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TOPIC HIGHLIGHT

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Alimentary regimen in non-alcoholic fatty liver disease: Mediterranean diet

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide. The mechanisms of the underlying disease development and progression are awaiting clarification. Insulin resistance and obesity-related inflammation status, among other possible genetic, dietary, and lifestyle factors, are thought to play the key role. There is no consensus concerning the pharmacological treatment. However, the dietary nutritional management to achieve weight loss is an essential component of any treatment strategy. On the basis of its components, the literature reports on the effectiveness of the Mediterranean diet in reducing cardiovascular risk and in preventing major chronic diseases, including obesity and diabetes. New evidence supports the idea that the Mediterranean diet, associated with physical activity and cognitive behaviour therapy, may have an important role in the prevention and the treatment of NAFLD.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Insulin resistance; Nutrition; Mediterranean diet

Core tip: The Mediterranean diet, a dietary pattern typical of the Mediterranean area is a very healthy dietary regimen. Several studies have shown that the people with high adherence to this diet secure a longer life expectancy and a lower risk of suffering from certain chronic diseases, including cardiovascular disease, metabolic disorders and cancer. The beneficial effects of the Mediterranean diet on non-alcoholic fatty liver disease have recently been investigated.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide[1]. NAFLD is defined as the accumulation of lipids within the hepatocytes exceeding 5% of liver weight in the absence of excessive ethanol intake (conventionally defined as an intake of ethanol

20 g/d) and without other causes of liver diseases[2]. The reported prevalence of NAFLD in the Western world is between 20%-30% in the general adult population, and in particular in the countries of Mediterranean area (*i.e.,* Italy and Greece)[3-5] and between 15%-20% in Asian countries (*i.e.,* India, China, Japan)[6,8]. The prevalence of NAFLD is 80%-90% in obese, 30%-50% in patients with diabetes and up to 90% in patients with hyperlipidemia[1]. It is estimated that 2%-3% of NAFLD present an active disease with inflammation (non-alcoholic steatohepatitis, NASH), which may progress to advanced fibrosis, liver cirrhosis and hepatocarcinoma[9,10]. The Dallas Heart Study and the Dionysos Nutrition and Liver Study reported that 30% and 25% of United States and Italian adults are affected by NAFLD respectively[4,11,12]. In these studies, 79% of the United States patients and 55% of the Italian patients with NAFLD had normal transaminase levels, showing that the liver enzymes were not surrogate markers of NAFLD. The prevalence of NAFLD/NASH continues to rise in parallel with obesity rates. As a result, NASH cirrhosis has become a common indication for liver transplantation. Currently, NASH is the third most common indication for the liver transplantation in the United States, behind hepatitis C and alcoholic liver disease, but it is estimated to become the first between 2020 and 2025[13].

The mechanisms involved in the occurrence of fatty liver and in the progression to a more serious disease are unclear and are probably due to a metabolic profile expressed in a context of a genetic predisposition[14,15]. Insulin resistance, oxidative stress, cytokines and obesity are identified as the major risk factors involved in NAFLD/NASH pathogenesis. These factors can promote intrahepatic fat accumulation and lipotoxicity, development of an inflammatory status, oxidative stress, apoptosis and fibrogenesis that determine the progression of the disease[16]. The evaluation of the levels of serum alanine amino-transferase (ALT) and aspartate amino-transferase (AST), has been used in clinical practice as a screening test to detect NAFLD. It was reported that using the ALT cut-off value of > 40 UI/L, diagnosed steatosis with a sensitivity of 45% and specificity of 100%[17].

Genetic and environmental factors are involved in the pathogenesis of NAFLD. Thus, nutrition is reasonably considered to be a potential environmental factor affecting the risk for this disease[18,19]. The impact of both positive energy balance and diet composition on the development of NAFLD has been explored[20-23]. Currently, lifestyle modifications, including dietary restrictions and exercise, should be recommended as the cornerstone of the NAFLD management. The general recommendations for the diet are individualized and one should aim to achieve energy deficit of 500-1000 kcal/d depending on the body mass index (BMI) of the patient. Reduced saturated fat and total fat should constitute less than 30% of the total energy input, and the intake of refined sugars should be decreased with an increase in soluble fibre intake. The recommended physical activities are 60 min/d for at least 3 d a week and the exercise should be progressively increased to five times a week[9,10]. The degree of hepatic fat reduction is proportional to the intensity of the lifestyle intervention and generally requires a body weight loss between 5% and 10%.

