-term liver complications and multiple extra-hepatic comorbidities like cardiovascular disease and chronic kidney disease.[5]

Currently, there are no precise criteria for non-obese NAFLD/MASLD patients.[6]

- Non-obese NAFLD/MASLD is associated with weight gain, and a population-based intervention study found that 97% of Asian patients who lost more than 10% of their body weight experienced resolution of NAFLD/ MASLD.
- The most recent clinical practice recommendations advocate the Mediterranean diet as the diet of choice for all NAFLD/MASLD patients.
- The Mediterranean diet, which includes increased omega-3 and monounsaturated fatty acid intake and decreased carbohydrate intake, is recommended as the diet of choice for all NAFLD/MASLD patients. Adherence to this diet leads to a substantial decrease in liver steatosis even without weight reduction, making it an interesting choice for lean NAFLD/MASLD patients.
- Increased physical activity has beneficial effects on NAFLD/MASLD independent of weight loss, with both resistance and aerobic exercise decreasing hepatic steatosis in NAFLD/MASLD patients.
- The guidelines recommend 150 to 200 minutes/week of moderate-intensity aerobic physical activity in three to five sessions. However, there are no specific guidelines or evidence focused on lean NAFLD/ MASLD patients.[6]

B. Physical Activity, Weight Loss and Surgical Interventions

Physical activity, especially recreational, is linked to weight loss and protects against liver steatosis, even when weight loss is not achieved. Aiming for at least 45 minutes of moderate-intensity exercise three times a week, including aerobic and anaerobic workouts is recommended.[3]

Lifestyle interventions are hampered by a low success rate in weight loss (less than 10%). Furthermore, only around one-fourth of those who lose weight can keep it off, and 60% of patients regain it within the first year.[3]

Losing 3% to 5% of the body weight has been demonstrated to lower fat levels in the liver, whereas losing 5–10% of the body weight will also help reduce inflammation.[7] In patients with weight-associated steatotic liver disease (SLD), a well-balanced diet along with gradual loss of weight has been recommended.[8]

A minor increase in weight in lean individuals has a negative influence on metabolic functioning because it increases visceral adipose tissue.[9]

Weight loss can help NAFLD/MASLD and nonalcoholic steatohepatitis (NASH) sufferers. Diet and physical activity that results in a 7–10% reduction in body weight over time can help with LF content, NASH, and fibrosis. Fortunately, NAFLD/MASLD and NASH, as well as liver fibrosis, are reversible, particularly before cirrhosis occurs. Weight loss is the cornerstone of therapy, as a 5% drop in BMI is associated with a 25% relative decrease in LF as evaluated by MRI.[10]

Bariatric surgery is effective in treating MASLD, promoting long-term effects lasting at least 5 years. Observational studies show that bariatric surgery promotes steatosis resolution, MASH resolution without worsening fibrosis in around 80%, and fibrosis regression in 70%. Over 50% of patients may achieve complete fibrosis resolution, even with advanced fibrosis at baseline. The beneficial effects depend on weight loss. A recent open-label trial randomized 300 patients with MASH for lifestyle intervention or bariatric surgery, showing a 70% higher chance of fibrosis improvement and a 50% decreased risk of worsening fibrosis.[3]

A recent meta-analysis of 863 patients suggests that interventions like intragastric balloons may result in histologic improvement in MASLD patients. Intragastric balloons have a transient effect on weight, with most patients regaining weight after removal. Endoscopic sleeve gastroplasty has shown a sustained effect on weight and liver histology in obese MASLD patients. A randomized controlled trial comparing surgical and endoscopic gastric sleeve interventions, the TESLA-NASH study, is ongoing. Endo barrier and duodenal mucosa resurfacing have shown preliminary improvements in steatosis and fibrosis assessed by NIT.[3]

Endoscopic bariatric metabolic treatment (EBMT) is often recommended for people who do not satisfy the BMI criteria for surgery, are unable to reduce weight by lifestyle changes, or are unable to maintain weight loss.[11]

The Obesity and Metabolic Surgery Society of India recommends bariatric/metabolic surgery for the following conditions: BMI 35 kg/m^2 or BMI 30 kg/m^2 with two or more obesity-related co-morbidities, or as a non-primary treatment option for BMI 27.5 kg/m^2 with uncontrolled T2DM despite optimal medical care.[11]

