

The Mediterranean Dietary Pattern Ameliorates Nonalcoholic Fatty Liver Disease: Clinical Evidence, Biological Mechanisms and Practical Implications

Dian Wang

CDUTCM-Keele Joint Health and Medical Sciences Institute, Chengdu University of Traditional Chinese Medicine, Chengdu, China
wang.dian@stu.cdutcm.edu.cn

Abstract. Non - alcoholic fatty liver disease (NAFLD), which is a global metabolic - related chronic liver disease, has an extremely high prevalence. As of now, there are still no specific and effective drugs for this condition. Thus, dietary intervention serves as the core treatment strategy. Currently, the Mediterranean Diet (MD) has been proven to effectively improve NAFLD. Yet, the related research has some limitations. These limitations are due to the diversity of its plan, insufficient universality, and the short follow - up period after intervention. This review systematically summarizes the core nutritional components of the Mediterranean diet, such as monounsaturated fatty acids, high dietary fiber, and antioxidant components. It also clarifies the intervention effects of these components on liver function. Moreover, it elaborates in detail on some possible underlying mechanisms, like anti - inflammatory effects, antioxidant effects, and metabolic regulation. This review offers a comprehensive theoretical reference for clinical dietary intervention in NAFLD. Nevertheless, the long - term prognosis effect of the Mediterranean diet on NAFLD and the more precise molecular mechanism impact still need further verification and research. Future studies should focus on formulating standardized plans to reduce the differences in intervention effects caused by different regional conditions

Keywords: Mediterranean Diet, NAFLD, Chronic disease, Liver disease, Public health

1. Introduction

Most people agree that the most prevalent chronic liver disease in the world is NAFLD. Excessive lipid buildup in hepatocytes is its defining feature, and it can progressively progress into serious liver conditions including cirrhosis and hepatic fibrosis [1]. According to studies, 38% of people worldwide have NAFLD. Its pathophysiology is thought to be mostly influenced by oxidative stress and chronic inflammation [2]. Because it can effectively reduce inflammation and act as an antioxidant, the Mediterranean diet (MD) is linked to a lower risk of metabolic disorders. It has also been demonstrated that following the MD lowers the prevalence of metabolic syndrome in adults. Since there is currently no medication that has been shown to be both safe and effective for treating NAFLD, lifestyle modifications are the main course of treatment. A key factor in this is dietary

control. A large body of research indicates that MD can significantly enhance the prognosis of NAFLD. It has been demonstrated to help treat a number of chronic conditions, including as obesity, NAFLD, and type 2 diabetes mellitus (T2DM) [3].

Therefore, conducting further research on the relationship between the MD and non - NAFLD has significant research value in the field of chronic disease management. Previous studies specifically carried out an analysis of the impact of obesity on the pathogenesis of NAFLD, while metabolic regulation therapy through the MD reduces patients' weight via dietary intervention, thus alleviating NAFLD. Additionally, some studies have shown [4] that patients with NAFLD usually present insulin resistance (IR), low high - density lipoprotein cholesterol (HDL-C), and elevated triglyceride levels. According to research [5], the most prevalent risk factors for NAFLD are visceral obesity, IR, high fructose intake, as well as high cholesterol intake. The feature of metabolic regulation therapy is that it contains a high amount of dietary fiber, polyunsaturated fatty acids, and antioxidants, which are thought to be capable of reducing risks [6].

However, as a result of the limitations of this research and the insufficiency of the data, the role that dietary patterns play in NAFLD has not been fully clarified. Thus, this study intends to further explore the analyses in the existing literature about the impact of dietary patterns on NAFLD patients, and summarize the main mechanisms of their components in this regard.

2. Core characteristics and nutritional composition of the MD

MD is a dietary pattern that has been proven to have numerous health benefits. It is characterized by the rational combination of natural foods to implement targeted intervention measures for the pathological mechanisms of NAFLD. This diet is mainly composed of plant-based foods, emphasizing high intakes of vegetables, fruits, whole grains, and legumes rich in dietary fiber, vitamins, and polyphenols. The daily dietary fiber intake of MD can reach 25 - 30 grams, significantly higher than the intake of the Western diet [7].