The Mediterranean diet is a dietary pattern that has extensively been associated with a favourable health outcome, mainly in relation to mortality, cardiovascular disease risk factors and cancer[24,25]. In relation to the metabolic syndrome, adhering or adopting a Mediterranean dietary pattern has a beneficial effect both on the prevention and the treatment of the metabolic syndrome, as well as on individual metabolic parameters[25].

The aim of the present review is to describe the effects and the clinical impact of the Mediterranean diet on the NAFLD patients.

PATHOGENESIS OF NAFLD

The pathogenesis of NAFLD involves interplay of multiple complex mechanisms (Figure 1). There is a clear link between NAFLD and obesity and between NAFLD and diabetes not caused by obesity[26,27]. It has been reported that insulin resistance is the major factor involved in the pathogenesis of NAFLD. Day and James were the first to propose a direct link between NAFLD and insulin resistance and suggested the "two hits hypothesis"[13]. The first "hit" presents the insulin resistance leading to the fat accumulation resulting in steatosis. The second "hit" is an oxidative stress, determining lipid peroxidation and increasing cytokine production, that causes the inflammation and necrosis. However, this pathogenetic hypothesis has been challenged with a "multi-hits" theory, in which insulin resistance is still the key risk factor for the development of NAFLD[28]. Metabolic syndrome is considered as a pro-inflammatory status characterised by the increased plasma levels of various pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6)[29,30]. The increased circulating levels of cytokines, plasma free fatty acid (FFA) levels and hyperglycemia are thought to contribute to the development and progression of NAFLD[16,31]. The production of IL-6 and TNF-α induce the activation of various signal transduction pathways, such as serine/threonine kinases, *i.e.,* protein kinase-C (PKC), c-JUN NH2-terminal kinase-1 and inhibitor of kappa B kinase as the key events in the pathway of the fat-induced hepatic insulin resistance[32]. The activation of PKC may also interfere with the ability of insulin to phosphorylate insulin receptor substrate-2[33]. Downstream effects include: nuclear factor-kappa B and activator protein-1 translocation to the nucleus resulting in an increased production of inflammatory cytokines which inhibit the insulin action[34]. Insulin resistance is a usual implication in the patients with a metabolic syndrome; fasting and post-prandial hyperglycemia are linked to hepatic steatosis. Conversely, NAFLD worsens insulin resistance that may lead on to type 2 diabetes mellitus (T2DM) in predisposed subjects[35]. Insulin

