

## Dietary Strategies in Metabolic-Associated Steatotic Liver Disease: Effects of Mediterranean, Ketogenic, and Plant-Based Diets on Liver Fibrosis Progression

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### Abstract

**Background and Aims:** Metabolic-associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease globally, ranging from simple steatosis to fibrosis and metabolic-dysfunction associated steatohepatitis (MASH), which may progress to cirrhosis and hepatocellular carcinoma (HCC). Dietary patterns significantly influence MASLD progression, particularly fibrosis, but evidence for specific interventions remains incomplete. This review evaluates the efficacy of Mediterranean, ketogenic, and plant-based diets in reducing fibrosis and improving MASLD outcomes.

**Methods:** A comprehensive review of the literature was conducted using PubMed, Scopus, and Web of Science to identify studies published within the last 15 years. Keywords included "MASLD," "MASH," "dietary patterns," "Mediterranean diet," "ketogenic diet," "plant-based diet," and "liver fibrosis." Inclusion criteria focused on studies evaluating dietary interventions with outcomes such as fibrosis markers, hepatic triglyceride content, liver enzymes, and metabolic parameters. Studies were filtered for relevance, language (English), and methodology, with exclusion criteria including alcohol-related or secondary liver diseases.

**Results:** The Mediterranean diet (MedDiet), characterized by high monounsaturated fats, fiber, and antioxidants, consistently reduced liver inflammation, fibrosis markers, and hepatic fat accumulation. The ketogenic diet (KD) demonstrated improvements in hepatic triglyceride reduction and insulin sensitivity but raised concerns about long-term cardiovascular and hepatic safety. Plant-based diets showed promise in mitigating fibrosis through anti-inflammatory and antioxidant effects, although nutrient deficiencies and adherence challenges were noted. In contrast, the Western diet exacerbated MASLD progression due to high saturated fat, refined sugar, and low fiber intake. Mechanistic insights highlighted the roles of insulin resistance, oxidative stress, and inflammation in dietary effects.

**Conclusion:** Dietary interventions, particularly the Mediterranean diet, offer a non-invasive and sustainable strategy for managing MASLD and mitigating fibrosis progression. While the ketogenic and plant-based diets show potential, their long-term safety and effectiveness require further research. Personalized dietary approaches, combined with lifestyle modifications, are critical to optimizing outcomes in MASLD management. Future studies should focus on long-term, patient-centered strategies to enhance adherence and assess the durability of dietary impacts on liver fibrosis.

**Keywords:** MASLD, MASH, dietary patterns, Liver fibrosis, Mediterranean diet, Ketogenic diet, Plant-based diet.

### Introduction

Metabolic-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), encompasses a spectrum of liver conditions characterized by  $\geq 5\%$  steatosis in hepatocytes without secondary causes such as alcohol use, drugs, or viral infections. It includes simple steatosis, fibrosis, and metabolic dysfunction-associated steatohepatitis (MASH), the latter involving inflammation and liver cell injury that may progress to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) (Pouwels et al., 2022; Sahu et al., 2023). While liver biopsy remains the diagnostic gold standard, non-invasive methods like ultrasound, magnetic resonance imaging, and elastography (e.g., FibroScan) are increasingly utilized but cannot differentiate between simple

steatosis and MASH (Martinou et al., 2022). The need for effective non-invasive diagnostic tools highlights the urgency to address this growing global health challenge.

MASLD is now the most common cause of chronic liver disease worldwide, with an estimated prevalence ranging from 23.5% in the United States to 17–46% in Western countries (Francque et al., 2021). Early-stage MASLD is often asymptomatic, but advanced stages, including MASH and fibrosis, significantly impact patients' quality of life and increase the risk of complications such as cardiovascular disease, renal impairment, and HCC (Kosmalski et al., 2023). Key risk factors include obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and arterial hypertension, collectively termed "metabolic

syndrome.” These factors contribute to MASLD progression and associated mortality, underscoring the importance of effective interventions.

Lifestyle modification is the cornerstone of MASLD management. Evidence suggests that weight loss through dietary changes can reverse disease progression, with reductions of 5–10% body weight improving the MASLD activity score (NAS) and >10% weight loss benefiting MASH patients by slowing fibrosis progression (Petagine et al., 2023; Dyńska et al., 2024). The Mediterranean diet (MedDiet) is widely recommended due to its high content of olive oil, vegetables, fruits, and seafood, alongside limited red and processed meats. Emerging evidence also highlights the potential of ketogenic and plant-based diets in MASLD management, though further investigation is warranted. The ketogenic diet shows promise for reducing hepatic triglyceride accumulation and improved insulin sensitivity. This review explores the role of dietary patterns in slowing fibrosis progression and improving MASLD outcomes.

### Methodology

This paper employed a comprehensive review of the existing literature to explore the impact of dietary patterns on the management of metabolic-associated steatotic liver disease (MASLD) and the progression of liver fibrosis. A structured approach was adopted to ensure a thorough identification, analysis, and synthesis of relevant studies.

