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REVIEW

Nutritional Strategies for Battling Obesity-Linked Liver Disease: the Role of Medical Nutritional Therapy in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Management

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Abstract

Purpose of Review This narrative review explores the role of Medical Nutritional Therapy (MNT) in managing Metabolic-Associated Steatotic Liver Disease (MASLD), previously known as nonalcoholic fatty liver disease. It aims to examine the effectiveness of specific nutritional strategies in preventing and treating this obesity-linked liver disease.

Recent Findings Emerging evidence underscores the benefits of the Mediterranean diet, low-carbohydrate diets, and intermittent fasting in reducing liver fat, improving insulin sensitivity, and mitigating inflammation. Supplementing with vitamin E, omega-3 fatty acids, and silymarin can potentially reduce liver fibrosis and promote liver health.

Summary MNT is a key intervention for MASLD management, emphasizing dietary patterns, caloric restriction, and nutraceutical supplementation. Integrating these strategies with lifestyle modifications, including regular physical activity, offers a comprehensive approach to improving metabolic and liver outcomes in patients with MASLD. Further research is needed to refine and personalize these therapeutic interventions.

Keywords Obesity · Medical Nutritional Therapy (MNT) · Metabolic-Associated Steatotic Liver Disease (MASLD) · Mediterranean diet · Nutraceutical supplementation · Liver fibrosis

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Introduction

Obesity has emerged as a major global public health challenge, with its prevalence steadily increasing and its association with a broad spectrum of chronic diseases becoming more evident [1]. Defined by an unusual buildup of body fat that may impair health, obesity now affects more than 890 million people worldwide, according to the World Health Organization [1]. This condition is closely linked not only to type 2 diabetes (T2D), cardiovascular diseases, and certain types of cancer [2–4], but also to liver diseases, including Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) [5].

MASLD, a term introduced in 2023, refers to a spectrum of liver conditions marked by the accumulation of fat in the liver due to metabolic dysfunction, excluding significant alcohol consumption as a cause [6]. This new terminology evolved from earlier concepts such as Non-Alcoholic Fatty Liver Disease (NAFLD) [7] and Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) [8, 9], with a stronger emphasis on metabolic dysfunction as the primary driver of the disease [10]. MASLD includes a spectrum of liver conditions, ranging from simple hepatic steatosis, which may be asymptomatic, to steatohepatitis, an inflammatory state that can progress to fibrosis, cirrhosis, and, in advanced cases, hepatocellular carcinoma [11].

The relationship between obesity and MASLD is both complex and bidirectional [5]. Approximately 75% of individuals with obesity are affected by MASLD [5], with this connection largely driven by the impact of adipose tissue on insulin resistance and metabolic syndrome, both key factors in the pathophysiology of MASLD [10]. Obesity, particularly visceral obesity, not only increases the risk of developing MASLD but also influences the progression and prognosis of the disease [12]. Furthermore, obesity exacerbates the risk of both hepatic and extrahepatic complications, such as chronic kidney disease, cardiovascular diseases, T2D, and various cancers. These factors collectively increase the morbidity and mortality of patients with MASLD, complicating its clinical management [13].

Given the close link between MASLD, metabolism dysfunction, and nutrition, Medical Nutritional Therapy (MNT) has emerged as a crucial strategy for managing this condition. MNT is a therapeutic approach that utilizes food and nutrition to prevent, treat, and manage diseases. In the context of MASLD, MNT focuses on modifying dietary and lifestyle patterns to reduce liver fat, improve liver function, and address metabolic comorbidities such as obesity and insulin resistance [14, 15]. This includes adopting specific diets, calorie restriction, optimizing macronutrient and micronutrient intake, and implementing behavioral and lifestyle interventions, such as increased physical activity [16–18].

Dietary interventions within the MNT framework have shown significant effectiveness in managing MASLD [19]. Among the most studied approaches, the Mediterranean diet (MD) [20, 21], stands out for its beneficial effects on liver and metabolic health, primarily attributed to its rich content of unsaturated fatty acids and antioxidants. Low-carbohydrate diets have also effectively reduced hepatic steatosis and improved insulin resistance [22]. Additionally, emerging dietary strategies, such as intermittent fasting and very low-energy ketogenic therapy (VLEKT), are being explored for their potential to decrease liver fat and enhance metabolic health in MASLD patients [23].

In this context, this narrative review aims to comprehensively examine the relationship between obesity and MASLD, focusing on the effectiveness of MNT. The goal is to provide an integrated perspective that can inform clinical practice and support the development of new nutritional and therapeutic strategies for managing MASLD more effectively.

Pathophysiology of MASLD

Definition of MASLD/Difference Between MASLD, NAFLD and MAFLD

NAFLD, MAFLD, and MASLD describe similar liver conditions characterized by fat accumulation stemming from metabolic dysfunction. These conditions can vary from simple steatosis to steatohepatitis, which may occur with or without fibrosis and can progress to cirrhosis and hepatocellular carcinoma (HCC). These terms differ in their conceptual approach. NAFLD, introduced in the 1980s, is defined fatty liver disease without significant alcohol use or other causes [24]. In 2020, MAFLD emerged, shifting the focus to metabolic dysfunction as the defining criterion, even if other factors like alcohol use are present [9]. MASLD, coined in 2023, further emphasizes metabolic dysfunction as the primary cause while excluding alcohol-related liver disease. In contrast, a new term, metabolic and alcohol-related liver disease, is proposed for mixed cases involving both metabolic dysfunction and significant alcohol intake. The shift from "fatty liver" to "steatotic liver" reflects a more precise medical term aiming to reduce stigma. MASLD thus represents an evolved understanding, focusing solely on metabolic origins [6].