Despite its efficacy for weight loss, bariatric surgery and EBMT are not recommended as the main treatments for people with NAFLD/MASLD. This is due to the accompanying morbidity and mortality, as well as a lack of randomized clinical trials.[11]

A study investigated the impact of metabolic surgery on liver injury in people with low BMI. Histological data on NASH resolution after metabolic surgery have been reported in cohorts with a mean BMI >45 kg/m². All patients were operated according to standard bariatric-metabolic surgery protocols. This cohort was operated outside these guidelines, with a BMI <35 kg/m² as an inclusion criterion (and thus a mean preoperative BMI difference of >10 kg/m² compared to all other published studies). It focused specifically on metabolically sick patients (insulin-treated T2DM) with histologically proven liver injury (steatohepatitis with fibrosis), which is prototypical for MASLD.[9]

The complete histological resolution of MASLD and fibrosis regression 36 months after RYGB (Roun-e Y Gastric Bypass) suggest that metabolic surgery may be an effective therapeutic option for MASLD and maybe NASH in low-BMI patients outside of the usual reasons for bariatric-metabolic surgery. Furthermore, the discovery that liver injury recovered fully despite prolonged T2DM shows that the effects of metabolic surgery on metabolic sequelae are unaffected by glycemic management.[9]

Conclusions

In conclusion, even modest amounts of moderate exercise of various forms, whether aerobic or resistance training, as well as dietary adjustments(Mediterranean diet) can improve liver fat in addition to weight loss and surgical procedures, and should be included in NAFLD/MASLD treatment. More research is needed to confirm the role of non-pharmacological interventions in treating NAFLD or MASLD.

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Review

Pharmacological Management of MASLD

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ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD, formerly non-alcoholic fatty liver disease, NAFLD) refers to a range of fatty liver diseases, including steatotic liver disease (SLD) with ≥ 5% hepatic steatosis, metabolic dysfunction-associated steatohepatitis (MASH, formerly known as non-alcoholic steatohepatitis, NASH) with or without fibrosis, and later stages of cirrhosis, liver failure, and liver cancer.[1] MASLD is linked not only to an increased risk of liver complications but also to an increased risk of developing multiple extrahepatic manifestations such as cardiovascular disease (CVD), chronic kidney disease (CKD), and certain types of extrahepatic cancer.[2]

Non-alcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction-associated fatty liver disease (MAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD), has emerged as the primary cause of hepatocellular carcinoma (HCC) in light of an increase in type 2 diabetes mellitus (T2DM) and obesity patients worldwide. By 2030, the annual incidence of MASLD-driven HCC is predicted to rise by 45% to 130%.[3]

Future research is required because, despite MASLD's growing worldwide hazard to public health, the precise molecular processes behind MASLD-driven HCC are yet unknown. Emerging research, meantime, is concentrating on the potential of bioactive substances to stop the development of MASLD into MASLD-driven HCC.[3]

Materials and Method: Review and extracting data from articles which have published data related to the pharmacological management of MASLD.

Results and Conclusion: Studies suggest that GLP-1 analogues, SGLT2 inhibitors, Pioglitazone, and Vitamin E are the most recommended and beneficial pharmacological classes for MASLD.

Keywords: HCC, MASLD, metabolic, pharmacological, treatment, guideline, surgical

Introduction

Aim: This review aimed to gain more understanding of the pharmacological treatment for the management of MASLD.

Methods: Several articles related to the topic of discussion which included medications employed in the management of MASLD were reviewed and data was extracted from them.

Results: By 2030, the incidence of MASLD will grow to 45% or higher. Pharmacological therapy options are critical for preventing MAFLD from deteriorating. More research is needed to optimize patient care to avoid progression and enhance outcomes.