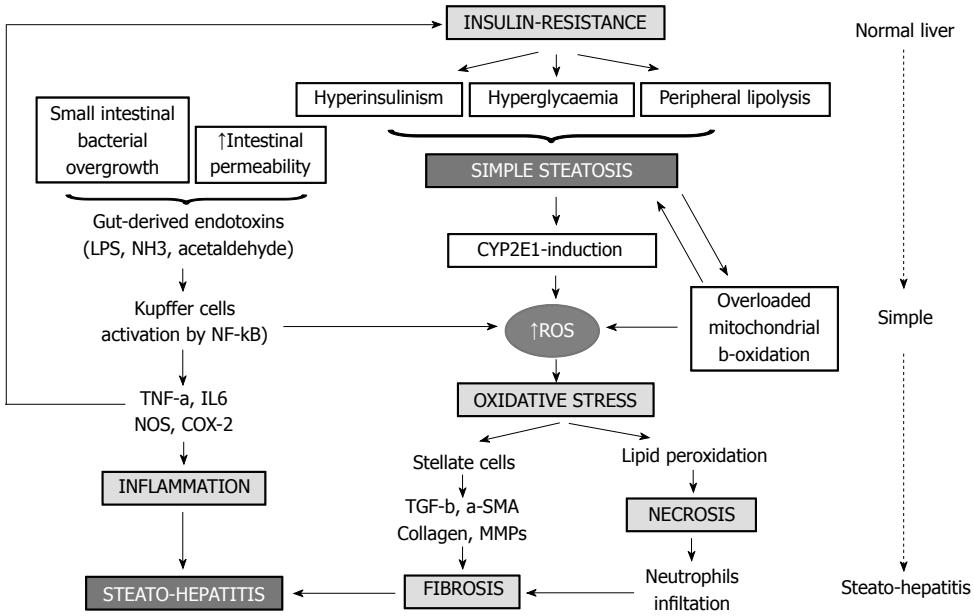

Figure 1 Mechanisms involved in multistep pathogenesis of non-alcoholic fatty liver disease. The development of an inflammatory status and oxidative stress can induce fibrosis, necrosis and steato-hepatitis. Insulin resistance promotes the activation of cytochrome P450 2E1, that induces cellular higher levels of reactive oxygen species (ROS) and oxidative stress, determining lipid peroxidation leading to necrosis, and activation of stellate cells with liver fibrosis. The activation of Kuppfer cells by nuclear factor-kappaB (NF-κB) resulting in an increased production of inflammatory cytokines such as tumour necrosis factor-α (TNF-α), cyclooxygenase-2 (COX-2) and interleukin-6 (IL-6) that cause the development of an inflammatory status, steato-epatitis and improve the insulin resistance. MMP: Matrix metalloproteinases; TGF: Transforming growth factor; α-SMA: α-smooth muscle actin; LPS: Lipopolysaccharide; iNOS: Inducible nitric oxide synthase.

resistance is a condition in which the body becomes less sensitive to insulin, and, therefore, the greater levels of the hormone are required to exert the same metabolic effects. In the absence of the sufficient levels of additional insulin, the body triglyceride metabolism becomes deranged. There is an increased amount of FFA in the circulation which, in turn, causes the increased levels of circulating triglycerides, measurable in the patients with NAFLD and T2DM.

The increased circulating triglycerides are the consequence of the increased dietary intake of lipids and de novo synthesis by liver, the increased lipolysis due to the peripherally educed effects of insulin, the lack of inhibition of hormone-sensitive lipase, which continues to break down very low density lipoproteins (VLDL) into FFA. The liver responds to the increase in plasma triglyceride levels by producing more VLDL, with storage of the lipids in hepatocytes, with subsequently steatosis, as a "vicious circle"[35,36]. In addition to the increased production of FFA, the increased hepatic gluconeogenesis causes worsening of hyperglycemia and insulin resistance in the NAFLD patients[37,38]. The progression to NASH is heralded by the oxidative stress that results in lipid peroxidation, release of pro-inflammatory cytokines which, then, result in the mitochondrial damage, fibrosis and inflammation. Approximately, 30% of the simple steatosis patients progress to NASH, and about 20% of these develop cirrhosis[1,16].

WEIGHT LOSS AND NAFLD

The NAFLD patients are inclined to a higher energy intake and a higher simple carbohydrate intake when compared with the healthy controls[39]. The current standard of care for treating the NAFLD patients focuses on the lifestyle interventions, especially a diet and exercise. In particular, a healthy diet has benefits beyond the weight reduction for all NAFLD patients with and without obesity. A systematic review and meta-analysis of the randomized trials by Musso *et al*[40] suggests that weight loss is safe and both liver and cardio-metabolic disease may benefit in NAFLD: although a ⩾ 5% of weight loss improves steatosis and cardio-metabolic variables, a ⩾ 7% of weight loss also improves histological disease activity in NASH. The American Association for the Study of Liver Diseases guidelines recommend a weight loss of at least 3%-5% of body weight to improve steatosis and a weight loss of up to 10% may be needed to improve necro-inflammation[10]. However, only few studies have evaluated histological improvement in NAFLD based on the biopsy results. At least three studies on weight loss in the NAFLD patients have documented the histological improvements in steatosis and inflammation with biopsies, including one in children[41-43]. Subsequently, in the largest randomized controlled trial of the lifestyle intervention in NASH, the patients were randomized 2:1 to the combination of a diet, exercise, and lifestyle modification (intervention group) or a control group, with a goal of 7% to 10% of weight reduction[44]. The primary outcome measure was an improvement in the histological NAFLD activity score after 48 wk of the treatment. The subjects in the lifestyle intervention group (n = 21) were assigned to an energy goal, based on their starting weight (1000 to 1200 kcal/d if the baseline weight < 90

