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## Mediterranean diet and non-alcoholic fatty liver disease: New therapeutic option around the corner?

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### Abstract

Non-alcoholic fatty liver disease (NAFLD) represents the most common chronic liver disease in Western countries, being considered as the hepatic manifestation of metabolic syndrome. NAFLD has a common pathogenic background to that of metabolic syndrome, and shares many risk factors such as obesity, hypertension, insulin resistance and dyslipidemia. Although there is no currently available evidence-based established treatment for NAFLD, all the recommendations from the medical associations indicate that the most effective treatment is to reduce weight through lifestyle modifications. Diet, indeed, plays a key role in the management of NAFLD patients, as both the quantity and quality of the diet have been reported to have a beneficial role in the onset and severity of the liver disease. Among all the diets that have been proposed, a Mediterranean diet was the most effective dietary option for inducing weight loss together with beneficial effects on all the risk factors associated with metabolic syndrome and NAFLD. Over the last few years, research has demonstrated a beneficial effect of a Mediterranean diet in NAFLD. In this review, we

will examine all the available data on the association between diet, nutrients and the Mediterranean diet in association with onset and severity of NAFLD.

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**Key words:** Mediterranean diet; Diet; Prevention; Metabolic syndrome; Non-alcoholic fatty liver disease

**Core tip:** In this review, we examine all the available data on the association between diet, nutrients and the Mediterranean diet in association with onset and severity of non-alcoholic fatty liver disease.

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### INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in industrialized countries, and is characterized by increased hepatic fat accumulation in individuals not consuming excessive alcoholic beverages (typically a threshold of < 20 g/d for women and < 30 g/d for men is adopted)<sup>[1]</sup>. NAFLD is emerging as one of the most common causes of liver disease worldwide<sup>[2]</sup>, particularly in Western countries such as the United States where approximately 30% of the population now has NAFLD<sup>[3]</sup>. It refers to a wide spectrum of liver disorders ranging from simple steatosis (more than 5% hepatocytes showing fat accumulation), to non-alcoholic steatohepatitis (NASH), which increases the risk of end-stage liver disease, namely liver cirrhosis and hepatocellular carcinoma<sup>[4]</sup>.

The true prevalence of NAFLD is unknown because only a liver biopsy can distinguish simple steatosis from NASH, but it is unethical to perform liver biopsies on unselected asymptomatic patients from the general population. However, various strategies including unexplained alanine aminotransferase (ALT) elevation or fatty liver on ultrasound in nondrinking but otherwise unselected patients gives an estimated prevalence of NAFLD in the adult population of around 15%-30%<sup>[5]</sup>. Moreover, the problem is not limited to adults only because nearly 10% of obese children may have NAFLD<sup>[6]</sup>. Actually, NAFLD is considered as the hepatic manifestation of metabolic syndrome, sharing a common pathogenic background and with similar disease states such as obesity, type 2 diabetes mellitus, insulin resistance and dyslipidemia<sup>[1-4]</sup>.

Several studies have recently shown the association of NAFLD with cardiovascular disease (CVD)<sup>[7]</sup>. In a study of biopsy-proven NAFLD with a follow-up of about 21 years, the main causes of death in patients with NAFLD were CVD and malignancy<sup>[8]</sup>. In addition, several studies showed that NAFLD might itself contribute to the increased CVD risk. The possible explanation for such a relationship between CVD and NAFLD includes the occurrence of many risk factors including insulin resistance, obesity, dyslipidemia, and an altered inflammatory state in both pathologies<sup>[7]</sup>.

Cornerstones of NAFLD therapy are lifestyle interventions, and especially diet. These interventions are effective not only for improving NAFLD itself, but also associated conditions such as metabolic syndrome, type 2 diabetes, and the related risk of CVD<sup>[9]</sup>.

In this review, we report data supporting the role of dietary approaches, including a Mediterranean diet, on the management of patients with NAFLD.

## DIET AND NON-ALCOHOLIC FATTY LIVER DISEASE

Dietary habits are significantly linked with health state. A correct dietary intake, associated with a healthy lifestyle, may in fact contribute to the maintenance of a healthy status. Conversely, poor dietary habits may favor the occurrence of various disease states such as cancer, obesity, diabetes, dyslipidemia and hypertension, the combination of which may lead to metabolic syndrome that in turn increases the risk of death from cardiovascular and other chronic degenerative diseases.

Diet and lifestyle can significantly affect the clinical picture of NAFLD since most patients with NAFLD have excess body weight and other cardiometabolic risk factors, such as hypertension, dyslipidemia and diabetes<sup>[10,11]</sup>. Although promising pharmacological treatments are emerging, only a significant and sustained weight loss is the basis of any treatment plan for patients suffering from NAFLD<sup>[9]</sup>.