The pathogenesis of MASLD is complex and involves multiple interconnected factors that reinforce each other in a vicious cycle. The disease is intricately linked to insulin resistance and metabolic syndrome and, therefore, to obesity and T2D, reflecting the impact of modern lifestyle

factors such as unhealthy diet, physical inactivity, chronic stress, etc. Abnormal hepatic fat accumulation results from increased de novo lipogenesis, elevated hepatic uptake of circulating fat (mainly of endogenous origin, but also exogenous/dietary), reduced hepatic mitochondrial fat oxidation, and impaired hepatic fat export via very low-density lipoprotein. Lipotoxicity and inflammation play important roles in the pathogenesis and progression of MASLD. Genetic variants are considered disease modifiers rather than causative factors [25].

Mechanisms Linking Obesity to MASLD

Selective Insulin Resistance, Chronic Hyperinsulinemia and MASLD

Systemic insulin resistance is the most common metabolic dysfunction in the industrialized world and is highly relevant to the pathogenesis of MASLD [26]. Chronic hyperinsulinemia, always present in insulin resistance, is particularly significant for MASLD. Insulin resistance is not homogeneous; certain insulin pathways are impaired to various degrees in some organs and tissues, while others remain sensitive and become overstimulated by hyperinsulinemia. The liver is a prime example, where hepatocytes, while becoming insulin-resistant in the gluconeogenesis pathway, seem to maintain insulin sensitivity in the lipogenic pathway. This pathway becomes overstimulated by hyperinsulinemia, resulting in hepatic fat accumulation through de novo lipogenesis via Sterol Regulatory Element Binding Protein-1c [27]. Furthermore, when insulin is chronically elevated, fat oxidation is suppressed [28] (Fig. 1).

Fructose and MASLD

Fructose, abundant in modern diets, is a potent driver of hepatic de novo lipogenesis in humans, partly through non-caloric pathways [29]. It is primarily metabolized in the liver and enters cells via type 5 glucose transporters (GLUT5). Unlike glucose, fructose metabolism bypasses key regulatory, rate-limiting enzymatic checkpoints, feeding directly into lipogenic pathways. This bypassing becomes particularly relevant when large amounts of fructose are ingested rapidly, such as when consuming soft drinks, leading to unregulated and excessive conversion of fructose into hepatic fat [29]. More specifically, consuming large amounts of fructose produces significant quantities of acetyl-CoA during pathways following glycolysis. When fructose intake is high, excess acetyl-CoA is channeled into de novo lipogenesis, resulting in increased production of fatty acids and triglycerides, which accumulate in the liver and contribute to the development of MASLD [30]. Furthermore, fructose impairs mitochondrial function by increasing the production of reactive oxygen species (ROS) and uric acid, directly

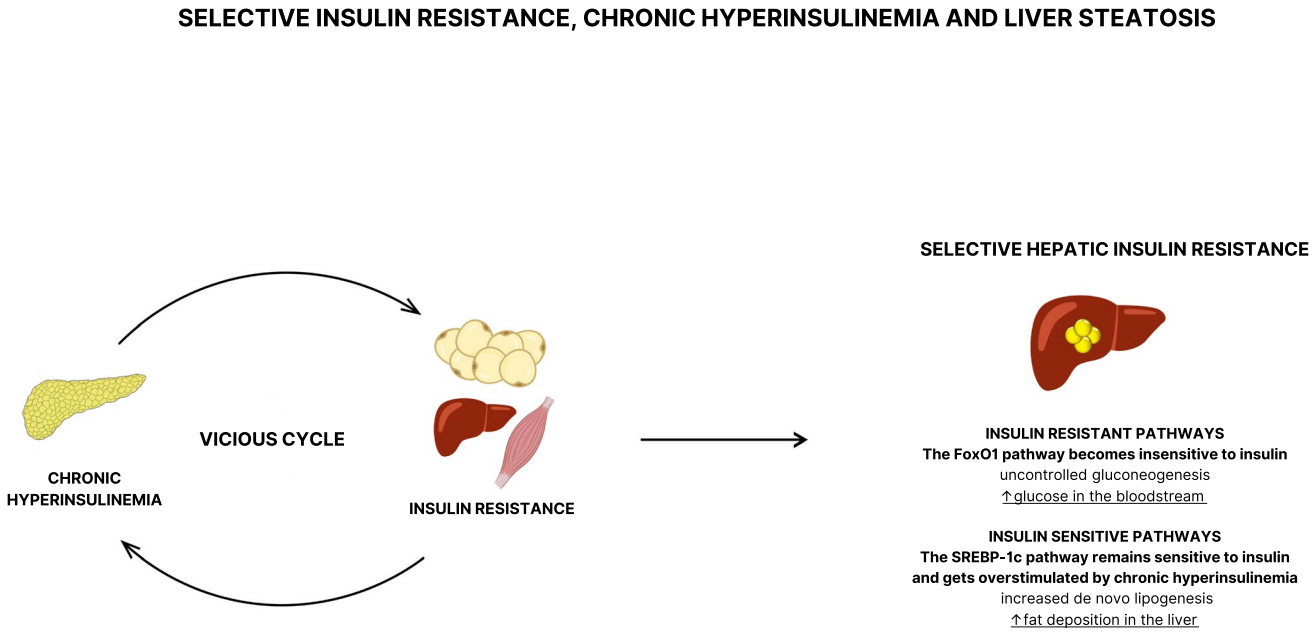

Fig. 1 Selective insulin resistance and the impact of hyperinsulinemia on hepatic lipogenesis and gluconeogenesis. Chronic hyperinsulinemia is a hallmark of insulin resistance, which is selective rather than uniform. While certain insulin signaling pathways are impaired, others remain sensitive and become overstimulated due to elevated insulin levels. In the liver, pathways involved in gluconeogenesis and glycogen synthesis become resistant to insulin, whereas the lipogenic pathway remains insulin-sensitive. This selective sensitivity leads to overstimulation of lipogenesis, resulting in hepatic fat accumulation

inhibiting mitochondrial enzymes. This inhibition impairs fat oxidation, further aggravating steatosis and promoting hepatic insulin resistance [31, 32]. Excessive fructose consumption also disrupts intestinal permeability and alters the gut microbiota, translocating endotoxins to the liver and promoting the development and progression of MASLD through gut-liver axis dysfunction [33].