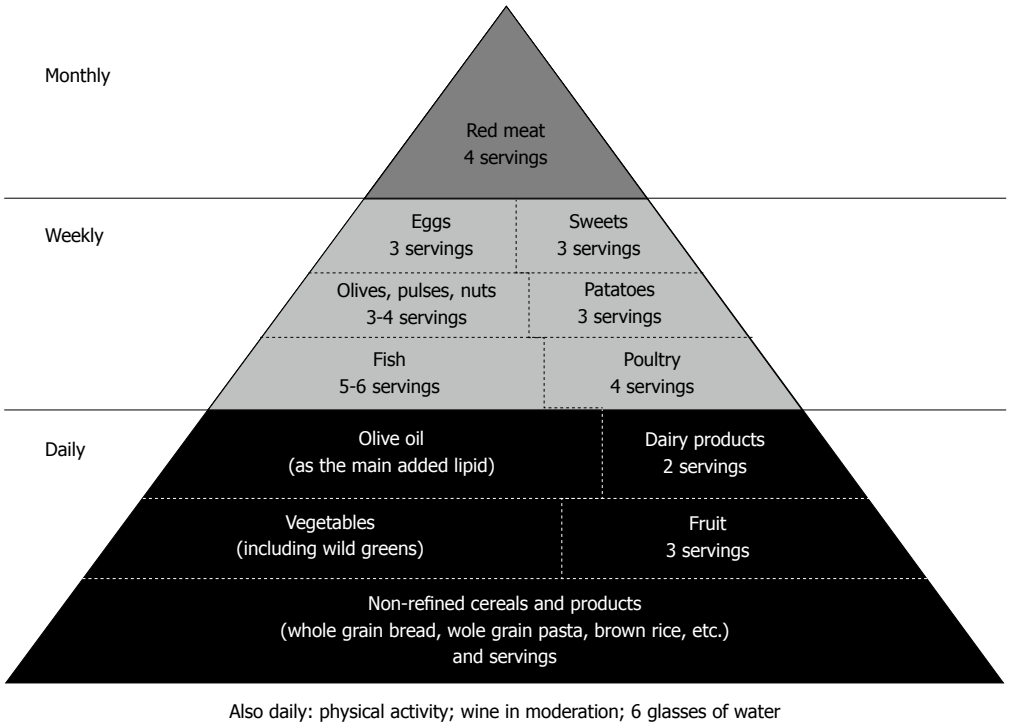

Figure 2 The traditional Mediterranean diet pyramid. The Mediterranean dietary plan emphasizes daily consumption of cereal, vegetables, bread, pasta, fruit, olive oil and dairy products. Eggs, sweets, fish, poultry, potatoes, pulses and nuts are recommended weekly, and red meat a few times per month and in a very small amount.

kg, or 1200 to 1500 kcal/d if the baseline weight > 90 kg) and were instructed to consume a 25% of fat diet. The participants in the control group (n = 10) attended the group sessions providing the basic education about NASH and the principles of healthy eating and physical activity. The lifestyle intervention group had an average weight loss of 9.3% of their weight compared with only 0.2% in the control arm (P = 0.005). Furthermore, after the treatment, the NAFLD activity score was lower in the lifestyle intervention group compared with the control group (P = 0.05). Those who lost ⩾ 7% of their body weight had significant improvements in liver steatosis (P < 0.001), lobular inflammation (P = 0.03) and NAFLD activity score (P < 0.001). Other studies, using magnetic resonance spectroscopy in assessing hepatic steatosis, demonstrated that the degree of improvement in steatosis was proportional to the amount of weight loss an individual attained, if a diet with or without exercise was implemented[45,46].

MEDITERRANEAN DIET COMPONENTS

The Mediterranean diet is the heritage of millennia of exchanges of people, cultures and foods of all the countries around the Mediterranean Sea basin. It has been the basis of food habits during the twentieth century in all countries of the region, originally based on Mediterranean ethnological life-styles. The UNESCO report claims: "The Mediterranean diet is a set of traditional practices, knowledge and skills passed on from generation to generation, providing a sense of belonging and continuity to the concerned communities"[47]. It has been difficult to define the Mediterranean diet because the Mediterranean region represents a large diversity of cultures and lifestyles. Nonetheless, the traditional Mediterranean diet is a pyramid characterised with the abundance of vegetable foods and cereals, such as green and yellow vegetables, salads, legumes, bread, pasta, fruits and nuts[48]. Olive oil is the main source of fat and the intake of fish, poultry, dairy products and eggs is moderate. In addition, different amounts of wine are usually consumed in moderation with meals. Animal fats used in butter, cream and lard are not included in this diet (Figure 2).