Being the primary fat source, olive oil contains a high percentage of monounsaturated fatty acids (MUFA), with oleic acid being the most common one, and comprising 35% to 40% of total fat consumption. It can also restrict saturated fats and trans fats. Besides this, medical doctors advise people to eat fish, nuts and fermented dairy products in moderation and reduce the amount of red meat and processed foods; moderate amounts of red wine can also be consumed by some particular groups of people. This diet is a nutritional model that is defined by high fiber, high antioxidants and low refined sugar, which has intrinsic anti-inflammatory, antioxidant and metabolic regulatory effects thus providing material basis for the intervention of NAFLD [7].

The primary nutrients that are responsible for the protection of NAFLD by MD include MUFAs, high fiber diet, and high anti-inflammatory and antioxidant levels. The action of these constituents is synergistic because they have several well defined signaling pathways [8]. First of all, oleic acid-based olive oil (MUFAs) has been found to enhance the lipid metabolism and insulin sensitivity of the liver, as it activates adenosine monophosphate-activated protein kinase (AMPK) which inhibits sterol regulatory element-binding protein-1c (SREBP-1c) and acetyl-CoA carboxylase (ACC), which in turn suppresses the synthesis of metabolically active fats in the liver [9].

Secondly, dietary fiber from whole grains, legumes, fruits, etc., is important for regulating glucose metabolism by slowing intestinal glucose absorption and assisting with postprandial glycemic stability, which may contribute to improvements in IR. In addition, dietary fiber fermentation by gut microbiota produces SCFAs that activate GPR41/43 signaling pathways to improve intestinal barrier integrity and decrease translocation of lipopolysaccharides into circulation.

Besides, it is also reported that bioactive agents like olive polyphenols, flavonoids and omega-3 FAs have strong antioxidant effect as well as anti-inflammatory effect. The synergistic effects of these factors are such that they contribute to the breakdown of the positive feedback loop between oxidative stress and inflammatory response, which in turn leads to metabolic dysfunction and accumulation of lipids in the liver, hepatic inflammation and damage. These mechanisms together are very powerful theoretical reasons why dietary control should be considered first-line intervention in NAFLD [10]. It has been noted that there is a chronic inflammation and oxidative stress, which contributes to the development of NAFLD. It has also been found out that the body mass index (BMI) is one of the most significant predictors of steatosis in the liver, which means that the high amount of energy intake and obesity are important contributors to the occurrence of the disease. Moreover, the genetic predisposition is an important factor since it is associated with the risk of developing the disease and its progression, especially in the form of non-alcoholic steatohepatitis (NASH), due to the presence of polymorphism p.I148M in the patatin-like phospholipase domain-containing protein 3 (PNPLA3).

In combination with NAFLD development and evolution, it is a complex process of metabolic, inflammatory, and genetic changes. The protective effects of fiber and bioactive components in diet have been shown to be effective in all three aspects of glucose metabolism, gut microbiota structure, as well as inflammation and oxidative stress. Hence, a better approach to prevent and manage NAFLD could be through nutritional strategies coupled with an awareness of personal risk factors based on their metabolic and genetic characteristics.

Lifestyle change is the main focus of treatment in NAFLD. There are no drugs available yet. The disease can be prevented by making a suitable lifestyle, which would help to regulate metabolism and prevent fat accumulation in the liver, as well as slow down the development of the disease. Dieting is the best way to treat the condition. This can be done by eating foods that are low in calories and high in fiber, low in sugar and fats, and avoiding refined carbohydrates (white rice, white bread, red meat). It was found that even 3%-5% weight loss may be helpful in terms of liver performance and fat deposits and 7%-10% weight loss has a significant effect on liver steatosis and inflammatory reaction. Such a diet will fit very well with the nature of the MD since it is based on plant-based food, olive oil, fish and nuts [8].

3. Research progress on MD intervention for NAFLD

MD is primarily accomplished with the help of anti-inflammatory and antioxidant effects, which are the two major processes in the body. It also prevents the inflammation and oxidative stress of NAFLD, increases insulin sensitivity, improves lipid metabolism and intestinal barrier by reducing the amount of fat in the liver, as well as slowing down the process of this disease development and decreasing the likelihood of complications related to cardiovascular diseases (CVDs) through the use of synergistic action of different chemical substances like olive polyphenols, Omega-3 and dietary fiber.