Adipose Tissue Dysfunction and MASLD

In obesity, adipose tissue undergoes pathological changes characterized by adipocyte hypertrophy and hypoxia, increased infiltration of immune cells, and altered secretion of adipokines and pro-inflammatory cytokines. These changes result in chronic low-grade inflammation, another primary cause of insulin resistance [34]. When adipose tissue becomes insulin-resistant, unregulated lipolysis occurs, releasing free fatty acids into the bloodstream. The liver then takes up these acids and stores them as triglycerides under the influence of hyperinsulinemia [35].

Lipotoxicity and Inflammation

The accumulation of fat in the liver is not inert; however, triglycerides in hepatocytes are not inherently pathogenic. The same applies to triglycerides in myocytes, which, despite being a characteristic of muscle insulin resistance, are also present in insulin-sensitive endurance athletes, as illustrated in the "athlete's paradox" [36]. Lipotoxicity seems to be induced by lipid intermediates, notably diacylglycerols, and ceramides, rather than triglycerides per se. Diacylglycerols and ceramides interfere with insulin signaling and impair mitochondrial function, promoting oxidative stress and causing chronic liver inflammation, another central factor in the pathogenesis and progression of MASLD. Kupffer cells ignite inflammation, while hepatic stellate cells are crucial to developing liver fibrosis and cirrhosis [37].

Links to Obesity

Obesity is one of the strongest risk factors for MASLD. Approximately 60–70% of individuals with MASLD have obesity, and 70–90% of individuals with obesity have MASLD [38, 39]. The risk of MASLD increases with the degree of obesity, particularly central (visceral) obesity [40]. Obesity significantly influences the natural history of MASLD, impacting its progression and prognosis, including morbidity and mortality related to both liver-related disease (like cirrhosis and liver cancer) and extrahepatic conditions (like cardiovascular diseases, T2D, chronic kidney disease, and extrahepatic cancers) [41].

Natural History

The health burden of MASLD stems from both hepatic and extra-hepatic complications. MASLD begins with simple steatosis; for many patients, the disease remains stable at this stage and does not progress. In approximately 20–30% of patients, simple steatosis progresses to steatohepatitis. Then, around 40–50% of patients with steatohepatitis will progress towards fibrosis, which is the most important predictor of prognosis in MASLD [42]. Fibrosis can progress to cirrhosis in 10–20% of cases for 10–20 years. The annual incidence of HCC in MASLD patients with cirrhosis ranges from 2–7%, but 1–2% of patients can develop HCC even in the absence of cirrhosis [43]. In advanced MASLD stages, the degree of steatosis often decreases, and in the past, this led to misclassification of many cases as cryptogenic cirrhosis [44].

In addition to hepatic complications, MASLD is strongly associated with extra-hepatic conditions such as atherosclerosis, coronary artery disease, heart attacks, strokes, T2D, chronic kidney disease, extra-hepatic cancers such as colorectal, breast, and pancreatic cancers, obesity, sarcopenia, etc. These are indeed the most relevant causes of morbidity and mortality in MASLD. The relationship between MASLD and extra-hepatic diseases is bidirectional, meaning that each condition increases the risk of developing the other and worsens its progression [45]. This interplay is primarily driven by shared mechanisms such as insulin resistance, chronic inflammation, mitochondrial dysfunction, and lipotoxicity.

Medical Nutritional Therapy for MASLD

Diet plays a crucial role in the management of MASLD. Alongside drug therapy, it is an integral part of MNT and should be interpreted therapeutically and preventively, particularly by addressing unhealthy dietary habits. Evidence suggests that patients with MASLD often adhere to unhealthy nutritional patterns or, at the very least, have eating habits that deviate from a strictly healthy and balanced diet. Observational studies have examined patients' dietary habits diagnosed with MASLD, comparing them to healthy controls [46, 47]. These studies found that patients with MASLD consumed higher amounts of calories and carbohydrates [46, 47], fat, refined cereals, high-fat dairy products, and red and processed meats [47] compared to healthy counterparts, who consumed more whole grains, vegetables, and nutrients like vitamin C, selenium, vitamin E, and vitamin A [46, 47].

In addition to analyzing the intake of individual macro- and micronutrients, the diet quality was assessed using the Diet Diversity Score (DDS) and the Alternative Healthy Eating Index (AHEI). The DDS is an index assessing overall

dietary intake. It is correlated with higher consumption of macronutrients and micronutrients, better dietary adequacy, and higher intake of fiber, antioxidants, and other nutrients [48]. The AHEI, calculated using data from food-frequency questionnaires, incorporates various aspects of the original AHEI developed by Kennedy et al. [49, 50]. The AHEI considers eleven components: fruit, vegetables, whole grains, nuts and legumes, long-chain n-3 fats (docosahexaenoic acid and eicosapentaenoic acid), polyunsaturated fatty acids, consumption of wine, sugary drinks and fruit juices, red and processed meat, trans fats and sodium intake [47]. After adjusting for variables like age, sex, BMI, smoking, and physical activity, a significant inverse correlation was found between DDS and the risk of MASLD [47]. This finding remained consistent even after adjusting for dietary energy intake, showing that participants in the highest DDS quartile had a 59% lower likelihood of developing MASLD than those in the lowest quartile [47]. Additionally, a significant negative relationship was identified between the AHEI score and the likelihood of MASLD, with participants in the top quartile of AHEI having a 76% lower risk than those in the lowest quartile [47]. These studies suggest that appropriate nutritional interventions should be designed as preventive strategies to slow the progression of MASLD in at-risk individuals. Furthermore, recent evidence suggests that these interventions should also be developed as MNT, capable of positively affecting disease management [47].

Dietary Interventions

To be optimal, a dietary intervention for the management of MASLD must perfectly combine the qualitative and quantitative aspects of proper nutrition, considering both the role of individual macro- and micronutrients in the onset and development of the disease and the importance of modulating their daily intake to promote weight loss and counteract collateral pathological conditions [51].