Some intervention studies reported that weight loss

induced by diet is able to reduce liver enzymes and hepatic steatosis. One of the most relevant studies has been conducted in NASH patients, where a dietary intervention study demonstrated that weight loss led to an improvement in liver histology and enzymes<sup>[12]</sup>. Patients were randomized into two groups, a combined lifestyle intervention group and a control group. At the end of the intervention period, patients who followed the lifestyle recommendations had an average weight loss of about 10% compared with only 0.2% in the control group. Interestingly, patients who lost more than 7% of their body weight had significant improvements in terms of activity score and inflammation, suggesting that the reduction in body weight resulting from lifestyle changes was beneficial in reducing the severity of NAFLD. The rapidity of weight loss is also extremely important in NAFLD treatment. It has been demonstrated that only modest weight loss (about 1 kg per week) is significantly associated with a decreased incidence of metabolic syndrome and improvement in the histological features of NAFLD, whereas fast weight loss, as seen in bariatric surgical procedures, often worsen the clinical features of NAFLD<sup>[13]</sup>.

Quality modifications of dietary composition can also directly influence the clinical course of NAFLD beyond the "simple" caloric restriction. Indeed, diet composition, with modulation of either macro or micro-nutrients, can significantly affect most of the risk factors associated with fatty liver such as hypertension, serum lipids and insulin<sup>[10,11]</sup>.

### Carbohydrates and non-alcoholic fatty liver disease

As regarding carbohydrates, data from the literature report that a diet high in carbohydrates might worsen the clinical conditions of patients with NAFLD<sup>[14]</sup>. Actually, hepatic triglycerides showed a greater decrease among individuals treated with a carbohydrate-restricted diet than with an energy-restricted one, whereas a diet rich in carbohydrates may lead to increased levels of insulin, contributing to high levels of triglycerides and blood glucose. In an intervention study, Ryan *et al*<sup>[15]</sup> randomized NAFLD patients to hypocaloric diets containing different proportions of carbohydrates. After 16 wk, patients receiving a low percentage of calories from carbohydrates (40%) showed lower levels of liver enzymes compared to those receiving a high-carbohydrate diet, despite equal weight loss. Similarly, another intervention study using two energy-restricted diets with equal energies, but different proportions of carbohydrates, showed similar weight loss but a greater decrease in triglycerides in the group with a lower proportion of carbohydrates<sup>[16]</sup>. The type and quality of carbohydrates appear to be relevant for the occurrence of NAFLD, because the glycemic index seems to play a relevant role in the pathogenesis of NAFLD. Thus current recommendations of many scientific associations indicate a carbohydrate intake > 50% of the total energy, and choosing whole grain and low-

glycemic index foods<sup>[9]</sup>.

### **Dietary fats and non-alcoholic fatty liver disease**

Patients with NAFLD often have a high-fat diet that may be an independent risk factor for the development of the disease<sup>[17]</sup>. In a study by Yamamoto *et al.*<sup>[18]</sup> the reduction of fat consumption for 6 mo induced a decrease in liver enzymes. Moreover, an increased fat intake in the diet has been linked to many components of metabolic syndrome and NAFLD. In particular, saturated fatty acids (SFA) have been reported to have deleterious effects on both lipid and glucose metabolism. A randomized, double-blind, crossover study examined the effects of three different diets in 86 healthy men: a control diet (14% SFA), the National Cholesterol Education Program Step I diet (9% SFA), and the National Cholesterol Education Program Step II diet (6% SFA). Although all reduced-fat diets decreased low-density lipoprotein (LDL)-cholesterol, they also decreased high-density lipoprotein (HDL)-cholesterol and increased triglycerides after 6 wk compared with the control diet. Furthermore, in response to the 6%-SFA diet, subjects with insulin resistance and higher body fat showed smaller reductions in LDL-cholesterol, larger reductions in HDL-cholesterol and increases in triglycerides as compared to subjects with normal insulin sensitivity<sup>[19]</sup>.

The quality of dietary fats plays a key role in the pathogenesis of NAFLD as shown by the beneficial effect of monounsaturated fatty acids (MUFA). The replacement of carbohydrate and SFA with MUFA leads to reductions in glucose and blood pressure and to an increase in HDL-cholesterol in patients with diabetes. A MUFA-rich diet (40% of energy as fat) has also been demonstrated to decrease VLDL-cholesterol and triglycerides, and to be more acceptable to patients with diabetes than a high-carbohydrate diet (28% of energy as fat). Therefore, an increase in the intake of MUFA, particularly as a replacement for SFA and as a higher proportion in the diet in lieu of carbohydrates, may be beneficial for NAFLD patients<sup>[20]</sup>.

Accordingly, polyunsaturated fatty acids (PUFA) may also have beneficial effects in patients with NAFLD. In a recent human dietary intervention study, we showed positive effects of n-3 PUFA administration in NAFLD patients<sup>[21]</sup>. Moreover, a meta-analysis demonstrated that n-3 PUFA have substantial beneficial effects in ameliorating liver steatosis and its related components<sup>[22]</sup>. More recently, we reported a significant amelioration in lipid variables, insulin and adiponectin levels as well as in the severity of fatty liver by introducing a n-3 PUFA-enriched olive oil into the diet of patients with NAFLD, thus indicating that PUFA might represent a therapeutic option for treating NAFLD<sup>[23]</sup>.