The Mediterranean diet is associated with a lowered incidence of cardiovascular diseases, metabolic disorders, Parkinson's and Alzheimer's diseases and several types of cancer. The protective effect is attributed, at least in part to the high concentration of antioxidants[49,50]. Vegetables are the most important sources of phenolic compounds in the Mediterranean diet, and, in particular, the flavonoids are thought to be the essential bioactive compounds that provide health benefits[51]. Several studies have reported that the traditional diets, which consist largely of vegetables, show a low incidence of chronic diseases with numerous health benefits and the improvement in life expectancy in older people[52]. Although the exact mechanisms of these protective properties are not fully understood, it is hypothesized that carotenoids, folic acid and fibres, characteristic for this diet, can play a pivotal role in the prevention of oxidative stress[53]. In addition, vegetables are also an important source of phytosterols that reduce cholesterol serum levels and, subsequently, the cardiovascular risk[54].

Various fruits, another important element of the

diet, provide fibres, vitamins, minerals, flavonoids and terpenes that possess protective actions against oxidative mechanisms. The omega-3 polyunsaturated fatty acids, found in fish (eicosapentaenoic and docosahexaenoic acids), regulate haemostatic factors effectively and provide the protection of several chronic diseases[55]. Olive oil contains high levels of monounsaturated fatty acids and it is a source of several phytochemicals (*i.e.,* polyphenolic compounds, squalene and α-tocopherol). Some evidence suggests that olive oil, the main source of calories in the Mediterranean diet, has health benefits on the reduction of a coronary heart disease risk, the prevention of several types of cancers, the modification of the immune and inflammatory responses and the reduction of the osteoporosis risk[55,56]. The dairy products of the Mediterranean diet, such as cheese and yoghurt, are better tolerated by the lactose-intolerant subjects. In addition, lactic acid bacteria provide the probiotic benefits, including the improvement in gastrointestinal motility and of the immune tropism[57]. The constant yoghurt intake might induce favourable changes in the gut microflora and can have a positive effect on the colon cancer risk indices[58].

Garlic, onions, herbs and spices are used as condiments in the Mediterranean diet and may increase the palatability and the nutritional value of the food. Some of them contain large quantities of flavonoids (fennel and chives) or allicin (garlic and onion), the latter may have cardiovascular benefits and can help the improvement of the cognitive functions[52,59]. The caper, containing flavonoids (kaempferol and quercetin derivatives) and hydrocinnamic acids, is used in traditional medicine for its anti-hypertensive actions and for the treatment of rheumatic conditions[60].

Some of the health effects of the Mediterranean diet on chronic diseases have been attributed to the polyphenols in red wine[61]. Wine exerts its protective effects by changing lipoprotein profile, coagulation and fibrinolytic cascades, platelet aggregation, oxidative mechanisms and endothelial function. The endothelium regulates vascular tone *via* the balance between the vaso-relaxation (*via* nitric oxide, NO) and vaso-constriction (*via* endothelins) factors, produced by the endothelium itself in response to different stimuli[61,62]. The researchers have reported that a moderate red wine consumption determines the cardioprotective effects, stimulating the up-regulation of NO production mediated to its polyphenol components, and, in particular, by reservatrol, a stilbene polyphenol[61,63].

Since the 1950s, Keys *et al*[64] have studied the diets of the Mediterranean area. The people of Greece, particularly on the island of Crete, had the longest life expectancy in the world until the 1960s, followed by the people of southern Italy, Spain, and France. Subsequently, other studies among the elderly in Greece and other European countries showed that the overall Mediterranean dietary pattern was more important for longevity than the single nutrients, and it was associated with the significant improvements in health status by a marked reduction in overall mortality[25]. These data seem to be relevant for the public health, and, in particular, for encouraging the prevention policy based on the Mediterranean-like dietary patterns for the primary prevention of the major chronic diseases.