3.1. Pathological characteristics and current treatment methods of nonalcoholic fatty liver disease

The manifestation of the metabolic syndrome related to obesity in the liver is NAFLD. Once the causes of this condition are excluded, such as excessive consumption of alcohol and autoimmune disease of the liver, it is a pathological condition that involves an abnormal accumulation of triglycerides within the cells of the liver. The extrahepatic effects of NAFLD have also been

identified as a multisystemic disorder that can be manifested outside the liver. In addition, NAFLD contributes greatly to the occurrence of non-communicable diseases, both chronic, CVDs, coronary heart disease, T2DM. It is estimated that during the period between 2015 and 2030 the death rate due to cirrhosis of the liver, hepatocellular carcinoma, and NAFLD will increase in most countries [7].

3.2. Clinical interventions of MD on NAFLD

Extensive clinical studies and meta-analyses have confirmed the significant intervention value of the MD for NAFLD. A systematic review involving 3,037 NAFLD patients demonstrated that MD intervention significantly reduced alanine aminotransferase (ALT) levels ($P=0.02$), with particularly notable improvement in the fatty liver index (FLI) ($P<0.001$). It also effectively reduced liver stiffness ($P=0.05$), suggesting potential benefits for hepatic fibrosis [4]. Another randomized controlled trial (RCT) meta-analysis further validated that the MD improved the lipid profile, reduced central obesity, and lowered liver enzyme levels in NAFLD patients, with statistically significant differences compared to the control group ($P<0.05$) [1].

The MD has specific benefits in NAFLD intervention compared to other dietary patterns. The MD decreases the risk of NAFLD by 23% as opposed to Western diets (high in processed foods, red meat and refined grains) [7]. In contrast to simple caloric restriction, the MD improves hepatic steatosis in patients with mild to moderate NAFLD even without substantial weight loss due to its anti-inflammatory and metabolic regulating effects instead of simply reducing energy [6]. But when used in conjunction with caloric restriction (daily caloric deficit of 500-1000 kcal), the decrease in fat content of the liver can reach up to 12%-20%, which is more effective clinically [4].

The MD was also beneficial in certain subgroups of NAFLD patients. In NAFLD patients with metabolic syndrome, each 1 point increase in MD adherence was associated with a decreased NAFLD risk by 18% ($OR=0.82$, $OR=0.82$, $CI: 0.71-0.95$), indicating its specific benefit in high-risk population [7]. By region, patients in the Mediterranean region had higher adherence to the MD and better improvement in ALT levels, while those in non-Mediterranean region (e.g. Asia) obtained similar benefits by modifying the diet according to local dietary habit (e.g. replacing part of the olive oil with tea seed oil) [3]. According to disease stage, the MD was most effective in NAFLD patients, while combination therapy with caloric restriction or exercise might be needed in NASH patients to obtain satisfactory outcome [11].

3.3. Mechanistic effects of MD on NAFLD

The MD alleviates oxidative stress and inflammation, two major pathogenic pathways that contribute to the development of NAFLD. It has been demonstrated that omega-3FAs from fish, polyphenols in olive oil, and flavonoids found in nuts and vegetables all prevent the synthesis of pro-inflammatory cytokines [10]. Evidence from the ATTICA study, with a 10-year follow-up, indicated that people with NAFLD who followed the MD more closely had far lower concentrations of inflammatory biomarkers like TNF- and C-reactive protein (CRP), as well as a roughly 30% lower chance of concomitant CVD [10]. Additionally, these bioactive substances can increase the activity of native antioxidant enzymes. By doing so, they help attenuate reactive oxygen species (ROS)-induced hepatocellular damage and reduce lipotoxicity, thereby contributing to the protection of liver function [9].

3.4. Improvement of IR and metabolic regulation

Dietary pattern is the cause of NAFLD and the combination of nutrients in a rational manner, which is carried out by the MD will enhance the metabolic disorders. The whole grain and legumes have high levels of dietary fiber that may slow down the process of absorption of carbohydrates and decrease post - prandial blood sugar changes [8]. Oleic acid (found in olive oil) can be used to increase the sensitivity of insulin receptors as it causes a 25% decrease in homeostatic model assessment of IR in patients with NAFLD [8]. Besides this, the lipid metabolism is controlled by the MD by decreasing the triglyceride (TG) concentration and increasing the high-density lipoprotein cholesterol (HDL-C) content, which decreases the production and accumulation of fat in the liver [1].