In line with such evidence, recommendations in the recent guidelines in terms of dietary fats suggest a total fat contribution < 30%-35% of the total daily energy intake, with preference for MUFA and PUFA rather than SFA (recommended to be < 7% of total energy)<sup>[9]</sup>.

## **MEDITERRANEAN DIET AND NON-ALCOHOLIC FATTY LIVER-RELATED CONDITIONS**

Over the past decades, several dietary models have been proposed as the ideal diet for preventing NAFLD and metabolic-related conditions. However, among all the diets that have been proposed, only the Mediterranean diet demonstrated a beneficial effect according to scientific data.

Mediterranean diet was firstly discovered in the early 1960s by Ancel Keys who invented this term after the results of an epidemiological study, the “Seven Countries’ Study” which demonstrated that the populations bordering the Mediterranean Sea (Italy and Greece) had a reduced incidence of cardiovascular disease and cancer in comparison to the other populations. In this study, the dietary profile of 12763 subjects aged between 40 and 59 years living in different countries of the world were analyzed: the United States of America, Finland, the Netherlands, Italy, Greece, the former Yugoslavia and Japan. The results of this study were that countries bordering the Mediterranean basin had the lowest rates of mortality and incidence of cardiovascular disease in comparison with the other countries. After these first results, other studies have confirmed these findings and the Mediterranean diet were recognized all over the world as a healthy diet, effective in reducing the risk of cardiovascular disease and cancer<sup>[24]</sup>.

### **Mediterranean diet and cardiovascular disease**

Much of the available data supporting the beneficial effect of Mediterranean diet on health derive from studies linking diet with CVD, the leading cause of mortality and morbidity all over the world and closely related to NAFLD. With regard to the primary prevention, the most relevant study is the EPIC-Elderly Prospective Cohort Study, a multicenter study that analyzed subjects living in 10 different European countries. In a paper published in the New England Journal of Medicine by Trichopoulou *et al.*<sup>[25]</sup> a score of adherence that takes into account the main dietary variables, divided into food groups, typical of the Mediterranean diet was computed. This adherence score, based on food groups typically present in the Mediterranean diet (bread, pasta, fruit, vegetables, fish, legumes, moderate red wine consumption, and olive oil), gives a positive score to people consuming more than the median of the overall population in term of “Mediterranean” typical foods, and a negative score to those who consume a higher amount of foods which are not typical of the Mediterranean diet. A 2-points increase of this score was significantly associated with a 33%-reduced risk of mortality from cardiovascular causes (RR = 0.67, 95%CI: 0.47-0.94)<sup>[25]</sup>.

Recently, a large intervention study conducted in Spain confirmed the beneficial effects of a Mediterra-

nean diet on the risk of CVD in primary prevention<sup>[26]</sup>. In a sample of 7747 adults (age range: 55-80 years) at high risk of cardiovascular disease but without a manifest disease who were followed for an average of 4.8 years, three different dietary interventions were tested. The participants were randomly assigned to a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with nuts or a control diet with a low contribution from fats. At the end of the follow-up, subjects who had followed the Mediterranean diet with either supplementation of extra-virgin olive oil or mixed nuts demonstrated a reduced risk of CVD. The hazard ratios were 0.70 (95%CI: 0.54-0.92) and 0.72 (95%CI: 0.54-0.96) for the group assigned to a Mediterranean diet with extra-virgin olive and the group assigned to a Mediterranean diet with nuts, respectively, *versus* the control group.

Alongside, Mediterranean diet has been also found protective versus cardiovascular disease in non-Mediterranean populations, such as in the United States. In two large United States cohort studies, Mediterranean diet was found to ameliorate the cardiovascular risk profile<sup>[27,28]</sup>. The first, published by Mitrou *et al*<sup>[27]</sup>, analyzed over than 200000 people aged between 50 and 71 years for a median follow-up period of 10 years; a greater adherence to the Mediterranean diet demonstrated a 22%-reduced risk of cardiovascular mortality in men (RR = 0.78; 95%CI: 0.69-0.87) and 29% in women (RR = 0.81; 95%CI: 0.68-0.97). The second, conducted in a population of over than 74000 women enrolled in the Nurses' Health Study confirmed the significant protective role of the Mediterranean diet, since women with a higher adherence to the Mediterranean diet had a reduced risk of coronary heart disease by 29% (RR = 0.71, 95%CI: 0.62-0.82), and of overall mortality from CVD by 39% (RR = 0.61, 95%CI: 0.49-0.76)<sup>[28]</sup>.

Our group conducted two systematic reviews and meta-analyses of prospective epidemiological studies that evaluated the adherence to the Mediterranean diet through the adherence score in relation to different health outcomes<sup>[29,30]</sup>. In the updated analysis a 2-points increase of the adherence score to the Mediterranean diet resulted in a 10% reduction in the incidence and/or mortality from CVD (RR = 0.90, 95%CI: 0.87-0.93,  $P < 0.0001$ )<sup>[30]</sup>.