The literature search involved systematic queries across databases including PubMed, Scopus, and Web of Science. Articles published within the last 15 years were targeted, using keywords such as "metabolic-associated steatotic liver disease," "MASLD," "MASH," "dietary patterns," "Mediterranean diet," "ketogenic diet," "plant-based diet," "liver fibrosis," and "metabolic syndrome." Studies were filtered for relevance, language (English), and methodology, focusing on randomized controlled trials, cohort studies, systematic reviews, and meta-analyses.

Inclusion criteria encompassed studies evaluating dietary interventions (Mediterranean, ketogenic, and plant-based diets) in MASLD and MASH patients, with outcomes including liver fibrosis markers, hepatic triglyceride content, liver enzymes, and metabolic parameters. Articles discussing MASLD pathophysiology and mechanisms underlying dietary effects were also included. Exclusion criteria ruled out studies lacking primary data, such as opinion pieces, or those focusing on alcohol-related liver disease or secondary liver dysfunction.

Key data points extracted included study design, sample size, duration, dietary interventions, and clinical outcomes. Findings were categorized by dietary patterns and analyzed for their impact on hepatic health, metabolic parameters, and fibrosis progression. Mechanistic insights, such as the roles of insulin resistance, inflammation, and oxidative stress, were integrated to provide a comprehensive understanding of dietary efficacy.

The review employed a comparative framework to assess the relative efficacy of Mediterranean, ketogenic, and plant-based diets in reducing liver fibrosis and improving metabolic health. Challenges such as adherence, sustainability, and long-term outcomes were also examined to provide actionable recommendations. Since this was a review-based study, no

primary data were collected, and ethical approval was not required. All sources were appropriately cited and acknowledged.

### Pathophysiology of Liver Fibrosis in MASLD

The accumulation of lipids, including free fatty acids (FFAs), within hepatocytes disrupts cellular signaling and contributes to inflammation, oxidative stress, and fibrosis, which are key drivers in the progression of metabolic-associated steatotic liver disease (MASLD). The "multiple hit" model has been widely adopted to describe the complex cellular processes underlying MASLD, emphasizing the interplay between lipid accumulation and associated cellular dysfunction (Shabalala et al., 2020). Given the multifactorial nature of MASLD pathogenesis, it is unlikely that a single therapeutic approach will suffice for its treatment.

One significant "hit" is insulin resistance, commonly associated with metabolic syndrome, obesity, and type 2 diabetes mellitus (T2DM). Insulin resistance disrupts lipolysis in non-hepatic adipose tissue during the postprandial state, contributing to increased circulating FFAs (Buzzetti et al., 2016). Another contributing factor is an altered gut microbiome, which enhances fatty acid absorption and elevates circulating lipid levels (Buzzetti et al., 2016). Together, these mechanisms overload the liver with FFAs, precipitating lipotoxic effects such as impaired intracellular signaling and mitochondrial dysfunction, resulting in reduced ATP production (Buzzetti et al., 2016). These disruptions lead to oxidative stress, the formation of reactive oxygen species (ROS), and lipid peroxidation (Sharma et al., 2023). ROS production and low-density lipoprotein (LDL) oxidation further exacerbate inflammation, activate hepatic stellate cells, and promote fibrous tissue deposition (Buzzetti et al., 2016). Preventing MASLD progression before extensive cellular damage and hepatic fibrosis occur is essential to improve patient outcomes.

Distinct cellular mediators involved in MASLD pathogenesis provide potential targets for therapy. FFAs, oxidative stress, and pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  activate inflammasomes, which directly influence hepatic stellate cells (Buzzetti et al., 2016). Kupffer cells, the resident macrophages of the liver, also contribute to inflammasome activation by producing IL-1 $\beta$ , which amplifies the immune response, tissue damage, and stellate cell-mediated fibrosis (Buzzetti et al., 2016). Targeted therapies addressing these mediators are under investigation. For instance, adiponectin has shown promise in reducing inflammation and improving cellular signaling (Shabalala et al., 2020). Thiazolidinediones, despite their ability to enhance adiponectin levels, have limited use due to their side effect profile (Sharma et al., 2023). Similarly, glucagon-like peptide-1 (GLP-1) receptor agonists have been proposed as potential agents for slowing hepatic fibrosis progression, particularly in patients with metabolic syndrome (Nevola et al., 2023). These pharmacological approaches may benefit patients who struggle to manage their condition through lifestyle modifications alone, though the risk of adverse effects must be carefully considered.

### Dietary Patterns and Their Nutritional Characteristics

#### The Mediterranean Diet

The Mediterranean diet, rich in vegetables, fruits, legumes, whole grains, nuts, seeds, and olive oil, has garnered significant attention for its role in managing metabolic-associated steatotic

liver disease (MASLD) and liver fibrosis. Its anti-inflammatory and antioxidant properties make it a cornerstone dietary intervention for these conditions. By mitigating inflammation and oxidative stress—key contributors to liver disease progression—the Mediterranean diet reduces hepatic triglyceride accumulation, a hallmark of MASLD, primarily due to its high content of unsaturated fats, particularly from olive oil (Zelber-Sagi et al., 2017; Godos et al., 2017). Unsaturated fats improve lipid metabolism, decrease fat storage within liver cells, and enhance insulin sensitivity, thereby addressing critical mechanisms underlying MASLD progression.