Discussion

NAFLD's rebranding as MASLD

Within the medical community, there has been continuous discussion over the categorization and terminology of NAFLD. The goals of MASLD and MAFLD, which have been developed recently, are to alleviate the constraints related to NAFLD. Recent years have seen an increase in the body of information pointing to the metabolic component of steatotic liver disease (SLD), as well as important discoveries about the pathophysiologic processes behind the development of MAFLD/MASLD.[4]

Treatment for MASLD

MASLD is caused by metabolic overload, a condition where excess caloric intake is not balanced by physical activity. The severity of this overload depends on an individual's ability to cope, influenced by factors like genetics, epigenetics, environmental factors, age, and gender. Overcoming this capacity can lead to ectopic lipid accumulation and adipose tissue dysfunction, causing metabolic-inflammatory stress in end-organs like the liver.[5]

Ectopic lipid accumulation and metabolic-inflammatory stress can lead to MASH, depending on the severity and liver's ability to cope with these stressors. The liver's defense and repair mechanisms determine the ultimate damage. These factors result in inter-individual differences and patient heterogeneity.[5]

The complex pathophysiology of MASLD/MASH highlights the need for a holistic multidisciplinary approach that considers both liver-centred and extrahepatic drivers and consequences. This oversimplification of the pathophysiology highlights the importance of a multidisciplinary approach.[5]

Cardiovascular disease (CVD) is the leading cause of death in patients with MASLD, and MASLD contributes independently to CVD development. This highlights the need for CVD prevention in MASLD management. MASLD also increases the risk of type 2 diabetes, chronic kidney disease, and non-hepatic malignancy, requiring a holistic approach.[5]

Comprehensive evaluations are crucial for assessing MASLD and MetALD, and identifying potential comorbidities. Recent guidance papers guide on managing metabolic and cardiovascular co-morbidities in MASLD/MASH.[5]

The development of a non-pharmacological treatment for MASLD/MASH requires defining potential indications and goals, as drugs come with safety and tolerability concerns. The disease progresses slowly, making it challenging to establish short-term clinical goals, especially in non-cirrhotic patients. Histological improvement is likely to reflect a positive change in the disease's natural history. Traditional endpoints for assessing treatment efficacy include resolution of steatohepatitis without worsening of fibrosis, regression of fibrosis without worsening of steatohepatitis, and more recently, a combined resolution of steatohepatitis and regression of fibrosis.[5]