### **Mediterranean diet and diabetes**

A Mediterranean diet has also been proposed as a valid and effective non-pharmaceutical option for diabetes mellitus treatment. In a Spanish cohort study, that comprised a large number of participants analyzed for a period of 4 years, the possible association between adherence to Mediterranean diet and diabetes has been investigated<sup>[31]</sup>. This study demonstrated that patients with greater adherence to the Mediterranean diet had a concomitant reduction of developing diabetes by 83%. Furthermore, it was reported that a 2-points increase of the score was also related to a 35%-reduced risk (RR =

0.65, 95%CI: 0.44-0.95). These data were confirmed also in some intervention studies. In the first, Esposito *et al*<sup>[32]</sup> studies 215 patients with a new diagnosis of diabetes. Patients were randomized to a Mediterranean diet and a low-fat diet. It was reported that the Mediterranean diet ameliorates the glycemic status of these subjects, helps controlling the cardiovascular risk factors, and posticipates the need for hypoglycemic therapy when compared with a diet low in fat and low in carbohydrates. Another study, conducted by Estruch *et al*<sup>[33]</sup> reported similar results since 772 patients asymptomatic for CVD were randomized to a low-fat diet or to a Mediterranean diet. After only 3 mo of follow-up, subjects who followed the Mediterranean diet reported a significant reduction of blood glucose.

Moreover, the datum was also reported in a large case-control study, comprising about 340000 subjects enrolled in the EPIC study. The authors were able to demonstrate that a higher adherence to the Mediterranean diet was associated with a 12%-reduction of diabetes (OR = 0.88, 95%CI: 0.79-0.97)<sup>[34]</sup>.

### **Mediterranean diet and obesity**

The role of the Mediterranean diet in the development and/or modification of overweight-obesity has always been of great interest in clinical research. Recently, a sub-analysis of the EPIC study analyzed a cohort of 497308 people, by showing that a higher adherence to the Mediterranean diet was associated with a significantly lower body mass index and waist circumference within 3 years<sup>[35]</sup>. These results were confirmed by other studies in different populations. Indeed, a Spanish study conducted on over than 3000 men and women showed a significant inverse relationship between Mediterranean diet and obesity<sup>[36]</sup>. Likewise, the SUN study demonstrated that subjects reporting low adherence to the Mediterranean diet had a higher weight gain during follow-up than those who had followed the principles of the Mediterranean diet more strictly. Notably, a greater adherence to the Mediterranean diet was associated with a reduced risk of obesity (OR = 0.76, 95%CI: 0.64-0.90).

Finally, similar results were also obtained from a further study in a large Spanish population<sup>[37]</sup>.

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## **MEDITERRANEAN DIET AND NON-ALCOHOLIC FATTY LIVER DISEASE**

Recently, the interest of investigators on the possible association between a Mediterranean diet and fatty liver disease has increased (Table 1). Although there is limited data linking a Mediterranean diet to NAFLD risk and severity, there is strong evidence from clinical studies supporting the hypothesis that such a diet might be beneficial for NAFLD-related disease states such as metabolic syndrome, CVD, and their risk factors<sup>[10,11]</sup>.

In 2008, a *post hoc* analysis of an open label, quasi-randomized, controlled trial evaluated the possible influ-

**Table 1** Studies investigating a Mediterranean diet and non-alcoholic fatty liver disease

Study	Country	Study design	Patients	n	Outcome	Intervention	Follow-up	Results
Fraser <i>et al</i> <sup>[38]</sup> , 2008	Israel	Post hoc analysis of a quasi-randomized trial	Obese with diabetes	259	Reduction of liver enzymes through diets	3 diets: ADA diet Low-GI diet Modified MD	12 mo	MD determined the greatest reduction of liver enzymes at 6 and 12 mo
Tzima <i>et al</i> <sup>[39]</sup> , 2009	Greece	Cross-sectional study (The ATTICA Study)	Healthy subjects	1514 M 1528 F	Association of MD with liver enzymes and MS	None	-	Greater adherence to MD determines a moderate association between liver enzymes and MS
Pérez-Guisado <i>et al</i> <sup>[42]</sup> , 2011	Spain	Prospective study	Obese with NAFLD	14	Effect of SKMD on NAFLD	SKMD	12 wk	SKMD determines reduction of liver enzymes and severity of steatosis
Ryan <i>et al</i> <sup>[40]</sup> , 2013	Australia	Randomised cross-over dietary intervention	Non-diabetic NAFLD	12	Improvement of liver steatosis	MD Low-fat/ High-carbohydrate diet	6 wk	MD reduces liver steatosis and improves insulin sensitivity
Kontogianni <i>et al</i> <sup>[41]</sup> , 2013	Greece	Cross-sectional study	NAFLD	73	Adherence to MD and severity of NAFLD	None	None	Greater adherence to MD is associated with less severity of NAFLD and lower degree of insulin resistance