Adherence to the Mediterranean diet is associated with lower levels of fibrosis markers, such as Pro-C3, indicative of reduced collagen deposition and liver damage (Baratta et al., 2022; Younossi et al., 2021). By mitigating fibrosis progression, this diet demonstrates the potential to prevent more severe stages of liver disease. The diet's protective effects are further enhanced by polyphenols, omega-3 fatty acids, and monounsaturated fats, which suppress inflammation by inhibiting nuclear factor-kappaB (NF-κB) and reducing pro-inflammatory cytokines like TNF-α and IL-6 (Zelber-Sagi et al., 2017; Godos et al., 2017). These components also reduce oxidative stress through enhanced antioxidant enzyme activity, protecting hepatocytes from chronic inflammation—a primary driver of fibrosis.

Moreover, omega-3 fatty acids sourced from fish and nuts, alongside monounsaturated fats from olive oil, improve lipid metabolism by lowering LDL cholesterol, increasing HDL cholesterol, and reducing hepatic fat content (Assy et al., 2009; Monserrat-Mesquida et al., 2022; Quetglas-Llabrés et al., 2024). Through its multifaceted ability to alleviate inflammation, optimize oxidative balance, and improve lipid profiles, the Mediterranean diet offers a comprehensive strategy for preventing liver damage and supporting hepatic health.

### **The Role of Fiber in Glucose Regulation and Insulin Sensitivity**

A key attribute of the Mediterranean diet is its high fiber content, which plays a critical role in managing MASLD by stabilizing blood sugar levels and improving insulin sensitivity. Fiber-rich foods, such as whole grains, legumes, and vegetables, slow glucose absorption in the gut, preventing postprandial glucose spikes and reducing the strain on insulin-producing cells (Zelber-Sagi et al., 2017). Monounsaturated fats from olive oil further complement these effects by optimizing insulin signaling pathways and mitigating insulin resistance (Godos et al., 2017; Ryan et al., 2013). The diet has also been shown to reduce markers of collagen deposition, such as Pro-C3, through its ability to minimize chronic inflammation and oxidative stress—both significant drivers of liver fibrosis (Baratta et al., 2022; Younossi et al., 2021). These combined effects make the Mediterranean diet a holistic approach to addressing both metabolic and structural abnormalities in MASLD.

### **Clinical Evidence Supporting the Mediterranean Diet**

Numerous clinical studies demonstrate the Mediterranean diet's efficacy in managing MASLD. Randomized controlled trials and observational research show that adherence to this diet improves liver enzymes, reduces liver stiffness, and enhances metabolic outcomes (Kaliora et al., 2019; Quetglas-Llabrés et al., 2023). The reduction of hepatic fat accumulation and systemic inflammation underpins these improvements. Furthermore, the Mediterranean diet reduces platelet activation

and collagen deposition, thereby lowering the risks of thrombosis and fibrotic liver changes (Baratta et al., 2022). The European Association for the Study of the Liver (EASL) has endorsed the Mediterranean diet as the primary dietary intervention for MASLD, emphasizing its role in addressing both metabolic and structural challenges associated with liver disease (Zelber-Sagi et al., 2017).

### **The Ketogenic Diet: A Metabolically Targeted Intervention**

The ketogenic diet (KD) is characterized by high fat, moderate protein, and very low carbohydrate intake, which induces a state of ketosis. In ketosis, the body shifts from glucose to ketone bodies as its primary energy source, significantly reducing glucose availability for de novo lipogenesis, a key driver of hepatic fat accumulation. This dietary pattern promotes fatty acid oxidation and decreases hepatic triglyceride content, offering a targeted metabolic intervention for MASLD (Luukkonen et al., 2020).

Evidence suggests that KD improves hepatic insulin sensitivity by reducing serum insulin levels and enhancing mitochondrial function, with studies reporting up to a 58% reduction in insulin resistance (Jornayvaz et al., 2010). Furthermore, the KD enhances mitochondrial biogenesis and shifts ceramide production from harmful long-chain ceramides to protective very long-chain ceramides, which alleviate lipotoxicity and inflammation (Muyyarikkandy et al., 2020). This metabolic realignment reduces oxidative stress, improves cellular signaling, and supports overall liver health.

However, the long-term safety and practicality of the KD remain areas of concern. Prolonged adherence may lead to hepatic lipid accumulation, inflammation, and activation of fibrogenic genes, potentially exacerbating liver damage (Garbow et al., 2011; Jani et al., 2022). Additionally, the high saturated fat content in many KD protocols raises cardiovascular risks, particularly for patients with metabolic syndrome (Long et al., 2023). The restrictive nature of the diet also poses adherence challenges, limiting its use as a long-term strategy for MASLD management. Despite these limitations, the KD's ability to target insulin resistance and lipogenesis makes it a compelling short-term intervention for certain patients.