STUDIES ON MEDITERRANEAN DIET IN NAFLD PATIENTS

According to the recent systematic reviews and meta-analyses, adhering or adopting a Mediterranean dietary regimen presents the beneficial effect on the prevention and the resolution of the metabolic syndrome, as well as on individual metabolic parameters[65]. However, there is no consensus on which diet is the right one for the NAFLD/NASH patients, even though the Italian Association for the Study of the Liver guidelines indicate for all NAFLD patients a low carbohydrate and low saturated fat diet, avoidance of fructose-enriched soft drinks and with the increased consumption of fruits and vegetables[9]. The favourable health effects of the Mediterranean diet on the metabolic syndrome have been demonstrated by a number of studies[66-68]. In addition, it is well-known that by managing obesity, hypertriglyceridemia, diabetes mellitus and by moderating alcohol consumption liver fat accumulation may be prevented or minimized[69].

In the last few years, the studies have been published on the effects of the Mediterranean diet on the NAFLD patients (Table 1). Shai *et al*[70] compared the effectiveness and safety of three nutritional protocols in a 2-year randomized controlled trial: a low-fat, restricted-calorie diet; a Mediterranean, restricted-calorie diet and a low-carbohydrate, non-restricted-calorie diet in 322 obese patients (277 males). The rates of adherence to the study diets were high (95.4% at 1 year and 84.6% at 2 years). The Mediterranean-diet group consumed the largest amounts of dietary fibre and had the highest ratio of monounsaturated to saturated fat ($P < 0.05$). The low-carbohydrate group consumed the smallest amount of carbohydrates and the largest amounts of fat, protein and cholesterol and had the highest percentage of the participants with detectable urinary ketones ($P < 0.05$). The mean weight loss was 2.9 kg for the low-fat group, 4.4 kg for the Mediterranean-diet group, and 4.7 kg for the low-carbohydrate group ($P < 0.001$). The mean weight loss was 3.3 kg, 4.6 kg, and 5.5 kg respectively in the 272 participants who completed the intervention. The relative reduction in the ratio of the total cholesterol to high-density lipoprotein cholesterol was 20% in the low-carbohydrate group, and 12% in the low-fat group ($P = 0.01$). The changes in fasting plasma glucose and insulin levels were more favourable in the patients assigned to the Mediterranean diet than in those assigned to the low-fat diet ($P < 0.001$) in 36 patients with diabetes. Finally, the changes in bilirubin, alkaline phosphatase, and ALT levels were similar between the diet groups. However, the transaminases levels were significantly reduced from the baseline to 24 mo in the Mediterranean diet and the low-carbohydrate groups ($P < 0.05$). Subsequently,

Table 1 Main studies on Mediterranean diet in the treatment of non-alcoholic fatty liver disease

Ref.	Patients	Nutritional protocol	Metabolic and histological changes
Shai *et al*[73]	322 obese patients (277 males)	Low-fat diet MD Low-carbohydrate diet	Weight loss (kg): 2.9 low-fat diet, 4.4 MD, 5.5 low-carbohydrate diet TC/HDL reduction (20%) in the low-carbohydrate diet; decrease in fasting plasma glucose levels and HOMA-IR in MD Changes in adiponectin, leptin, ALP, ALT similar in all diet group
Tzima *et al*[74]	1514 males 1528 females	MD	Higher MD score was associated with lower likelihood of having the metabolic syndrome In patients without or with moderate adherence to the MD an increase in the AST/ALT ratio was associated with lower likelihood of having the metabolic syndrome In patients with greater adherence to the MD AST/ALT ratio was not associated with the presence of the metabolic syndrome
Pérez-Guisado *et al*[75]	31 obese patients (22 males)	Spanish ketogenic MD	Improvement in body weight Steatosis degree Reduction in BMI, systolic blood pressure and diastolic blood pressure, total cholesterol, triacylglycerols, glucose and LDLc Increase in HDLc
Ryan *et al*[77]	12 non-diabetic patients (6 males) with NAFLD	MD control diet (low fat-high carbohydrate diet)	Weight loss with both diets Significant reduction in hepatic steatosis with MD Insulin sensitivity improved with MD
Kontogianni *et al*[78]	73 overweight NAFLD patients (50 males)	MD	MD score was negatively correlated to serum alanine aminotransferase, insulin levels, insulin resistance index and severity of steatosis MD score was positively correlated to serum adiponectin levels
Trovato *et al*[79]	90 non-alcoholic non-diabetic patients (44 males)	MD	Significant decrease of bright liver score (BLS) Adherence to MD change and body mass index changes (multiple linear regression model) independently explain the variance of decrease of fatty liver involvement