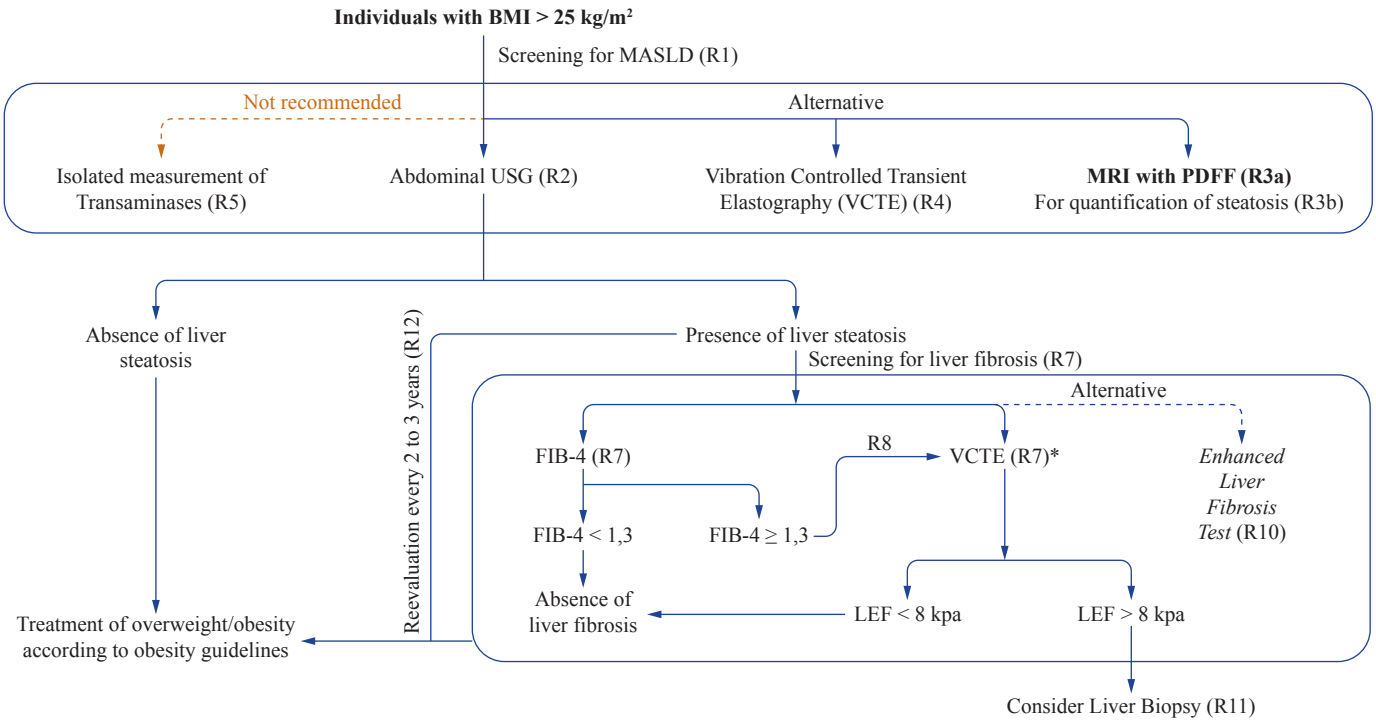
Guidelines for the Management of MASLD

MASLD patients should be managed by multidisciplinary teams including hepatologists, endocrinologists, cardiologists, physical and rehabilitation doctors, dietitians, and psychologists. The ideal treatment should target not only liver disease progression but also metabolic risk factors promoting cardiovascular disease and cancer. The most aspired endpoint is fibrosis reversal, as fibrosis severity is the main prognostic factor in MASLD. The treatment should have a solid safety profile to avoid harm in asymptomatic patients who may continue morbid event-free for decades. Currently, there is no approved drug for MASLD treatment, but efforts are underway to find new efficient drugs.[6]

The global prevalence of MASLD is increasing, and primary care providers are crucial in screening, diagnosing, and managing the condition. However, challenges exist due to limited healthcare resources and barriers to care.[7]

Guidelines have been developed to provide evidence-based recommendations for clinical assessment and management of MASLD/MASH patients.[7]

Theoretically, an ideal intervention for MASLD would impact histological findings and prevent 'hard' outcomes, such as clinical complications and increased mortality. However, due to the heterogeneity in MASLD clinical presentations and its long evolution, proving a single treatment affects multiple liver outcomes and complications is challenging. Randomized controlled trials require a large number of participants with advanced fibrosis and long follow-up, making this goal unattainable.[8]



* R9 - When FIB-4 ≥ 1.3, magnetic resonance elastography can be used as an alternative to VCTE, particularly in individuals with BMI equal to or higher than 35 kg/m².

Abbreviations: BMI, body mass index; FIB-4, Fibrosis-4 Score; VCTE, Vibration Controlled Transient Elastography; MASLD, metabolic dysfunction-associated steatotic liver disease, MRI, magnetic resonance imaging; PDFF, proton-density fat fraction; R, recommendation.

Fig 1. Algorithm for clinical assessment of patients with overweight or obesity and clinical suspicion of metabolic dysfunction-associated steatotic liver disease.[8]

Suggested but Still under Evaluation Pharmacological Treatment Recommendations

Glucagon-like peptide 1 (GLP-1) analogues

- To minimise steatosis in overweight or obese individuals with MASLD, GLP-1 analogues (liraglutide, semaglutide, or dulaglutide) or GLP-1 receptor agonists (exenatide) are indicated (I, A).[8]
- Liraglutide and semaglutide are suggested for individuals with overweight/obesity and MASLD who have documented steatohepatitis with or without fibrosis to ameliorate steatohepatitis without increasing fibrosis (I, A).[8]
- A meta-analysis by Manitoban et al. found that patients treated with liraglutide or semaglutide had lower hepatic fat, improved liver enzymes, and better histological resolution of inflammation without worsening fibrosis compared to other medications (e.g., dulaglutide, exenatide, and semaglutide). Notably, the majority of patients were overweight or obese, and only 30% had not been diagnosed with T2DM.[8]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