Macronutrient Composition and Type of Diets

Evidence shows that, regardless of total caloric intake, specific macronutrients are crucial in the development and progression of MASLD [34, 52]. Carbohydrates, particularly fructose, are closely linked to liver health. In this context, it is essential to regulate the overall dietary consumption of carbohydrates, especially those with a high glycemic index, as excessive intake can contribute to obesity and metabolic alterations [53]. Reducing carbohydrate intake can significantly improve MASLD-related outcomes, including hepatic triglyceride content, triglyceridemia, lipid oxidation, and insulin resistance, as demonstrated in a recent randomized trial involving patients with overweight or obesity without T2D and diagnosed with MASLD [54] (Table 1). These results support the use of specific dietary approaches, such as the very-low-calorie ketogenic diet (VLCKD), recently renamed VLEKT [55], whose effects on improving body composition and metabolic parameters have been well-documented [56–59] and can be effectively translated into the clinical context of MASLD. Three real-life prospective studies directly investigated the effects of VLEKT on men and women diagnosed with MASLD who were overweight or obesity [23, 60, 61] (Table 1). These studies confirm the efficacy of VLEKT in reducing weight, fat mass, and insulin resistance and emphasize its effectiveness in improving hepatic outcomes associated with MASLD [23, 60, 61], as well as in reducing inflammatory status [23, 60].

In addition to carbohydrates, particular attention must also be paid to the intake of lipids in quantitative and qualitative terms. The negative role of saturated fatty acid (SFA) and trans fatty acids on general and liver health is well-known. In contrast, monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), especially omega-3 fatty acids, have a beneficial effect [62, 63]. Omega-3 supplementation is associated with an overall improvement in liver function parameters [64], as well as anti-inflammatory and antifibrotic effects [65, 66]. Mechanisms include SFA-induced triglyceride accumulation driven by endoplasmic reticulum stress, oxidative stress, upregulation of lipogenic genes, and mitochondrial dysfunction. Conversely, MUFAs and PUFAs reduce triglycerides by being preferentially directed toward oxidative pathways and downregulating lipogenic gene expression [67].

In this context, the MD, although characterized by a higher lipid intake than other dietary approaches, emphasizes unsaturated fatty acids and regular fiber intake, contributing to its health-promoting properties and ability to improve clinical conditions related to MASLD [68]. The effects of the Mediterranean-style dietary patterns were evaluated in two Randomized controlled trials (RCTs) involving subjects with grade I obesity, comparing them with a Regional Mexican diet [69] and the American Heart Association's recommendations [70] (Table 1). These studies confirm the efficacy of the MD in improving outcomes related to nutritional status, body composition, MASLD [69, 70], and inflammation [70].

Other dietary approaches, excluding gluten and amylase trypsin inhibitors, have been proposed as MNT for MASLD. However, the evidence is still emerging, and further studies are needed to confirm their validity. A 6-week RCT on adults with overweight and obesity demonstrated that this dietary approach resulted in weight reduction, improved insulin resistance, and reduced markers of steatosis [71]. The rationale for this approach lies in understanding the gut-liver axis, which links altered intestinal permeability to the entry of pro-inflammatory substances into the bloodstream, stimulation of the immune system, and activation of gut-derived

Table 1 Main studies describing non-pharmacological interventions in patients with MASLD

Type of study	Intervention	Sample	Duration	Main results	Reference
Diet					
RCT	MD vs. regional Mexican diet	35 adults with grade I obesity on average	24 weeks	MD significantly reduced: • BW, BMI, VAT, WC, HC • ALT • CAP Regional Mexican diet significantly reduced: • BW, BMI, WC, HC • AST, ALT	[66]
RCT	MD-based FLiO diet vs. AHA diet	98 adults ($n=48$, AHA; $n=50$, FLiO) with grade I obesity on average	2 years	Both diets improved liver and metabolic parameters. The FLiO diet showed better results in: • Reduction of WC, TG and FLI (particularly at 12 and 24 months) • Reduction in markers of inflammation, specifically, reduction in chemerin and increase in adiponectin	[67]
RCT	Gluten/ATI-free diet vs. DGE diet	39 adults ($n=18$, ATI-free diet; $n=21$ DGE diet) with overweight and obesity	6 weeks	The Gluten/ATI-free diet significantly reduced: • BMI • CAP • IR	[68]
R, CO	Eucaloric low-CHO diet vs. high-CHO diet	11 adult men with overweight or obesity, without type 2 diabetes	4 days	Only 4 days of low-CHO diet significantly reduced: • Liver TG content and fasting plasma TG • Whole body RER Only 4 days of low-CHO diet significantly increased: • Fat oxidation • Hepatic insulin sensitivity index	[51]
Real-life prospective	VLEKT	87 adult men ($n=30$) and women ($n=57$) with grade II obesity on average	8 weeks	Significant reductions in: • BMI, WC, FM • prevalence of subjects with steaosis and fibrosis • CAP • ALT, γGT • IR • WBC and platelet counts	[23]
Real-life prospective	VLEKT	112 adult men ($n=37$) and women ($n=75$) with overweight/obesity	8-weeks	Significant reductions in: • BW, BMI, WC, FM • CAP • Liver stiffness (only in men) • ALT, γGT • AST (only in men) • IR • CRP (only in men)	[57]

Table 1 (continued)