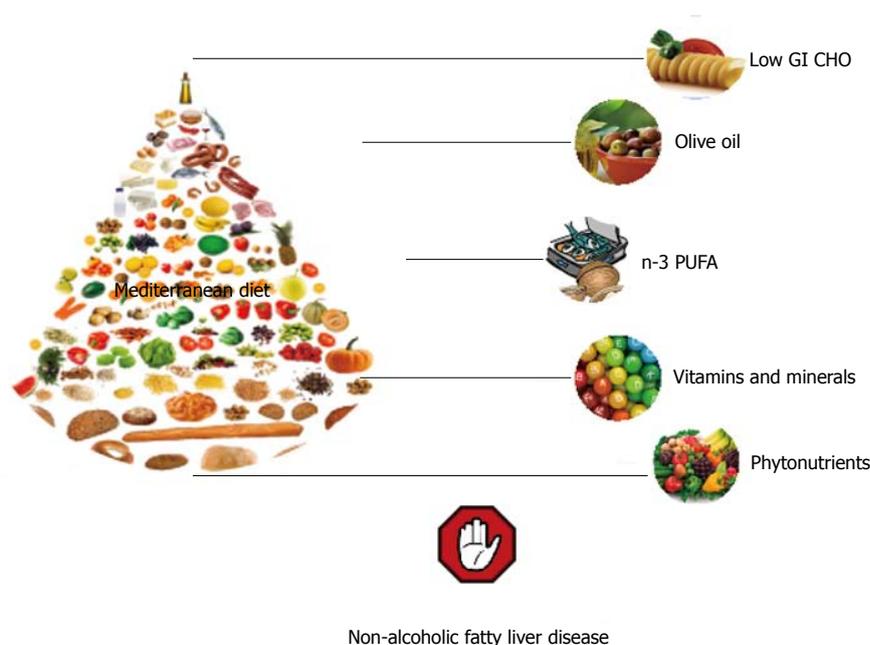
ADA: American Diabetes Association; GI: Glycemic index; MD: Mediterranean diet; MS: Metabolic syndrome; SKMD: Spanish ketogenic Mediterranean diet; NAFLD: Non-alcoholic fatty liver disease.

ence of three different diets on liver enzymes of 259 obese patients with type 2 diabetes<sup>[38]</sup>. Patients were randomized to a diet recommended by the American Diabetes Association, a low glycemic index diet and a modified Mediterranean diet. The three dietary profiles had a similar proportion of total fat but different proportions of carbohydrates and MUFA, as the Mediterranean diet had a higher intake of unsaturated fat and a lower percentage of energy coming from carbohydrates than the other two diets. In addition, the Mediterranean diet was modified in order to obtain all low-glycemic index foods. At 6 and 12 mo of follow-up, ALT levels decreased more significantly in the modified Mediterranean diet arm than in the other two dietary profiles, with mean values reduced from 19.8 to 14.4 U/L. Moreover, after adjustment for some traditional risk factors, including change in body mass, triglycerides, HOMA-IR and waist-to-hip index from baseline, ALT values were confirmed to be significantly reduced in the Mediterranean diet group with respect to the other groups. Although there were limitations related to the sample size and to clinical measurement that was limited to liver enzymes, this trial suggested for the first time that a Mediterranean diet could have a beneficial effect on ALT levels, and that this was not mediated by weight loss or decreases in other circulating biomarkers.

Later, the beneficial effect of a Mediterranean diet on liver enzymes was confirmed by the ATTICA study, that evaluated the prevalence of metabolic syndrome among over 3000 Greek adults<sup>[39]</sup>. The authors analyzed adherence to the Mediterranean diet through a scoring system named “MedDietScore”, and found a slight but significant positive correlation between the AST/ALT ratio and the MedDietScore itself ( $R = 0.17$ ).

Further evidence of the beneficial role of a Mediterranean diet on fatty liver came from the recent study by Ryan *et al*<sup>[40]</sup>. The authors carried out a randomized, crossover dietary intervention study in 12 diabetic subjects with NAFLD. All patients had biopsy-proven NAFLD and were randomized to either a Mediterranean diet or control diet for a duration of 6 wk in random order, interposed by a wash-out period. At the end of the intervention period, mean weight loss was similar between the two groups of patients but a significant reduction in liver fat content was found with magnetic resonance imaging only after the Mediterranean diet phase with respect to the control phase. Moreover, patients improved their insulin sensitivity, measured via a hyperinsulinemic-euglycemic clamp, and their circulating levels of insulin only after the Mediterranean diet phase and not during the control phase. Of interest, no significant differences in AST and ALT values were observed. This intervention study is of extreme importance for the management of NAFLD, despite the low number of patients considered.

Very recently, adherence to a Mediterranean diet was investigated in association with the severity of NAFLD in a group of 73 patients<sup>[41]</sup>. Adherence to a Mediterranean diet was estimated through the MedDietScore and severity of NAFLD was measured through transient elastography in 58 out of 73 patients and through liver biopsies in 34 patients. In addition, 58 healthy controls were compared with the study population. A significant negative correlation between the MedDietScore and ALT, insulin levels, stage of fibrosis, and severity of steatosis was evidenced in the group of patients with NAFLD. In addition, logistic regression analysis showed that one unit increase in the MedDietScore was associ-



**Figure 1** Beneficial properties of a Mediterranean diet on non-alcoholic fatty liver disease. PUFA: Polyunsaturated fatty acids.

ated with a 36% lower likelihood of having NASH after adjustment for confounders.