### **Plant-Based Diets: A Nutrient-Rich and Sustainable Option**

Plant-based diets, emphasizing vegetables, fruits, legumes, whole grains, nuts, and seeds, provide a nutrient-dense approach to managing MASLD. These diets are rich in fiber and bioactive compounds, such as polyphenols, which are key to their effectiveness in reducing inflammation, oxidative stress, and insulin resistance. Fiber regulates glucose metabolism by slowing carbohydrate absorption, stabilizing postprandial glucose levels, and optimizing insulin signaling (Li et al., 2021; Rodriguez-Ramiro et al., 2016). Meanwhile, polyphenols activate AMP-activated protein kinase (AMPK), enhancing glucose uptake and promoting fatty acid oxidation. Plant-based diets also reduce hepatic triglyceride content by suppressing lipogenic pathways. This is achieved through decreased expression of sterol regulatory element-binding protein 1c (SREBP-1c), a key regulator of de novo lipogenesis while increasing fatty acid oxidation via activation of peroxisome proliferator-activated receptor alpha (PPAR-α) (Markova et al., 2017). These mechanisms collectively address MASLD pathogenesis by reducing liver fat accumulation and preventing disease progression.

Clinical evidence highlights the benefits of plant-based diets in MASLD management. For example, trials have shown that these diets significantly reduce liver fat and inflammation in patients with type 2 diabetes and MASLD, independent of weight loss (Ji et al., 2020). However, potential challenges include nutrient deficiencies in vitamin B12, iron, and omega-3 fatty acids, which may arise due to limited animal product intake (Shao et al., 2022; Gao et al., 2021). Additionally, plant proteins often lack complete amino acid profiles, which could affect muscle mass and overall metabolic health, especially in individuals with MASLD (Takayama et al., 2021). Despite these limitations, with proper supplementation and planning, plant-based diets represent a sustainable and effective strategy for MASLD management.

### **The Western Diet: A Contributor to MASLD Progression**

The Western diet, characterized by high intakes of processed foods, saturated fats, refined sugars, and low fiber, significantly contributes to MASLD development and progression. This calorie-dense yet nutrient-poor diet promotes hepatic fat accumulation, systemic inflammation, and oxidative stress, creating a self-perpetuating cycle of liver damage (Hassani Zadeh et al., 2021; Berná et al., 2020). Elevated levels of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-6, further exacerbate liver inflammation and fibrosis (Garcia-Jaramillo et al., 2019). Additionally, the diet disrupts gut microbiota diversity, increasing gut permeability and enabling endotoxins like lipopolysaccharides (LPS) to enter the bloodstream, thereby exacerbating liver inflammation (Yang et al., 2023). Individuals adhering to a Western diet face a 2-4 times greater risk of developing advanced liver disease, including cirrhosis and hepatocellular carcinoma (Seki et al., 2018). Dietary modifications, therefore, are critical to mitigate these risks.

### **Dietary Modifications to Counteract the Western Diet**

To counteract the detrimental effects of the Western diet, interventions should focus on reducing saturated fats, trans fats, and refined sugars while increasing fiber, antioxidants, and healthy fats. Polyunsaturated fats, especially omega-3 fatty acids from fish and nuts, have been shown to lower hepatic fat and inflammation by modulating lipid metabolism (Fan et al., 2013). Similarly, antioxidant-rich foods, such as berries and leafy greens, combat oxidative stress, protecting hepatocytes from damage (Zelber-Sagi et al., 2011).

Enhancing dietary fiber intake through fruits, vegetables, legumes, and whole grains promotes gut microbiota diversity, strengthens the intestinal barrier, and reduces systemic inflammation (Vancells Lujan et al., 2021). Together, these dietary changes provide a comprehensive approach to managing MASLD and preventing its progression to more severe liver diseases.

In conclusion, the Mediterranean diet remains the gold standard for MASLD management due to its comprehensive benefits, including reductions in hepatic fat accumulation, inflammation, and oxidative stress. While the ketogenic and plant-based diets offer alternative strategies, their respective challenges, such as long-term adherence and nutrient adequacy, necessitate individualized approaches. In stark contrast, the Western diet exacerbates MASLD progression, emphasizing the critical need for dietary modifications. A tailored approach integrating evidence-based dietary patterns can optimize outcomes and prevent the progression of MASLD and liver fibrosis.

## **Evidence on Dietary Patterns and Liver Fibrosis in MASLD**

### **The Mediterranean Diet**

The Mediterranean diet (MedDiet) has consistently demonstrated the ability to reduce liver fibrosis in patients with metabolic-associated steatotic liver disease (MASLD). This dietary pattern emphasizes monounsaturated fats, dietary fiber, and polyphenol-rich foods while limiting the intake of red and processed meats. Through its nutrient composition, the MedDiet decreases hepatic collagen deposition and platelet activation, both of which are critical drivers of fibrosis progression. Evidence from the PLINIO cohort revealed that higher adherence to the MedDiet was associated with lower levels of thromboxane B2 and the N-terminal propeptide of type III collagen, reinforcing its role in mitigating fibrosis-related pathology (Tozzi G et al., 2022).