Type of study	Intervention	Sample	Duration	Main results	Reference
Real-life prospective	VLEKT	111 adult men ($n=37$) and women ($n=75$) with overweight/obesity	8 weeks	Significant reductions in: • BMI, WC, FM • CAP • ALT, γGT • IR	[58]
Supplements					
R, DB, PC	103.2 mg/d silymarin	83 adults ($n=41$, placebo; $n=42$, intervention)	24 weeks	Compared to placebo, silymarin supplementation significantly reduced: • Liver stiffness • γGT • ApoB Silymarin also significantly modulated microbiota composition and bacterial population abundance	[104]
R, DB, PC	4000 IU/d vitamin D	46 adults ($n=23$, placebo; $n=23$, intervention)	12 weeks	Compared to placebo, vitamin D supplementation significantly reduced: • AST, ALT • Laminin and hyaluronic acid • MiR-21 and MiR-122 s gene expression	[105]
R, DB, PC	Symbiotic (*Lactobacilli, Bifidobacteria*, and inulin)	84 adults with on average overweight ($n=43$, placebo; $n=41$, intervention)	12 weeks	Compared to placebo, symbiotic supplementation significantly reduced: • ATT • CRP	[106]
Physical activity					
RCT	35 to 50 min (week 1 to week 6) moderate-intensity (70–75% FCmax) continuous walking or cycling	24 men with on average obesity ($n=13$, control; $n=11$, intervention)	6 weeks	Moderate-intensity exercise does not appreciably change hepatic lipid composition compared to control	[116]
RCT	HIIT	40 adolescents with grade II obesity on average, at risk for MASLD ($n=6$, control; $n=34$, intervention)	4 weeks	HIIT significantly decreased intrahepatic triglyceride content, but no significant differences were observed compared to control	[117]

MASLD; metabolic dysfunction-associated steatotic liver disease, *di RCT;* randomized clinical trial, *MD;* Mediterranean Diet, *BW;* body weight, *BMI;* body mass index, *VAT;* visceral adipose tissue, *WC;* waist circumference, *HC*; hip circumference, *ALT;* alanine aminotransferase, *AST;* aspartate aminotransferase, *CAP;* controlled attenuation parameter, *FLiO;* Fatty Liver in Obesity, *AHA;* American Heart Association, *TG;* triglycerides, *FLI;* fatty liver index, *ATI;* amylase trypsin inhibitors, *DGE;* Deutsche Gesellschaft für Ernährung, *IR;* insulin resistance, *R;* randomised, *CO;* cross-over, *CHO;* carbohydrates, *RER;* respiratory exchange ratio, *VLEKT;* very low-energy ketogenic diet, *FM;* fat mass, *γGT;* gamma-glutamyltranspeptidase, *WBC;* white blood cell, *CRP;* C-reactive protein, *DB;* double-blind, *PC;* placebo-controlled, *ApoB;* apolipoprotein B, *MiR;* microRNA, *ATT;* attenuation coefficient, *HIIT;* high-intensity interval training

signals. This leads to systemic and local inflammation and morpho-functional alterations of extra-intestinal organs, including the liver [72]. Amylase trypsin inhibitors, proteins in gluten-containing foods, stimulate enteric innate immunity [73], promoting an inflammatory process in metabolic disease models, including MASLD [74]. However, the use of gluten-free diets remains debated due to the risk of unhealthy dietary patterns, potential micronutrient deficits, and excessive consumption of high-calorie-density foods and carbohydrates, especially fructose, which may increase the risk of MASLD [75].

Intermittent fasting (IF) [76, 77] and a vegetarian diet (VegD) [78] have also been considered for their potential effect on MASLD risk factors. Even though no clinical trials have been conducted explicitly on patients diagnosed with MASLD to date, a recent meta-analysis showed that two types of IF, the 5:2 diet and time-restricted eating, resulted in significant improvements in liver stiffness and steatosis, respectively, without other significant changes in liver, metabolic, or body composition parameters, except for alternate-day fasting, which improved these outcomes [76]. This suggests the need for an approach tailored to patient needs and characteristics. Although the evidence on IF's effects in managing obesity and related morbid conditions is conflicting, there is a broad agreement on using this approach to increase dietary compliance [79]. Therefore, IF could be a valid tool for managing MASLD by primarily reducing weight and fat mass (particularly visceral fat), improving metabolic and liver function parameters, and reducing inflammation [77], though further studies are needed. Similarly, VegD has been proposed as a possible dietary approach for managing MASLD due to its beneficial effects in controlling or counteracting the main modifiable risk factors [78]. However, the lack of specific studies on this patient group prevents definitive conclusions from being drawn.

It is essential to highlight that, irrespective of the type of MNT prescribed for MASLD patients, the diet must be carefully designed to ensure adequate protein intake, vital for preventing muscle mass loss. This is crucial as MASLD patients are prone to muscle catabolism, increasing their risk of sarcopenia [80, 81]. Regular fiber intake also reduces MASLD risk, [82] through mechanisms such as an increased sense of satiety [83], regulation of the gut microbiota with increased production of short-chain fatty acids [82, 84], and reduced intestinal absorption of nutrients [85, 86], particularly cholesterol and low-density lipoprotein, contributing to improved liver health [87] and weight management [86].

Caloric Restriction and Weight Loss

As discussed above, diet quality and macronutrient composition are critical factors in setting an optimal MNT. Nonetheless, in clinical contexts such as MASLD, where obesity plays a pivotal role, the quantity of individual macronutrients and daily caloric intake must also be finely controlled. This is because a negative energy balance positively affects improving MASLD [88]. Weight loss interventions have been significantly associated with improved liver parameters, including alanine aminotransaminase levels, steatosis, histologic NAFLD activity score, and nonalcoholic steatohepatitis [89]. In the studies reported in Table 1, improvements in liver function parameters were observed following a diet therapy protocol involving substantial calorie restriction, such as VLEKT [23, 60, 61].

The effects of weight loss on hepatic parameters appear to be dose-dependent. A meta-analysis of 43 studies reported that each kilogram of weight loss is associated with a 0.83-unit reduction in alanine aminotransferase and a 0.56-unit reduction in aspartate aminotransferase. Additionally, it is related to a reduction in steatosis: a 0.77 percentage point decrease when evaluated by histology or magnetic resonance imaging and a 0.03-point reduction when assessed using a 0–3 scale evaluated by histology or ultrasound [90]. Mechanistically, weight loss improves the hepatic metabolism of substrates by increasing muscle and adipose tissue sensitivity to insulin, observable with just a 5% reduction in weight [18]. A large prospective study reported a dose–response relationship between weight loss and liver outcomes, with a 10% or more significant decrease in weight leading to the resolution of steatohepatitis or improvement in fibrosis [14]. Similarly, weight reduction results in marked improvement in MASLD risk factors, particularly T2D, cardiovascular disease, and inflammation [91]. Based on these observations, current recommendations for weight management in MALSD patients suggest a weight loss of at least 5%, preferably 10% or more, as a nutritional goal [51, 92, 93].