The Mediterranean-style diet is not a specific diet, but rather a collection of eating habits traditionally followed by people in the different countries bordering the Mediterranean Sea. It refers to a dietary profile commonly present in the Mediterranean regions in the last century and is characterized by a high consumption of fruit, vegetables, legumes, and complex carbohydrates, with a moderate consumption of fish and the use of olive oil as the main source of fats, and a low-to-moderate amount of red wine during meals. This eating pattern has been promoted worldwide as a model for healthy eating and has been reported to contribute to a favorable health status and to a better quality of life, as well as allowing an optimal intake of antioxidant vitamins, polyunsaturated fats and other beneficial nutrients for the prevention of chronic degenerative diseases<sup>[24]</sup>. In terms of NAFLD prevention, the beneficial effects of such dietary habits can be explained through several mechanisms that can vary from an effective dietary approach for weight loss, to a model diet that is plentiful in some beneficial nutrients such as MUFA and vitamins, to the presence of olive oil as the main contributor of fats (Figure 1). Indeed, olive oil has been demonstrated to have several different beneficial effects on metabolic syndrome and NAFLD, by improving glucose and lipid metabolism and preventing atherogenesis<sup>[20]</sup>. All these factors likely contribute, as a whole, in determining the preventive and therapeutic role of a Mediterranean diet on fatty liver disease.

## CONCLUSION

In conclusion, a Mediterranean diet has recently been promoted as a healthy eating pattern for many condi-

tions including metabolic syndrome, cardiovascular and neoplastic diseases. Over the last few years, an interesting inverse association with NAFLD has also been reported in some studies, indicating the Mediterranean dietary pattern as a new therapeutic option “right around the corner”. To date, few studies have been conducted with the aim of investigating adherence to a Mediterranean diet in relation to the occurrence of NAFLD. Further studies are warranted to confirm these preliminary data and to suggest a reliable and easy-to-use tool for determining the adherence to the Mediterranean dietary pattern in a large population of patients affected by fatty liver disease.

## REFERENCES

- 1 **Ratziu V**, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol* 2010; **53**: 372-384 [PMID: 20494470 DOI: 10.1016/j.jhep.2010.04.008]
- 2 **Masuoka HC**, Chalasani N. Nonalcoholic fatty liver disease: an emerging threat to obese and diabetic individuals. *Ann N Y Acad Sci* 2013; **1281**: 106-122 [PMID: 23363012 DOI: 10.1111/nyas.12016]
- 3 **Browning JD**, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; **40**: 1387-1395 [PMID: 15565570 DOI: 10.1002/hep.20466]
- 4 **Bugianesi E**, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, Musso A, De Paolis P, Capussotti L, Salizzoni M, Rizzetto M. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002; **123**: 134-140 [PMID: 12105842 DOI: 10.1053/gast.2002.34168]
- 5 **Levene AP**, Goldin RD. The epidemiology, pathogenesis and histopathology of fatty liver disease. *Histopathology* 2012; **61**: 141-152 [PMID: 22372457 DOI: 10.1111/j.1365-2559.2011.04145.x]
- 6 **Bozic MA**, Subbarao G, Molleston JP. Pediatric nonalcoholic