Importantly, the MedDiet's benefits extend beyond weight loss. Improvements in hepatic steatosis and insulin sensitivity have been observed in the absence of significant weight reduction, highlighting that its protective effects stem primarily from its nutrient profile rather than calorie restriction alone (Ugarriza L et al., 2022). Additionally, a low-glycemic-index variation of the MedDiet has shown further reductions in liver stiffness, suggesting that refining carbohydrate quality can enhance its therapeutic effects (Bouzas C et al., 2023). By improving metabolic parameters, reducing systemic inflammation, and directly influencing collagen-related biomarkers, MedDiet creates a healthier hepatic environment. Its adaptability and compatibility with standard MASLD management strategies make it a sustainable and non-invasive option for mitigating fibrosis in MASLD.

### **The Ketogenic Diet**

The ketogenic diet (KD) has shown potential in reducing hepatic fat and improving metabolic health in MASLD patients, particularly in the short term. In a controlled trial, six days of KD reduced intrahepatic triglycerides by 31% and improved hepatic insulin resistance by 58%, despite only a modest weight loss of approximately 3% (Wu CY et al., 2021). These results underscore that ketosis-induced metabolic changes, rather than substantial weight reduction, drive the diet's hepatic benefits. This mechanism makes KD particularly appealing to patients who struggle with traditional weight-loss interventions.

Despite these promising short-term results, the long-term effects of KD on fibrosis remain uncertain. Experimental models have raised concerns, as a high-fat KD exacerbated fibrosis in mice with pre-existing liver injury, potentially due to cholesterol accumulation and activation of fibrogenic pathways (Davis RAH et al., 2021). These findings highlight the need for caution in applying KD in patients with advanced liver damage or predisposing conditions. It is also noted the possible benefits throughout the body from a KD. The ketogenic diet engages the body into a state of ketosis which allows for the induction of an anti-inflammatory state and proves helpful neurologically, with obesity and is potentially cardioprotective. The main ketone, beta-hydroxybutyrate (BHB), exhibits a number of anti-inflammatory effects and is at the center of therapy when utilizing a KD. BHB has the potential to alleviate inflammatory diseases mediated by the NLRP3 inflammasome. It inhibits the activation of the NLRP3 inflammasome in response to urate crystals, ATP and lipotoxic fatty acids (Dyńska, D et al. 2023). This signifies how the ketogenic diet can be beneficial in a

condition such as MASLD, which notes the accumulation of fatty acids and triglycerides. It is also worth noting the potential adverse effects metabolically in regards to the KD. Research has demonstrated that, when compared to low-fat diets, the ketogenic diet is more effective in improving metabolic factors such as body weight, lipid profile, and blood sugar control in individuals with excess body weight (overweight or obesity), especially in those with diabetes. The ketogenic diet, a very low-calorie plan designed for weight loss, not only helps reduce body weight but also appears to be safe for long-term use (Dyńska, D et al. 2023). This suggests that there is a potential role for the ketogenic diet moving forward as it has been shown to improve the factors directly contributing to the pathogenesis of MASLD.

Refinements to KD could mitigate these risks and enhance its anti-fibrotic potential. For example, the addition of ketone ester supplements has shown improved histological outcomes, including reduced steatosis, inflammation, and MASLD activity scores compared to calorie restriction alone (Maguire M et al., 2020). Subgroups with severe hepatic steatosis and pronounced insulin resistance appear to derive the most benefit from very low-calorie ketogenic diets (VLCKD). One study demonstrated that individuals with higher baseline liver fat experienced significant improvements in liver stiffness and steatosis after eight weeks of VLCKD (Bonfiglio C et al., 2024). However, further research is essential to define optimal treatment durations, refine dietary components, and identify patients who would benefit most. Balancing short-term metabolic advantages against potential long-term adverse outcomes remains critical when considering KD as part of MASLD management.

### **Plant-Based Diets**

Plant-based diets, emphasizing nutrient-dense foods such as vegetables, fruits, legumes, whole grains, nuts, and seeds, have shown strong correlations with reductions in liver fibrosis. By creating a more favorable metabolic and inflammatory profile, plant-based diets positively influence the gut-liver axis and mitigate fibrogenic signaling pathways (Li et al., 2021; Xu et al., 2023). Dietary fiber, a key component of plant-based eating, modulates gut microbiota composition, reducing hepatic and systemic inflammation. The introduction of bioactive compounds such as polyphenols through fruits, vegetables, and tea further enhances these benefits by reducing oxidative stress, improving gut dysbiosis, and limiting hepatocyte apoptosis (Li, Gan, Shang et al., 2021).