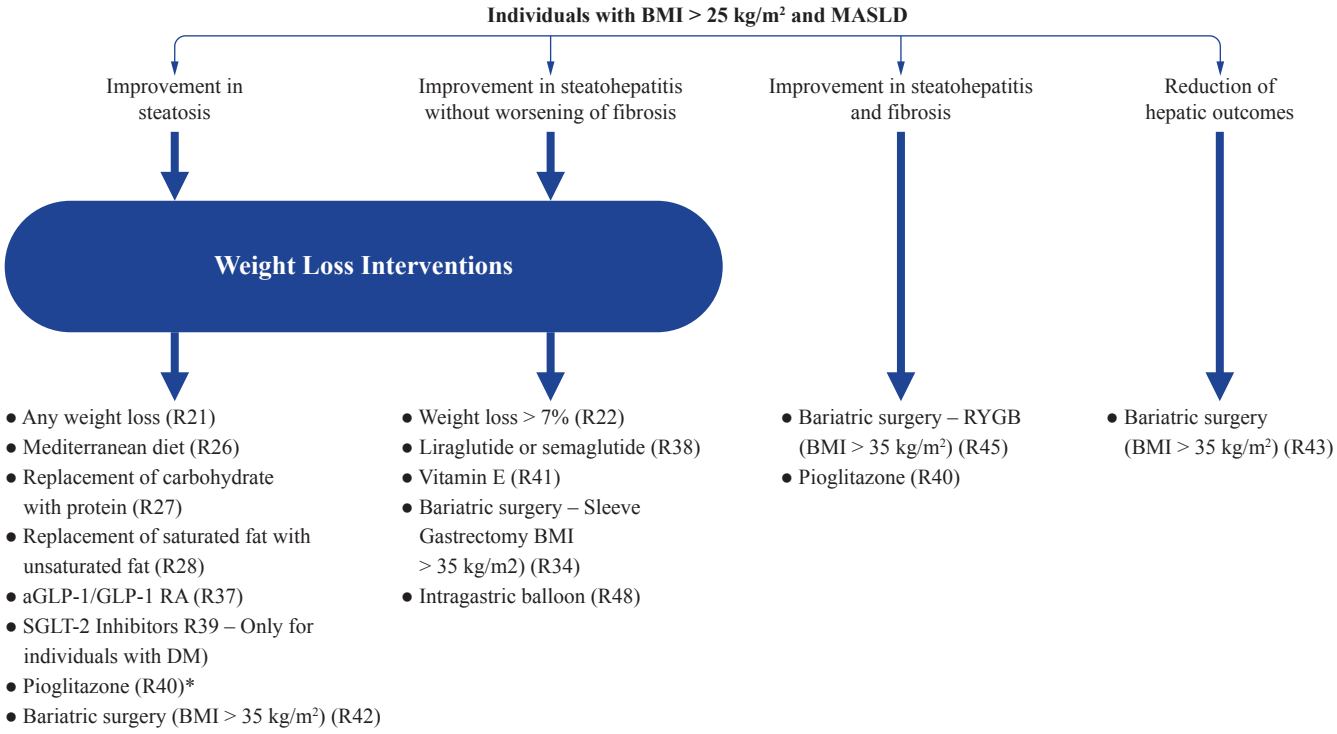
- SGLT2 inhibitors may reduce steatosis in individuals with overweight/obesity, T2DM, or MASLD (IIa, B).[8]
- A comprehensive evaluation indicated that using SGLT2 inhibitors (iSGLT2) resulted in a considerable decrease in liver fat content.[8]

Pioglitazone

- Pioglitazone medication is recommended for the improvement of steatosis, steatohepatitis, and fibrosis in individuals with overweight/obesity and MASLD who have documented steatohepatitis with or without fibrosis (I, A).[8]

Vitamin E

- Vitamin E medication may ameliorate steatohepatitis without aggravating fibrosis in persons with overweight/obesity, MASLD, and steatohepatitis (IIb, B), regardless of fibrosis diagnosis.[8]



* Pioglitazone should not be used for the treatment of isolated hepatic steatosis and should be used only for the treatment of steatohepatitis with or without fibrosis.

Abbreviations: aGLP-1, glucagon-like peptide 1 (GLP-1) analogues; BMI, body mass index; DM, diabetes mellitus; GLP-1 RA, GLP-1 receptor agonist; MASLD, metabolic dysfunction-associated steatotic liver disease; R, recommendation; RYGB, Roux-en-Y gastric bypass surgery; SGLT-2, sodium-glucose cotransporter-2.