NAFLD: Non-alcoholic fatty liver disease; MD: Mediterranean diet; TC: Total-cholesterol; HOMA-IR: Homeostasis model assessment for insulin resistance; ALP: Alkaline phosphatase; AST: Aspartate aminio-transferase; ALT: Alanine amino-transferase; LDLc: Low density lipoprotein-cholesterol; HDLc: High density lipoprotein-cholesterol; BMI: Body mass index.

the ATTICA study randomly enrolled 1514 adult males and 1528 females from the area of Athens to assess the adherence to the Mediterranean diet by the Mediterranean diet score[71]. The authors found that the higher score was associated with lower likelihood of having the metabolic syndrome in a multi-adjusted analysis (OR = 0.34, 95%CI: 0.16-0.73). Stratified analysis by the level of adherence to the Mediterranean diet revealed that an increase in the AST/ALT ratio was associated with lower likelihood of having the metabolic syndrome (OR = 0.33, $P < 0.05$ and OR = 0.34, $P < 0.09$, respectively) only in the patients without or with moderate adherence to the Mediterranean diet. However, when those with greater adherence to the Mediterranean diet were focused, the AST/ALT ratio was not associated with the presence of the metabolic syndrome (OR = 0.51, $P = 0.55$). A Spanish pilot study assessed the effects of the variant of the Mediterranean diet, called Spanish ketogenic Mediterranean diet, on the echographic liver parameters and biochemical liver functions in 14 overweight male patients with NAFLD and metabolic syndrome[72]. This diet is a protein ketogenic diet with the incorporation of high doses of virgin olive oil and omega-3 fatty acids from fish as the main source of fat, fish as the main source of protein, green vegetables and salads as the main source of carbohydrate and moderate red wine intake[73]. The regimen was administered for 3-mo. The authors reported a significant improvement in body weight ($P < 0.001$), steatosis degree and all the parameters associated with the metabolic syndrome, in particular, the body mass index, waist circumference, fasting plasma glucose, triglycerides, high-density lipoprotein-cholesterol and blood pressure. Ryan *et al*[74] examined the effects of the Mediterranean diet in terms of insulin sensitivity and steatosis degree. Twelve overweight adult non-diabetic patients (6 males) with biopsy-proved NAFLD were recruited for a randomised, cross-over intervention trial. All subjects took both the Mediterranean diet and the control diet (a low fat-high carbohydrate diet) in random order with a 6-wk wash-out period. The insulin sensitivity was determined with a 3 h hyperinsulinemic-euglycemic clamp study, and liver steatosis was assessed with localized magnetic resonance ^{1}H spectroscopy (^{1}H-MRS). At baseline, the subjects were abdominally obese with the elevated fasting concentrations of glucose, insulin, triglycerides and transaminases levels. Insulin-sensitivity at baseline was low (M = 2.7 ± 1.0 mg/kg per minute). The mean weight loss was not different between the two diets ($P = 0.22$). The significant reduction in hepatic steatosis was evident after the Mediterranean diet period, compared to the other diet (39% ± 4% *vs* 7% ± 3%), measured by ^{1}H-MRS ($P = 0.012$). In addition, the study reported the improvement in the insulin sensitivity only with the Mediterranean diet ($P = 0.03$). Kontogianni *et al*[75] explored the association between the adherence to the Mediterranean diet and the clinical and histological characteristics in seventy-three adult overweight NAFLD patients (50 males). The daily adherence to the diet was estimated by the Mediterranean

diet score. The liver stiffness was assessed by transient elastography in 58 patients and performed liver biopsies in 34 patients. Fifty-eight patients were matched with 58 healthy controls in terms of age, sex and body mass index. The authors showed that the diet score was negatively correlated to the transaminase levels ($P = 0.03$), insulin levels ($P = 0.001$), insulin resistance index ($P = 0.005$) and severity of steatosis ($P = 0.006$), and was positively correlated to the serum adiponectin levels ($P = 0.04$). In particular, the patients with NASH presented lower adherence to the Mediterranean diet (29.3 ± 3.2 *vs* 34.1 ± 4.4, $P = 0.004$), compared to the group with simple fatty liver.