Specific plant-derived nutrients demonstrate antifibrotic potential. For instance, polyphenols such as curcumin and resveratrol serve as potent antioxidants, mitigating oxidative damage and reducing collagen deposition, a hallmark of liver fibrosis (Li, Gan, Shang et al., 2021). Flavonoids like quercetin and genistein have been shown to influence cellular signaling pathways critical for tissue remodeling, potentially stabilizing or reversing fibrosis progression (Xu et al., 2023). These findings suggest that plant-based diets not only offer general health benefits but also enable targeted therapeutic interventions for liver fibrosis. Personalized dietary guidance incorporating specific plant-based foods or supplements could enhance the effectiveness of such interventions, transforming diet from a passive habit into an active therapeutic strategy.

Emerging evidence supports the efficacy of dietary interventions, particularly the Mediterranean diet, in mitigating liver fibrosis and improving metabolic health in MASLD patients. The ketogenic diet shows promise in reducing hepatic fat and improving insulin resistance in the short term but requires further refinement and long-term studies to ensure its safety and efficacy in fibrosis management. Similarly, plant-based diets demonstrate strong anti-inflammatory and antifibrotic effects, with specific nutrients such as polyphenols and flavonoids offering targeted therapeutic potential. Integrating these dietary approaches into personalized management plans, tailored to an individual's metabolic profile and disease stage, offers a non-invasive and sustainable strategy for addressing liver fibrosis in MASLD. Future research should focus on optimizing dietary regimens, elucidating their long-term effects, and establishing guidelines for patient selection to maximize therapeutic outcomes.

### **Intermittent Fasting**

New studies have demonstrated that Intermittent fasting (IF) can be beneficial for liver health and the reduction of liver fat content. In preliminary mice studies, it was also demonstrated that IF alleviated hepatic steatosis and inflammation through promoting the autophagy-lysosome pathway (Kim et al., 2023). Various IF regimens including time-restricted feeding, and alternate-day fasting, and a 5:2 model were linked to improved liver stiffness and steatosis. Through conducting metabolome analyses, Gallage et al. we're able to demonstrate that a 5:2 IF regime not only improved MASLD, but also showed a reduced risk of hepatocellular carcinoma through modulating hepatic PPAR $\alpha$  and PCK1 pathways (Gallage et al., 2024). IF has been compared to other dietary interventions such as that mediterranean diet, low-calorie diets and calorie restriction, however further research is needed to establish regime guidelines and to confirm any long-term benefits. While there has been evidence showing reduced liver fat content, inflammation and fibrosis with IF, the American Gastroenterological Association (AGA) recommends other dieting methods over IF (Younossi et. al, 2021). The AGA calls for more radiographic and histologic studies on IF before it can be routinely recommended for MASLD treatment.

### **Comparative Analysis**

Although studies that directly compare the effectiveness of the Mediterranean diet (MedDiet), ketogenic diet (KD), and plant-based diet in metabolic-associated steatotic liver disease (MASLD) management are limited, the MedDiet is supported by the strongest evidence for fibrosis reduction. To minimize the use of liver biopsy in detecting this reduction, non-invasive tests (NITs) have been introduced that can measure liver stiffness (LS), fibrogenesis biomarkers, and fibrosis scores, out of which LS was determined to be the most accurate (Armandi et al., 2023). Via transient elastography, Abenavoli et al. tracked the LS of 50 Caucasian patients and observed a 21% decrease in those who were prescribed the MedDiet for 6 months and an 8.7% increase in those who belonged to the control group. As LS and liver fibrosis share a positive correlation, these findings highlight the ability of MedDiet to reverse fibrotic changes and prevent disease progression. Higher adherence to the MedDiet is also associated with a decrease in plasma pro-c3 biomarker levels, fibrosis-4 index, fatty liver index, AST-to-platelets ratio, and other NITs which independently signify a reduction in hepatic fibrosis (Miryan et al., 2023; Baratta et al. 2022).

Beginning a KD or plant-based diet has resulted in favorable outcomes and multiple pathways have been identified by which these diets may reduce hepatosteatosis, inflammation, and fibrosis. However, further exploration is required to determine the direct relationship between KD or plant-based diet and LS or other NITs, which are not confounded by significant weight loss and associated caloric restriction. Additionally, using different research studies to compare the efficacy of the diets may not be reliable due to varying study durations, lack of generalizability due to cultural and geographic differences of the small sample populations, and limited ability to understand long-term effects as many studies adopt a cross-sectional design.