Specific Nutrients and Supplements

Nutraceuticals, food-derived bioactive compounds used in conjunction with (and not as a substitute for) drugs as add-on therapy, represent another important aspect of multifactorial MASLD management by supplementing the diet. Table 1 shows randomized, double-blind, placebo-controlled clinical trials conducted on MASLD patients investigating the effects of supplementation with silymarin [94], vitamin D [95], and symbiotics [96] on liver function parameters. These studies, conducted on an adequate number of subjects (ranging from 46 to 84), with appropriate randomization and suitable intervention durations (12 to 24 weeks), reported significant improvements in liver parameters compared with placebo. Both silymarin [94] and symbiotics [96] were found to help modulate the gut microbiota, suggesting a role in controlling the gut-liver axis, another important target in MASLD management. Vitamin D supplementation was observed to downregulate the expression of microRNAs (MiR)−21 and

122 s, which are implicated in MASLD pathogenesis [95]. Despite these findings, it should be emphasized that these are single studies on this specific patient population, and the overall evidence is not robust enough to draw definitive conclusions and recommendations regarding optimal supplementation in MASLD patients. However, several recent reviews have described the beneficial effects of specific nutraceuticals on liver health, suggesting the possibility of translating this information into MASLD management. Some key examples include:

- Vitamin E: As an antioxidant agent, vitamin E is listed in the European guidelines for the management of NAFLD because it reduces steatosis at a dosage of 800 IU/day. Although its supplementation is safe in trials investigating its effects, some concerns remain regarding its long-term use [88, 97].
- Omega-3: They exert significant immunomodulatory and anti-inflammatory effects, as well as being components of membrane phospholipids [98, 99]. Human studies have shown reductions in circulating liver enzyme levels following omega-3 supplementation. Mechanistically, they primarily reduce blood lipid levels by downregulating the expression of lipogenic genes and promoting fatty acid oxidation in place of glucose oxidation in the postprandial phase, resulting in decreased hepatic triglyceride accumulation [98, 99]. They also appear to act on peroxisomes and inhibit hepatic de novo lipogenesis, contributing to an antisteatotic effect. Since various studies define the dose of total EPA, DHA, or omega-3 administered differently, an optimal dosage cannot be identified [98, 99].
- Sylimarin: This mixture of flavonolignans extracted from milk thistle, with silybin as the main constituent [100], has historically been used as a hepatoprotective principle in various liver diseases. A recent meta-analysis investigating its supplementation effects in NAFLD patients demonstrated significant reductions in aspartate transaminase, alanine aminotransferase, and triglycerides [101].
- Curcumin: One of the curcuminoids, curcumin is a lipophilic compound extracted from the root of Curcuma longa and historically used in traditional medicine and nutraceuticals for its many health-promoting properties, including antioxidant, anti-inflammatory, and immunomodulatory effects [102]. Given its primarily hepatic metabolism, curcumin has long been studied for its potential effects on liver health, which may contribute to MASLD management. Curcumin modulates de novo lipogenesis by acting on lipogenic enzymes and upregulating lipolytic protein expression. These effects, combined with improved insulin sensitivity, help decrease the buildup of lipids in the liver [102]. The antisteatotic effect of curcumin is also attributed to its inhibitory action on lipolysis. Associated with these mechanisms are antioxidant, anti-inflammatory, and gut microbiota modulation effects, which together contribute to the multifactorial management of MASLD [102]. Despite these promising effects, concerns remain regarding its use, particularly its poor bioavailability after oral administration and potential side effects, especially in the liver.
- Vitamin C: It might inhibit fibrosis, thus preventing liver dysfunction. Though the precise mechanisms remain unclear, it is hypothesized that this effect may be attributed to vitamin C's role in collagen production and its essential antioxidant effect. No conclusive guidance is available regarding optimal dosing [99].
- Polyphenols: They are the largest class of bioactive compounds in foods, with potent antioxidant and anti-inflammatory activities, complemented by their effects on modulating the gut microbiota and counteracting obesity [103]. This makes them good candidates for MASLD management. Among the approximately 8,000 molecules in the polyphenol family, chlorogenic acid [104] and resveratrol [105] have been described for their potential effects in managing conditions predisposing to or aggravating MASLD. Although these molecules belong to different polyphenol subclasses and are extracted from other sources, they share similar antioxidant, anti-inflammatory, and antisteatotic effects, with mechanisms involving pathways common to almost all polyphenols, such as inhibition of NF-κB, stimulation of Nrf2, and activation of AMPK. Chlorogenic acid and resveratrol also stimulate insulin and PGC-1α [104, 105]. It is possible that other polyphenolic compounds could influence liver health through similar mechanisms, but further studies are needed to confirm this hypothesis. Concerns about the therapeutic efficacy of polyphenols persist, mainly due to their poor bioavailability.

Behavioral and Lifestyle Interventions

In addition to drug therapy and MNT, appropriate lifestyle interventions are necessary to prevent MASLD and slow disease progression. From a multidisciplinary perspective, a regular exercise program should accompany dietary interventions and possible nutraceutical supplementation. Exercise, in addition to optimizing the benefits of other interventions, is mandatory for the long-term maintenance of weight loss [88].

