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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]

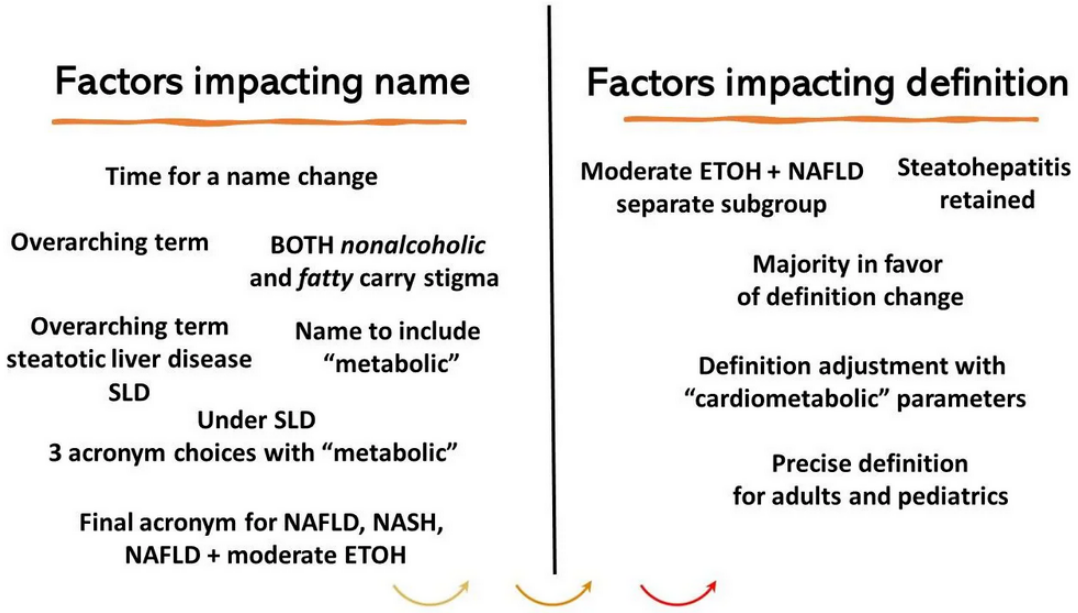

Fig 1. Difference in important predictors of NAFLD vs MASLD.[2]

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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