Assessing patient adherence to a new dietary intervention is essential in accurately depicting its effects. Introducing regular follow-ups with a dietician may allow participants to receive personalized guidance and motivation on any hurdles they may be encountering (Glass et al., 2022). Additional measures to increase adherence can include clearly defining the dietary guidelines, incorporating technology to utilize diet tracking applications or reminders, and assigning accountability partners when appropriate. Burke et al. conducted exit interviews to gather participant feedback on the positive and negative aspects of their nutrition and physical activity program. Similarly, retrospective analysis of factors limiting or increasing diet adherence can be conducted via exit interviews to formulate solutions for future studies. In multiple studies, dietary changes have been evaluated using self-reported measures including short food frequency questionnaires (SFFQ) or four-day diet diaries (4DDD). SFFQ requires participants to answer questions by rating the portion size and frequency at which they consume different food groups over a period, whereas a 4DDD records the type, time, and measured weight of a meal over four non-consecutive days (Bredin et al., 2019). Despite adopting different approaches, SFFQ and 4DDD share similar drawbacks. Both dietary tools can be subject to response bias, leading to underreporting of unhealthy habits, recall bias which may misrepresent dietary changes, and cultural bias as both tools are tailored towards specific regions (Miryan et al., 2023). Therefore, along with dietary adherence, the limitations of dietary assessment tools should be addressed to minimize bias and increase the external validity of findings.

The impact of the MedDiet, KD, or plant-based diet on liver fibrosis markers over a short period cannot be used to measure the long-term impact on fibrosis reduction. For example, while extensive research supports the immediate positive relationship between KD and improvement of MASLD, Garbow et al. reported that maintaining a KD for over 12 weeks increased hepatic steatosis in mice which could potentially exacerbate fibrosis. Furthermore, patients may demonstrate decreased compliance with maintaining specific dietary patterns over long periods due to limited access to healthy foods, social influences or stressors, or even decreased health literacy. These factors challenge the durability of dietary interventions and highlight the need to conduct longitudinal studies to evaluate chronic lifestyle changes. Ideally, studies should be extended to 3-5 years to adequately observe fibrosis outcomes with regular assessments in between to evaluate dietary compliance and fibrosis progression.

While the MedDiet, KD, and plant-based diet have all shown promise in the management of MASLD, it is imperative to consider how responses to dietary interventions may be influenced by variations in patient comorbidities. For example, certain vegetables and grains in the MedDiet may have a high content of potassium/phosphate or thyroid-disrupting goitrogen requiring careful modifications in patients with chronic kidney disease and hypothyroidism respectively (Perez-Torres et al., 2022; Bellastella et al., 2022). Similarly, patients with pancreatic disorders may find reduced benefit from the keto diet as the high fat content may aggravate pancreatic inflammation and even increase the likelihood and frequency of acute pancreatitis attacks (Shanti et al., 2024). Plant-based diets are associated with vitamin B12 deficiency and lower bone mineral density making it unsuitable for patients with macrocytic anemia with neuropathy or degenerative states such as osteoarthritis (Clem et al., 2021). It is also important to consider patients with eating disorders as they can be sensitive to dietary modifications and may require extra interventions to increase adherence. In addition, gut microbiota composition can influence individual responses to dietary interventions as they are shaped by an individual's genetics, environment, and diet (Xu et al., 2014). As a result, considerable diversity exists within the gut microbiota composition in the adult population across different cultures and geographies and even mildly within an individual as they age from a young adult to an elderly citizen (Healey et al., 2017). This variation limits the generalizability of the positive impact that the MedDiet, KD, and plant-based diets bring and further highlights the need for personalized nutrition to optimize dietary interventions.

### **Clinical Implications and Recommendations**

Dietary management is crucial in the management of MASLD. Mediterranean, ketogenic, and plant-based diets reduce liver fat, prevent further damage, as well as improve insulin sensitivity. (Buzzetti et al., 2016; Gupta et al., 2015). However, the success of dietary patterns depends on an individualized approach. Patient preferences, lifestyles, and circumstances must be considered to develop a sustainable plan. The Mediterranean diet plan is rich in fruits, vegetables, and healthy fats, and thus is generally well tolerated in the majority of patients. In contrast, some patients find the ketogenic diet difficult since it is relatively restrictive. Physicians should team up with patients to make real incremental changes for long-term care. (Nevola et al., 2023). Integrating diet into MASLD as a therapeutic tool requires a comprehensive and patient-centered approach to improve long-term outcomes.

Dietary changes can be combined with other therapeutic interventions and exercise to improve the outcomes for patients with MASLD. GLP-1 agonists or vitamin E have been shown to improve liver function and reduce liver fat when combined with dietary changes (Nevola et al., 2023). These medications can complement the action of diets in addressing some of the basic metabolic dysfunctions such as insulin resistance that participate in the progression of MASLD. Additionally, exercise plays a role in MASLD management. Physical activity improves insulin sensitivity, decreases inflammation, and reduces the overall hepatic fat accumulation and inflammation. Diet and exercise together prove to be a powerful duo in the prevention and management of MASLD (Sharma et al., 2023). The combination of diet, exercise, and pharmacotherapy allows managing MASLD, from multiple angles and improves long-term health

outcomes. This approach can be further optimized by the clinician, through regular monitoring of the progress of the patient, with modifications in treatments to meet the needs for effective care.