Only two RCTs have directly investigated the effects of specific exercise programs on adults with obesity and MASLD [106] and adolescents with obesity and at risk for MASLD [107] (Table 1). These studies provide inconclusive results, reporting that, although exercise alone leads to beneficial effects, no significant improvements in liver outcomes were observed compared to controls. The results

of these two studies do not permit definitive conclusions to be drawn for several reasons. Firstly, the study populations differed, as did the training programs: one study involved moderate-intensity walking or cycling with progressively increased duration from 35 to 50 min over six weeks [106]. While the other employed a high-intensity interval training program [107]. Secondly, the study on adults with MASLD had a limited sample size ($n = 24$), whereas the study on adolescents at risk for MASLD had an unequal distribution between intervention and control groups ($n = 6$ and 34, respectively). Therefore, appropriately designed studies are necessary to define suitable tailored training programs for this patient population.

Despite the lack of specific evidence for MASLD patients, previous studies have demonstrated the beneficial effects of exercise on improving liver parameters and have identified specific training programs that could be useful for MASLD management. A meta-analysis of sixteen RCTs showed that regular exercise reduces liver fat content even without dietary intervention [108]. Similarly, aerobic exercise reduced fibrosis, as assessed by liver biopsy, in most study participants (60%) over 12 weeks [109].

The benefits of exercise on liver health depend on factors such as the type of exercise (aerobic, anaerobic, mixed, or high-intensity interval exercise), the duration of the intervention, and the duration and frequency of exercise sessions. For long-term weight loss maintenance, exercise programs should include at least 200–300 min of aerobic activity *per* week (e.g., brisk walking) [93]. Specific guidelines differ significantly. The American Association for the Study of Liver Diseases recommends at least 150 min/week of moderate-intensity exercise (combined aerobic and resistance exercises) [92, 110]. This should be structured into 3–5 sessions *per* week, according to the joint European guidelines of the European Association for the Study of the Liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity [97]. The American Gastroenterological Association recommends 75–150 min/week of vigorous-intensity activity or 150–300 min of moderate-intensity activity [111]. The overall recommendation is encouraging patients to exercise regularly, with programs tailored to their needs and goals [92] (Fig. 2).

Outcomes of MNT

Several clinical trials consistently demonstrate that weight loss in adults with overweight or obesity, whether achieved through dietary changes or combined with increased

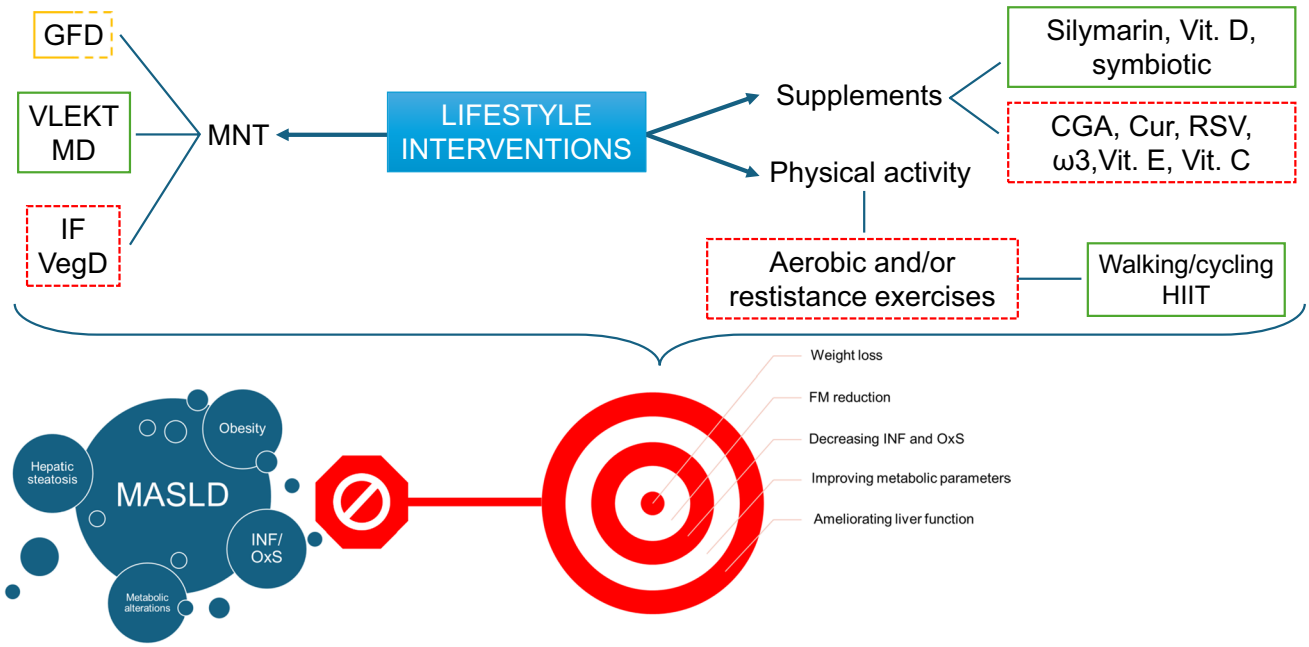

Fig. 2 Main lifestyle interventions and nutritional goals for the management of MASLD. The solid lines in the boxes represent evidence from studies specifically conducted on patients diagnosed with MASLD. The dashed lines indicate interventions that have been proposed or may be beneficial in managing MASLD, but for which specific studies on this patient group are lacking. The half-dashed, half-continuous box represents evidence that requires further confirmation. Abbreviations: GFD, gluten-free diet; VLEKT, very low-energy ketogenic therapy; MD, Mediterranean Diet; IF, intermittent fasting; VegD, vegetarian diet; MNT, medical nutrition therapy; Vit D-E-C, Vitamins D, E, and C; CGA, chlorogenic acid; Cur, curcumin; RSV, resveratrol; HIIT, high-intensity interval training; INF, inflammation; OxS, oxidative stress; MASLD, metabolic-associated steatotic liver disease

physical activity, results in significant metabolic improvements associated with MASLD [89, 112]. These improvements include reductions in liver enzymes, hepatic steatosis, and fibrosis, with a clear dose–response relationship between the magnitude of weight loss and enhancements in these biomarkers [90]. Specifically, a ≥ 5% reduction in body weight is typically required to significantly decrease hepatic lipid content, while 7–10% weight loss is needed to mitigate hepatic inflammation, and ≥ 10% is necessary to reduce fibrosis [14]. However, these weight loss targets remain difficult to achieve and maintain, with many patients unable to sustain ≥ 5% weight loss [14]. Furthermore, the impact of lifestyle-induced weight loss on advanced fibrosis and cirrhosis is less understood, given the limited representation of these stages in clinical trials and the lack of targeted subgroup analyses [14].