- fatty liver disease. *Nutr Clin Pract* 2013; **28**: 448-458 [PMID: 23917437 DOI: 10.1177/0884533613489153]
- 7 **Ahmed MH**, Barakat S, Almobarak AO. Nonalcoholic fatty liver disease and cardiovascular disease: has the time come for cardiologists to be hepatologists? *J Obes* 2012; **2012**: 483135 [PMID: 23320150 DOI: 10.1155/2012/483135]
  - 8 **Dam-Larsen S**, Becker U, Franzmann MB, Larsen K, Christoffersen P, Bendtsen F. Final results of a long-term, clinical follow-up in fatty liver patients. *Scand J Gastroenterol* 2009; **44**: 1236-1243 [PMID: 19670076 DOI: 10.1080/00365520903171284]
  - 9 **Loria P**, Adinolfi LE, Bellentani S, Bugianesi E, Grieco A, Fargion S, Gasbarrini A, Loguercio C, Lonardo A, Marchesini G, Marra F, Persico M, Prati D, Baroni GS. Practice guidelines for the diagnosis and management of nonalcoholic fatty liver disease. A decalogue from the Italian Association for the Study of the Liver (AISF) Expert Committee. *Dig Liver Dis* 2010; **42**: 272-282 [PMID: 20171943 DOI: 10.1016/j.dld.2010.01.021]
  - 10 **McCarthy EM**, Rinella ME. The role of diet and nutrient composition in nonalcoholic Fatty liver disease. *J Acad Nutr Diet* 2012; **112**: 401-409 [PMID: 22717200 DOI: 10.1016/j.jada.2011.10.007]
  - 11 **Zivkovic AM**, German JB, Sanyal AJ. Comparative review of diets for the metabolic syndrome: implications for nonalcoholic fatty liver disease. *Am J Clin Nutr* 2007; **86**: 285-300 [PMID: 17684197]
  - 12 **Promrat K**, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, Fava JL, Wing RR. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 121-129 [PMID: 19827166 DOI: 10.1002/hep.23276]
  - 13 **Luyckx FH**, Desai C, Thiry A, Dewé W, Scheen AJ, Gielen JE, Lefèbvre PJ. Liver abnormalities in severely obese subjects: effect of drastic weight loss after gastroplasty. *Int J Obes Relat Metab Disord* 1998; **22**: 222-226 [PMID: 9539189]
  - 14 **York LW**, Puthalappattu S, Wu GY. Nonalcoholic fatty liver disease and low-carbohydrate diets. *Annu Rev Nutr* 2009; **29**: 365-379 [PMID: 19575599 DOI: 10.1146/annurev-nutr-070208-114232]
  - 15 **Ryan MC**, Abbasi F, Lamendola C, Carter S, McLaughlin TL. Serum alanine aminotransferase levels decrease further with carbohydrate than fat restriction in insulin-resistant adults. *Diabetes Care* 2007; **30**: 1075-1080 [PMID: 17351275 DOI: 10.2337/dc06-2169]
  - 16 **Browning JD**, Baker JA, Rogers T, Davis J, Satapati S, Burgess SC. Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction. *Am J Clin Nutr* 2011; **93**: 1048-1052 [PMID: 21367948 DOI: 10.3945/ajcn.110.007674]
  - 17 **Vilar L**, Oliveira CP, Faintuch J, Mello ES, Nogueira MA, Santos TE, Alves VA, Carrilho FJ. High-fat diet: a trigger of non-alcoholic steatohepatitis? Preliminary findings in obese subjects. *Nutrition* 2008; **24**: 1097-1102 [PMID: 18640006 DOI: 10.1016/j.nut.2008.05.017]
  - 18 **Yamamoto M**, Iwasa M, Iwata K, Kaito M, Sugimoto R, Urawa N, Mifuji R, Konishi M, Kobayashi Y, Adachi Y. Restriction of dietary calories, fat and iron improves non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* 2007; **22**: 498-503 [PMID: 17376040 DOI: 10.1111/j.1440-1746.2006.04548]
  - 19 **Lefevre M**, Champagne CM, Tulley RT, Rood JC, Most MM. Individual variability in cardiovascular disease risk factor responses to low-fat and low-saturated-fat diets in men: body mass index, adiposity, and insulin resistance predict changes in LDL cholesterol. *Am J Clin Nutr* 2005; **82**: 957-963; quiz 1145-1146 [PMID: 16280425]
  - 20 **Assy N**, Nassar F, Nasser G, Grosovski M. Olive oil consumption and non-alcoholic fatty liver disease. *World J Gastroenterol* 2009; **15**: 1809-1815 [PMID: 19370776 DOI: 10.3748/wjg.15.1809]
  - 21 **Capanni M**, Calella F, Biagini MR, Genise S, Raimondi L, Bedogni G, Svegliati-Baroni G, Sofi F, Milani S, Abbate R, Surrenti C, Casini A. Prolonged n-3 polyunsaturated fatty acid supplementation ameliorates hepatic steatosis in patients with non-alcoholic fatty liver disease: a pilot study. *Aliment Pharmacol Ther* 2006; **23**: 1143-1151 [PMID: 16611275 DOI: 10.1111/j.1365-2036.2006.02885]
  - 22 **Parker HM**, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J. Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012; **56**: 944-951 [PMID: 22023985 DOI: 10.1016/j.jhep.2011.08.018]
  - 23 **Sofi F**, Giangrandi I, Cesari F, Corsani I, Abbate R, Gensini GF, Casini A. Effects of a 1-year dietary intervention with n-3 polyunsaturated fatty acid-enriched olive oil on non-alcoholic fatty liver disease patients: a preliminary study. *Int J Food Sci Nutr* 2010; **61**: 792-802 [PMID: 20465434 DOI: 10.3109/09637486.2010.487480]
  - 24 **Sofi F**, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health. *Biofactors* 2013; **39**: 335-342 [PMID: 23553669 DOI: 10.1002/biof.1096]
  - 25 **Trichopoulou A**, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003; **348**: 2599-2608 [PMID: 12826634 DOI: 10.1056/NEJMoa025039]
  - 26 **Estruch R**, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventós RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013; **368**: 1279-1290 [PMID: 23432189 DOI: 10.1056/NEJMoa1200303]
  - 27 **Mitrou PN**, Kipnis V, Thiébaud AC, Reedy J, Subar AF, Wirfält E, Flood A, Mouw T, Hollenbeck AR, Leitzmann MF, Schatzkin A. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. *Arch Intern Med* 2007; **167**: 2461-2468 [PMID: 18071168 DOI: 10.1001/archinte.167.22.2461]
  - 28 **Fung TT**, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation* 2009; **119**: 1093-1100 [PMID: 19221219 DOI: 10.1161/CIRCULATIONAHA.108.816736]
  - 29 **Sofi F**, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008; **337**: a1344 [PMID: 18786971 DOI: 10.1136/bmj.a1344]
  - 30 **Sofi F**, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* 2010; **92**: 1189-1196 [PMID: 20810976 DOI: 10.3945/ajcn.2010.29673]
  - 31 **Martínez-González MA**, de la Fuente-Arrillaga C, Nunez-Cordoba JM, Basterra-Gortari FJ, Beunza JJ, Vazquez Z, Benito S, Tortosa A, Bes-Rastrollo M. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. *BMJ* 2008; **336**: 1348-1351 [PMID: 18511765 DOI: 10.1136/bmj.39561.501007.BE]
  - 32 **Esposito K**, Maiorino MI, Ciotola M, Di Palo C, Scognamiglio P, Gicchino M, Petrizzo M, Saccomanno F, Beneduce F, Ceriello A, Giugliano D. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann Intern Med* 2009; **151**: 306-314 [PMID: 19721018 DOI: 10.7326/0003-4819-151-5-200909010-00004]
  - 33 **Estruch R**, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC, Vinyoles E, Arós F, Conde M, Lahoz C, Lapetra J, Sáez G, Ros E. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med* 2006; **145**: 1-11 [PMID: 16818923 DOI: 10.7326/00