Additional hepatoprotection in NAFLD management is provided by adjunctive dietary treatments, such as polyphenols, probiotics, omega-3 fatty acids, and vitamin E. Anti-inflammatory actions of polyphenols found in green tea, berries, and olive oil diminish oxidative stress and hepatic lipid (Buzzetti et al., 2016). Furthermore, probiotics promote liver metabolism and inflammation control through the triggering of gut microbial balance, while omega-3 fatty acids as supplements or ingested through fish reduce hepatic fat and raise lipid metabolism (Sharma et al., 2023). Vitamin E proved to be of value in modulating liver fibrosis and inflammation, especially for non-diabetic NAFLD patients as an efficient antioxidant (Nevola et al., 2023). These supplements treat essential metabolic dysfunctions and are used in combination with dietary and lifestyle changes. Their addition to clinical practice would add further benefits to treatment outcomes.

Several challenges must be overcome to implement dietary interventions in clinical practice among patients with MASLD. One of the most important barriers is feasibility. Adherence to a specific diet may be difficult for certain individuals due to personal preference, cultural factors, or economic reasons (Nevola et al., 2023). Clinicians should personalize dietary plans according to the patient's lifestyle while taking socioeconomic factors and support systems into consideration (Buzzetti et al., 2016). Cultural adaptability is another factor that needs to be considered. For instance, the Mediterranean diet may have to be modified in places where particular foods are not commonly accessible (Sharma et al., 2023). Affordability remains an issue, as certain dietary programs require more expensive ingredients, which can be a particular problem for populations with lower incomes. Clinicians must work with dietitians and other health professionals to establish a meal plan that is affordable and appropriate to the patient's cultural setting (Buzzetti et al., 2016). Educating patients about the long-term benefits of these diets will promote better compliance (Sharma et al., 2023). A comprehensive and patient-focused strategy is essential for realizing effective dietary interventions that are maintainable across various populations.

### **Gaps in Literature and Future Directions**

While dietary interventions such as the Mediterranean, Ketogenic, and Plant-Based diets are promising in managing metabolic-associated steatotic liver disease (MAFLD), longitudinal studies are needed to assess their long-term effect on liver fibrosis. Most trials currently are of short duration, with a stronger focus on measuring surrogate markers such as liver enzymes rather than direct fibrosis outcomes (Gepner et al., 2019). Future studies should enroll large cohorts with better-defined clinical endpoints, inclusion criteria, and consistent methods to appropriately approve regimens for treatment and use in MASLD. Currently, studies use variable diagnostic tools, such as imaging versus biopsy, to quantify reduction of weight, steatosis, and fibrosis, leading to further complications of result reliability (Plaz et al., 2019). The chronic nature of liver damage and the current limitations in conducting longitudinal studies have limited the exploration of dietary impact on fibrosis regression. Liver biopsies continue to be the gold standard for

measuring fibrosis, which is invasive and can deter individuals from participating in studies. With metabolic-associated steatotic liver disease becoming a primary global health concern, there is an increasing need for further studies to explore the prevention and treatment of this disease.

Future research directions regarding the influence of dietary patterns on the progression of liver fibrosis in MASLD should focus on personalized nutrition approaches. Considering the effect of factors such as comorbidities, age, and sex, the differential effectiveness of these diets will be better understood. For instance, studies utilizing nutrigenomics and metabolomics can help identify genetic markers or metabolic pathways that influence dietary responses, potentially enhancing adherence and therapeutic success by tailoring recommendations to individual biological and lifestyle characteristics (Monserrat-Mesquida et al., 2023; Swain & Shaheen, 2019). The priorities for future research include conducting longitudinal studies to assess the long-term effects of dietary interventions on liver fibrosis progression and randomized controlled trials to compare diverse dietary patterns in different populations. By leveraging these recommendations, researchers can refine dietary strategies, potentially improving the prevention and treatment of MASLD-related liver fibrosis.

### **Conclusion**

Dietary interventions play a pivotal role in the management and treatment of MASLD, offering significant potential to slow fibrosis progression and improve overall liver health. The Mediterranean diet stands out as the most extensively studied and effective approach, providing benefits that extend beyond hepatic health to include improved cardiovascular and metabolic outcomes. The ketogenic and plant-based diets also show promise, particularly for specific patient populations, but require further research to validate their long-term safety and efficacy.

Combining dietary strategies with pharmacologic interventions and regular exercise creates a multifaceted approach to managing MASLD. Pharmacologic agents, such as GLP-1 agonists, and structured physical activity programs complement dietary changes by addressing key metabolic dysfunctions and improving overall health outcomes. These combined approaches underscore the importance of tailoring interventions to individual patient needs and preferences, ensuring long-term adherence and success.

Despite the advancements in understanding dietary impacts on MASLD, challenges remain, including the need for more robust longitudinal studies, the refinement of non-invasive diagnostic tools, and strategies to improve patient compliance. Addressing these gaps will enable the development of more effective, patient-centered management plans.

As MASLD continues to rise globally, it is imperative to adopt an integrative, evidence-based approach that includes dietary, lifestyle, and medical interventions. Such a comprehensive strategy has the potential to reduce the burden of MASLD on individuals and healthcare systems, improving patient quality of life and long-term health outcomes.

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