In terms of improving liver-related metabolic outcomes, dietary strategies such as the MD have shown promise in enhancing hepatic health. The MD's effects on metabolic pathways involve improvements in lipid metabolism, insulin sensitivity, and a reduction in oxidative stress, driven by its high content of polyphenols and omega-3 fatty acids [113, 114]. Oxidative stress is a crucial determinant in the pathophysiology of NAFLD and obesity, contributing to mitochondrial dysfunction, hepatocyte stress, and inflammation, which accelerate disease progression toward non-alcoholic steatohepatitis [115]. Given these underlying mechanisms, the MD is often recommended due to its antioxidant properties. However, it remains debated whether MD adherence directly impacts NAFLD risk or does so indirectly through weight regulation. A study involving 336 subjects with overweight or obesity found that high adherence to the MD, as assessed by the PREvención con DIetaMEDiterránea (PREDIMED) questionnaire, was the main predictor of a lower Fatty Liver Index (FLI), independent of visceral adipose tissue [116]. In a 6-month intervention, patients following an MD and lifestyle program showed improved liver stiffness, body mass index, low-density cholesterol, and non-high-density lipoprotein cholesterol. However, other liver function markers did not show significant differences compared to controls [117]. Additionally, a study comparing the MD with a low-fat diet over 12 weeks found similar reductions in hepatic steatosis. However, the MD led to greater reductions in alanine aminotransferase, gamma-glutamyltransferase, hepatic fat, and markers of glycemic control such as hemoglobin A1c [118]. In patients with NAFLD and obesity, the MD improved the FLI compared to a low-fat diet, highlighting its role in managing liver-specific metabolic markers [119].

Other novel dietary patterns, like the VLEKT, have effectively targeted metabolic parameters central to MASLD, including reductions in body weight, hepatic steatosis, inflammatory markers, and improvements in glucose and lipid parameters [19, 120, 121]. A 25-day VLEKT intervention in patients with obesity led to reductions in gamma-glutamyltransferase and liver steatosis, with men showing more significant metabolic improvements than women [122]. Another 8-week study observed reductions in body mass index, liver steatosis, fibrosis, and low-grade inflammation, particularly in those with higher baseline steatosis, and improvements in glucose metabolism, lipid profile, and blood pressure [23].

IF, specifically time-restricted eating, has shown potential for achieving metabolic benefits similar to continuous calorie restriction. Time-restricted eating has been associated with more significant improvements in glycemic control and reprogramming of circadian rhythms, which may positively influence metabolic outcomes in MASLD [123]. Furthermore, evening chronotypes have been linked to more severe NAFLD, suggesting the relevance of chrononutrition in addressing circadian misalignment [124].

Lastly, caffeinated or decaffeinated coffee consumption consistently correlates with a reduced risk of fibrosis and modest effects on steatosis [125–127]. Regular intake of ≥ 3 cups daily has been associated with lower liver stiffness, reinforcing its role in mitigating fibrosis risk [127].

In summary, while these interventions show promise, sustaining these metabolic improvements remains challenging. Weight regains are expected after the initial 6-month period, leading to partial recovery of hepatic steatosis and stiffness. Long-term studies are needed to better understand the durability of metabolic outcomes and their impact on liver-related morbidity and mortality. Additionally, personalized approaches considering patient preferences, clinical profiles, and socioeconomic factors could enhance adherence and optimize long-term efficacy.

Conclusions

MNT is crucial in managing MASLD by reducing liver fat, improving metabolic parameters, and preventing both hepatic and extrahepatic complications. Evidence suggests that specific dietary interventions, such as the MD and low-carbohydrate diets, caloric restriction, and macronutrient quality control, can significantly improve clinical outcomes in patients with MASLD. Furthermore, nutraceutical supplements like omega-3 fatty acids and vitamin E have demonstrated potential benefits in reducing inflammation and hepatic fibrosis.

The importance of a multidisciplinary approach in managing MASLD cannot be overstated. Combining MNT with lifestyle interventions, including regular physical activity and pharmacological treatment, when necessary, provides a comprehensive strategy that addresses the multiple factors contributing to the progression of the disease. This holistic

approach is essential for optimizing long-term outcomes and enhancing patients' quality of life.

Despite advancements in the understanding and management of MASLD, there remains a clear need for ongoing research to refine MNT strategies and to personalize treatments based on individual patient characteristics. Future research should focus on long-term studies that evaluate the sustainability of metabolic and hepatic benefits achieved through MNT and the development of new dietary interventions that are both effective and straightforward to implement in everyday clinical practice.

In summary, MNT is a powerful tool in the fight against MASLD. Still, its success depends on a coordinated and continuous approach that integrates multiple disciplines and is guided by the latest evidence to inform clinical practice and future therapeutic innovations.

Abbreviations AHEI: Alternative Healthy Eating Index; DDS: Diet Diversity Score; FLI: Fatty Liver Index; HCC: hepatocellular carcinoma; IF: intermittent fasting; MASH: metabolic dysfunction-associated steatohepatitis; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease; MAFLD: Metabolic Dysfunction-Associated Fatty Liver Disease; MD: Mediterranean diet; MNT: Medical Nutritional Therapy; MUFA: monounsaturated fatty acid; NAFLD: Non-Alcoholic Fatty Liver Disease; PREDIMED: PREvención con DIeta-MEDiterránea; PUFA: polyunsaturated fatty acids; RCTs: Randomized controlled trials; ROS: reactive oxygen species; SFA: saturated fatty acid; T2D: type 2 diabetes; VegD: vegetarian diet; VLEKT: very low-energy ketogenic therapy

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Declarations

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