Fig 2. Clinical management of patients with overweight or obesity and metabolic dysfunction-associated steatotic liver disease.[8]

Resmetirom – Recently FDA-approved Drug

- The effectiveness of thyroid hormone-related treatment strategies for MASLD is gaining attention due to the link between thyroid dysregulation and the development of MASLD.[9]
- Thyroid hormone receptor (THR)-β is crucial for regulating liver metabolic pathways, which is often impaired in patients with nonalcoholic steatohepatitis (NASH). Resmetirom, an oral, once-daily, liver-targeted THR-β selective agonist, is being developed for treating NASH.[10]
- Thyroid stimulating hormone levels are linked to the risk of MASLD in euthyroid individuals, with T3 and T4 levels increasing the incidence of advanced liver fibrosis in patients with biopsy-proven euthyroid MASLD.[9]
- Thyroid hormones are primarily mediated through two receptors: THR-α and THR-β. THR-β is the dominant receptor in hepatocytes, responsible for lowering cholesterol, increasing bile acid synthesis, and fat oxidation. Thyromimetics inhibit TSH secretion, reducing the production of natural thyroid hormones.[9]
- Resmetirom, an orally active liver-targeted compound, selectively activates THR-β, reducing free T4 levels by 16–19% without affecting thyrotropin levels or the active thyroid hormone, free triiodothyronine. This downregulates thyroid hormone levels but improves liver lipid metabolism and outcomes. THR-β agonists, which stimulate β-oxidation in liver mitochondria, reduce lipoprotein production and secretion, and enhance LDL receptor expression, have been a principal approach for drug development for dyslipidemia, obesity, and hepatic steatosis.[9]

- In a randomized, double-blind trial, patients treated with Resmetirom showed a significant reduction in hepatic fat from baseline. Reduction of hepatic fat by 30% was associated with 37% NASH resolution and improved patient-reported outcomes. Patients who continued the trial with higher doses of 80 and 100 mg per day achieved a 50% and 64% reduction in hepatic fat respectively. The trial's efficacy and adverse event profile supported the selection of 80 and 100 mg Resmetirom for phase 3.[10]
- The FDA has approved Resmetirom, a drug that improves metabolic syndrome (MASH) by increasing hepatic fat metabolism and reducing lipotoxicity. This approval follows Madrigal Pharmaceuticals' previous designations for Breakthrough Therapy, Fast Track, and Priority Review. Resmetirom is liver-directed, mediated by liver-specific organic anion transporting polypeptides 1B1, and shows a 28-fold selectivity for thyroid hormone-β over thyroid hormone-α. This could potentially avoid systemic effects associated with thyroid hormone excess in bone and heart, which are primarily mediated through THR-α.[9]

Saroglitazar in MASLD

- Saroglitazar, a dual PPAR-α/γ agonist, promotes insulin resistance and protects against atherogenic dyslipidemia by decreasing small dense LDL and triglycerides. It also has beneficial effects in steatosis, MASH, and fibrosis by NITs, making it a promising drug.[6]
- Saroglitazar stimulates the expression of genes that regulate dyslipidemia, hypertriglyceridemia, and other related conditions like type 2 diabetes, non-alcoholic fatty liver disease, and cardiovascular disease.[11]
- Saroglitazar, a drug with potential benefits for metabolic syndrome patients, has been shown to reduce TGs, LDL cholesterol, VLDL cholesterol, and non-HDL cholesterol while increasing HDL cholesterol, a characteristic feature of diabetic dyslipidemia, according to preclinical and clinical studies.[11]
- Saroglitazar, a drug used to treat type 2 diabetes, has been shown to reduce blood glucose levels and HBA1c levels in both animal models and human clinical trials. These therapeutic actions are primarily achieved through the activation of PPAR-α/γ.[11]