3.5. Modulation of gut microbiota and the gut-liver axis

The gut microbiota has been directly involved in the development of NAFLD, so the MD is used to ensure the balance between the gut microbiota. The MD will prevent the proliferation of harmful bacteria and promote the growth of beneficial ones (*Lactobacillus* and *Bifidobacterium*) by promoting a high -fiber diet and limiting the intake of processed food [7]. This increase in diversity of the intestinal microbiota will also help to strengthen the intestinal wall, decrease the endotoxin penetration into the blood circulation and lower the inflammatory activity of the liver-gut axis, and indirectly reduce the steatosis of the liver [3]. It should be noted that the influence of the intervention of the MD is not related to one kind of food but it is the result of the interaction of several elements including olive oil, whole grains and fish. e.g., Omega-3 FAs and polyphenols are capable of suppressing lipotoxicity of hepatocytes [7].

4. Limitations and outlook

The majority of the evidence that is available has been provided by the Mediterranean countries or the high-income nations and does not provide any information on the ability of the MD to adapt to other cultures, as well as its sustainability in the long term among non-Mediterranean populations [7]. Then, insufficient research in mechanistic. The role of single components vs. synergistic effects is still unknown, and there are no experiments at a molecular level to prove it [10]. No prognostic data in the long run. In spite of the fact that the MD may be beneficial to short-term measures of liver functioning, the follow-up results of this study will take more than 5 years before they can be used to confirm the efficacy of the prevention of hepatocellular carcinoma and cirrhosis in patients with NAFLD [2].

Secondly, there is variation in how the MD was implemented, for example, consumption of olive oil varied between 20 and 50 g/day. The duration of follow up also varied between studies, from 2 weeks to 2 years, making it difficult to pool some outcome data [4]. Additionally, sample size is an issue; many of the RCTs had small sample sizes e.g. Milgrom et al. 2024 included just 40 patients [11].

It is necessary to direct the future studies in the following direction. To begin with, it would be useful to normalize the MD intervention procedures and make a local MD practice for other countries (not Mediterranean) to make it more adaptable and flexible [12]. Secondly, mechanistic researches. The mechanism of action of the main elements of the NAFLD (e.g., olive polyphenols, oleic acid) should be determined through the combination of experiments on animals and cohort

studies on people to determine the molecular mechanisms involved in the process, including the AMPK signaling pathway and NF- κ B.

Thirdly, perform long-term follow-up studies. Carry out cohort studies with follow-up longer than 5 years to confirm the long-term preventive effect of the MD on hepatocellular carcinoma and CVDs in NAFLD patients [2]. Fourth, perform subgroup studies for different populations. Investigate the efficacy and best intervention strategy of the MD in specific subgroups, such as obese NAFLD patients, elderly NAFLD patients, and NAFLD patients with comorbid T2DM [11]. Finally, improve methodological aspects. Increase the sample size of RCTs, use standardized outcome measurements (i.e., uniform liver stiffness measurement methods), and minimize heterogeneity between studies [4].

5. Conclusion

One of the most prevalent metabolic chronic liver diseases is NAFLD. There is currently no specific medication treatment for it, and dietary habits and other lifestyle changes are crucial to the therapeutic care of this illness. This review systematically summarizes the nutritional characteristics of the MD and its research progress in NAFLD intervention, clearly stating that MD can effectively improve liver function, hepatic steatosis, alleviate IR and lipid metabolism disorders through mechanisms such as anti-inflammatory, antioxidant and metabolic regulation. It also elaborates on the core mechanisms of its intervention from aspects such as signal pathway regulation, intestinal flora balance and enhancement of the intestine-liver axis, and demonstrates that the MD diet's therapeutic potential relies on the combined action of several functional components rather than the activity of a single nutrient.

The analysis results of this article provide a theoretical basis for dietary intervention of non-alcoholic fatty liver, offer clear mechanism support for the clinical application of metabolic regulation therapy, and provide practical references for the formulation of standardized lifestyle management plans in the future. However, the existing research in this field is limited by inconsistent intervention schemes, insufficient regional applicability, and insufficient long-term follow-up intervention data, which to some extent restricts the promotion and accurate application of the metabolic regulation therapy based on the MD diet pattern.

In the future, more high-quality studies following standardized schemes, with large sample sizes and long-term follow-up, should be conducted to verify long-term efficacy. At the same time, the molecular mechanisms of key components and local application schemes in non-Mediterranean regions should also be further explored to provide more reliable evidence for improving the clinical prognosis of NAFLD.

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