In a recent study Trovato *et al*[76] reported the effect of Adherence to Mediterranean Diet as a predictor of changes in the fat content of the liver in overweight patients with NAFLD. The study included 90 non-alcoholic non-diabetic patients with evidence of fatty liver by ultrasound (F 46, M 44), aged 50.13 ± 13.68 years and BMI 31.01 ± 5.18 kg/m^2. After only 6 mo of intervention a significant decrease of bright liver score was observed; by a multiple linear regression model adherence to Mediterranean Diet change ($P = 0.015$) and body mass index changes ($P < 0.0001$) independently explain the variance of decrease of fatty liver involvement ($r^2 = 0.519$, $P < 0.0001$). This data suggested that adherence to Mediterranean Diet is a significant predictor of changes in the fat content of the liver in patients with NAFLD.

Finally, recently it has been suggested that lower body iron stores induced by dietary components of Mediterranean diet could be involved in the beneficial action of this dietary pattern in NAFLD. Mounting evidence suggests a link between serum ferritin, insulin resistance, and NAFLD. Body iron excess has frequently been found in patients with metabolic syndrome, with serum ferritin showing a linear increase with the increasing number of metabolic syndrome features[77,78]. Moreover, it has been suggested that the relation between serum ferritin and most of metabolic syndrome features might be mediated by the presence of NAFLD at population-based level[79]. Excessive hepatic iron accumulation in NAFLD can be one of the potential cofactors involved in the enhanced oxidative stress, which triggers liver cell necrosis and activation of hepatic stellate cells, both leading to fibrosis[80]. On the other hand, it has been proposed that the balance between the average bioavailability of dietary iron and the overall effects of inhibitors and enhancers of iron absorption may lead to lower iron stores in people consuming a Mediterranean dietary pattern[81]. In fact, it has been reported that elderly men from Crete, in the Mediterranean south of Europe had consistently lower levels of indicators of oxidative stress and iron status than elderly men from Zutphen in the north of Europe. In particular, serum ferritin, a good marker of the iron stored in the body, were 2-fold lower in men from Crete than in men from Zutphen (69.8 and 134.2 lg/L, respectively)[82].

CONCLUSION

NAFLD is the most common cause of chronic liver disease in the developed world and the progression to simple steatosis, to steato-hepatitis and, finally, to cirrhosis represents an emerging problem of the public health. Unfortunately, a "golden standard" drug therapy for NAFLD is not currently available and the management must focus on the treatment of metabolic syndrome, and, therefore, NAFLD is often considered as an individual entity in the clinical practice. The influence of the dietary nutrients in the pathogenesis of NAFLD has been reported. The cornerstone in the management of NAFLD implies a dietary modification to decrease the body weight and to increase the physical exercise in order to reduce insulin resistance and to normalize the transaminases levels. These "easy" concepts seem to be clinically relevant in terms of cost/effectiveness, in particular, to reduce the risk of pre-mature death in general population. A diet regimen rich in monounsaturated fatty acids and omega-3, fruit, vegetables, fibre and reduced intake of saturated fats, simple carbohydrates, sweetened drinks and moderate alcohol intake should be recommended to the NAFLD patients. On the basis of its components, it is well known that the Mediterranean diet presents health benefits and can prevent obesity, diabetes and cardiovascular conditions. It is a highly palatable and favourable diet and may lead to a higher adherence among dieters in the long term.

Considering the data currently available in literature, the prescription of the Mediterranean diet by the physicians and nutritionists for the NAFLD patients may present an appropriate therapeutic option associated with lifestyle changes. It can play the primary role in the prevention and the treatment of several chronic diseases, including the spectrum of NAFLD. The well-designed dietary intervention trials are needed to define the exact dietary guidelines for NAFLD and to explain the role of the Mediterranean dietetic pattern, as the indispensable reference diet.

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