Ursodeoxycholic Acid and Obeticholic Acid in Management of MASLD

- The farnesoid X receptor (FXR) regulates the synthesis and circulation of bile acids, cholesterol derivatives made up of cholic (CA) and chenodeoxycholic acids (CDCA).[12]
- Intestinal microbiota enzymes in the colon convert primary bile acids into secondary bile acids, deoxycholic acid (DCA) and ursodeoxycholic (UCA) and lithocholic acid (LCA). Secondary bile acids are more lipophilic than primary bile acids and are resorbed at the colonic mucosa and reach the liver through systemic circulation. FXR, located in the liver and intestine, inhibits cholesterol conversion into primary bile acids and prevents bile acid resorption at the ileum level, affecting enterohepatic circulation and modulating the inflammatory process underlying MASH and fibrosis.[12]
- Obeticholic acid (OCA) is a synthetic analogue of CDCA that activates FXR with greater potency.[12]
- FXR activation increases the expression of fibroblast growth factor-19 and FGF-21, which possess anti-steatogenic and anti-fibrotic properties.[6]
- It is approved for treating primary biliary cirrhosis when ursodeoxycholic acid is insufficient.[12]
- OCA is a pleiotropic agent that regulates various aspects of life, including bile acids, cholesterol, glucose metabolism, lipogenesis, vascular remodelling, inflammation, fibrogenesis, and intestinal barrier integrity. It is highly expressed in the liver and small bowel. OCA, conjugated with FXR, reduces primary bile acid synthesis, lipogenesis, and gluconeogenesis, thereby indirectly reducing fibrosis.[6,12]
- A phase 3 trial involving 2,477 patients with pre-cirrhotic MASH, treated with OCA 10 or 25 mg, showed positive results in two interim analyses at 18 months. The study showed a higher percentage of patients achieving fibrosis improvement (22% versus 10%) and MASH resolution (6.5% versus 3.5%) when treated with 25 mg of OCA compared to the placebo. Liver stiffness and NITs for fibrosis decreased regardless of histologic response. However, pruritus occurred in one-third

of patients with the lowest dose and around half with the highest dose. Dyslipidemia was frequent in almost half of the patients, and gallstone-related events increased slightly. No differences were found between OCA and placebo in cardiovascular events.[6]

However, OCA did not receive US FDA approval for this indication, primarily because of their conclusion that the side effect profile was unacceptable.

Treatment of MASLD in T2DM Patients

- MASLD is linked to metabolic disturbances, such as insulin resistance, which causes tissue damage to hepatocytes. Hypoglycemic agents like glucagon-like-1 receptor agonists (GLP-1RAs) and peroxisome proliferator-activated receptor-gamma agonists (PPARγ) have been studied to reduce liver fat and improve liver injury.[12]
- The NATIVE trial tested lanifibranor, a first-in-class pan-PPAR agonist, in patients with non-alcoholic steatohepatitis (NASH). The study showed that a 1200 mg dose of lanifibranor decreased the histologic steatosis, activity, and fibrosis (SAF) score by at least two points, making it a promising treatment option. However, the findings will be confirmed in phase 3 clinical trials.[12]
- The most recommended treatment for MASLD patients with obesity or T2DM is GLP-1RA molecules, particularly liraglutide and semaglutide.[12]
- A phase 2 randomized controlled trial showed significant improvement in liver fat content using these molecules. Another small phase 2b trial showed liraglutide treatment led to histologic resolution of NASH and decreased fibrosis progression. Dipeptidyl peptidase 4 inhibitors and sodium-glucose co-transporter type 2 inhibitors are currently in phase 2 study trials.[12]
- Pioglitazone has been shown to improve liver histology in patients with and without DM2 with biopsy-proven NASH. The EASL suggests that using pioglitazone in these patients may improve histologic features in steatosis and possibly fibrosis.[12]
- However, the American Association for the Study of Liver Diseases (AALSD) recommends pharmacological treatments be limited to those with biopsy-proven NASH and fibrosis, with a weight loss of 7–10% needed to improve most histopathological features of NASH, including fibrosis.[12]
- The American Association of Clinical Endocrinology recommends GLP-1RAs for patients with T2DM and NASH, offering additional cardiometabolic benefits. However, due to a lack of efficacy evidence, metformin, acarbose, dipeptidyl peptidase IV inhibitors, and insulin are not recommended for NAFLD treatment. Biguanides, particularly metformin, are the preferred first-line oral blood-glucose-lowering agent for managing T2DM, and reducing hepatic glucose production.[12]

Limitations of Study: This review is limited to the information available in published articles or studies.

Conclusion

The disease MASLD, the most common cause of chronic liver disease, has been renamed and increased in awareness. It is the leading cause of liver-related morbidity and mortality.[13] To effectively manage obesity and related diseases, a clear assessment and referral pathway is crucial. This helps identify and refer patients with severe MASLD to specialist care, while those with less severe diseases remain in primary care, enhancing the shared role between primary and specialist care providers.[13] Further studies are needed to optimize patient management to prevent progression and improve outcomes.[13]

Conflict of Interest

No conflict of interest.

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