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Review

Pharmacological Management of MASLD

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Article information

Received date: 30/4/2024; **Accepted date:** 27/05/2024; **Published date:** 03/06/2024

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]

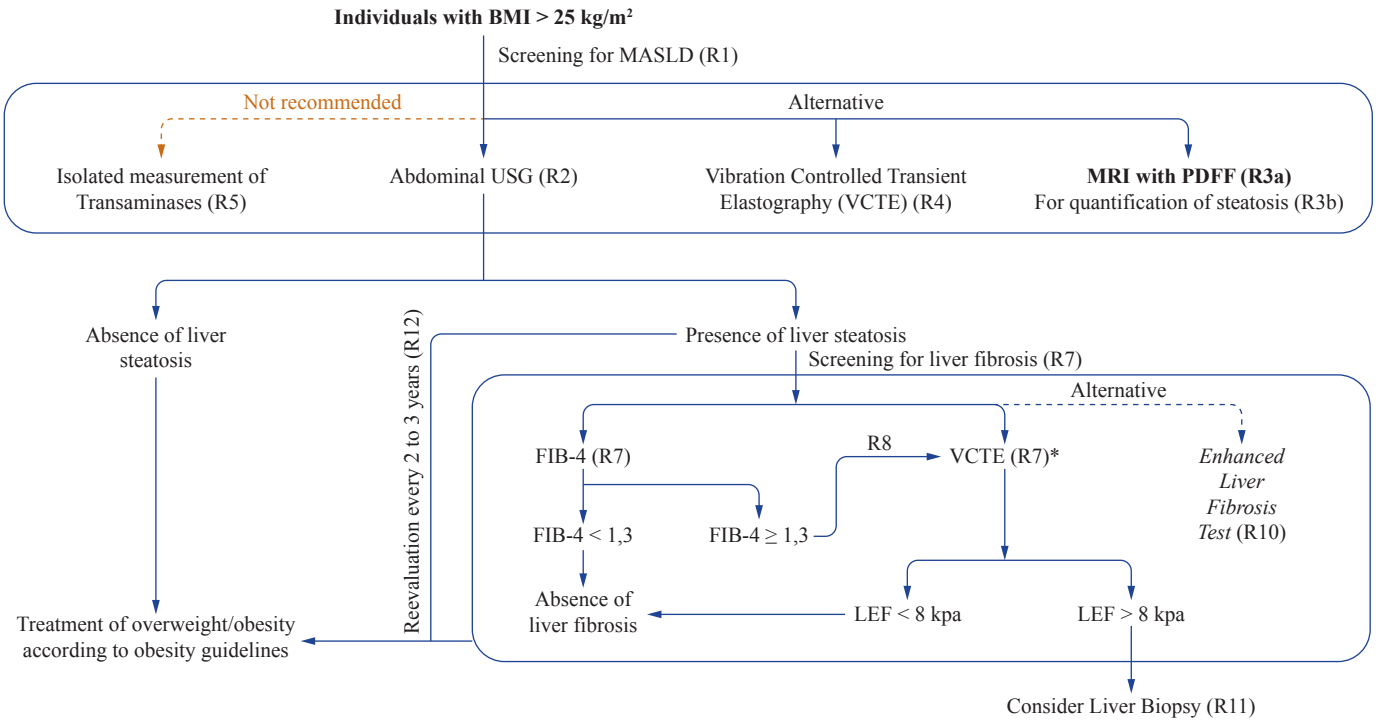
Guidelines for the Management of MASLD

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

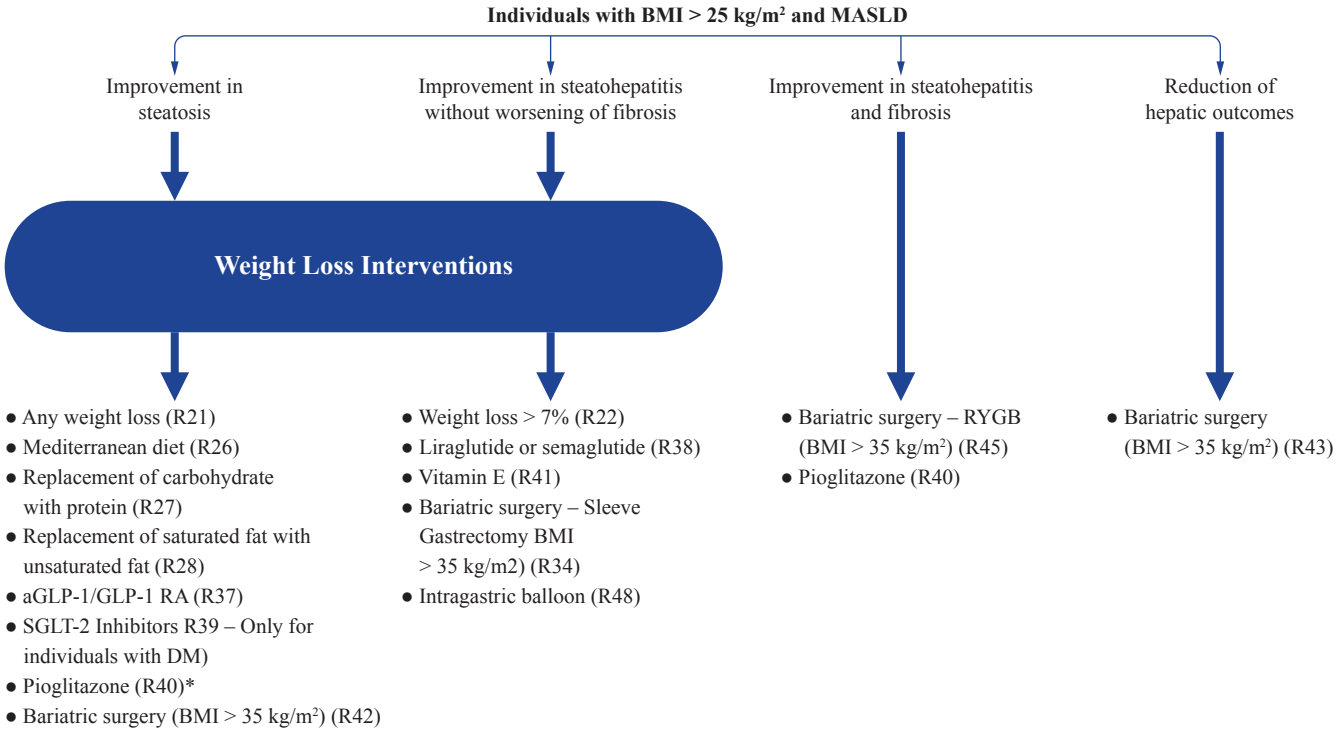
- SGLT2 inhibitors may reduce steatosis in individuals with overweight/obesity, T2DM, or MASLD (IIa, B).[8]
- A comprehensive evaluation indicated that using SGLT2 inhibitors (iSGLT2) resulted in a considerable decrease in liver fat content.[8]

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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