- 03-4819-145-1-200607040-00004]
- 34 **Romaguera D**, Guevara M, Norat T, Langenberg C, Forouhi NG, Sharp S, Slimani N, Schulze MB, Buijsse B, Buckland G, Molina-Montes E, Sánchez MJ, Moreno-Iribas MC, Bendinelli B, Gioni S, van der Schouw YT, Arriola L, Beulens JW, Boeing H, Clavel-Chapelon F, Cottet V, Crowe FL, de Lauzon-Guillan B, Franks PW, Gonzalez C, Hallmans G, Kaaks R, Key TJ, Khaw K, Nilsson P, Overvad K, Palla L, Palli D, Panico S, Quirós JR, Rolandsson O, Romieu I, Sacerdote C, Spijkerman AM, Teucher B, Tjønneland A, Tormo MJ, Tumino R, van der AD, Feskens EJ, Riboli E, Wareham NJ. Mediterranean diet and type 2 diabetes risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study: the InterAct project. *Diabetes Care* 2011; **34**: 1913-1918 [PMID: 21788627 DOI: 10.2337/dc11-0891]
- 35 **Romaguera D**, Norat T, Mouw T, May AM, Bamia C, Slimani N, Travier N, Besson H, Luan J, Wareham N, Rinaldi S, Couto E, Clavel-Chapelon F, Boutron-Ruault MC, Cottet V, Palli D, Agnoli C, Panico S, Tumino R, Vineis P, Agudo A, Rodriguez L, Sanchez MJ, Amiano P, Barricarte A, Huerta JM, Key TJ, Spencer EA, Bueno-de-Mesquita HB, Büchner FL, Orfanos P, Naska A, Trichopoulou A, Rohrmann S, Kaaks R, Bergmann M, Boeing H, Johansson I, Hellstrom V, Manjer J, Wirfält E, Uhre Jacobsen M, Overvad K, Tjønneland A, Halkjaer J, Lund E, Braaten T, Engeset D, Odysseos A, Riboli E, Peeters PH. Adherence to the Mediterranean diet is associated with lower abdominal adiposity in European men and women. *J Nutr* 2009; **139**: 1728-1737 [PMID: 19571036 DOI: 10.3945/jn.109.108902]
- 36 **Schröder H**, Marrugat J, Vila J, Covas MI, Elosua R. Adherence to the traditional mediterranean diet is inversely associated with body mass index and obesity in a spanish population. *J Nutr* 2004; **134**: 3355-3361 [PMID: 15570037]
- 37 **Beunza JJ**, Toledo E, Hu FB, Bes-Rastrollo M, Serrano-Martínez M, Sánchez-Villegas A, Martínez JA, Martínez-González MA. Adherence to the Mediterranean diet, long-term weight change, and incident overweight or obesity: the Seguimiento Universidad de Navarra (SUN) cohort. *Am J Clin Nutr* 2010; **92**: 1484-1493 [PMID: 20962161 DOI: 10.3945/ajcn.2010.29764]
- 38 **Fraser A**, Abel R, Lawlor DA, Fraser D, Elhayany A. A modified Mediterranean diet is associated with the greatest reduction in alanine aminotransferase levels in obese type 2 diabetes patients: results of a quasi-randomised controlled trial. *Diabetologia* 2008; **51**: 1616-1622 [PMID: 18597068 DOI: 10.1007/s00125-008-1049-1]
- 39 **Tzima N**, Pitsavos C, Panagiotakos DB, Chrysohoou C, Polychronopoulos E, Skoumas J, Stefanadis C. Adherence to the Mediterranean diet moderates the association of aminotransferases with the prevalence of the metabolic syndrome; the ATTICA study. *Nutr Metab (Lond)* 2009; **6**: 30 [PMID: 19642977 DOI: 10.1186/1743-7075-6-30]
- 40 **Ryan MC**, Itsiopoulos C, Thodis T, Ward G, Trost N, Hofferberth S, O'Dea K, Desmond PV, Johnson NA, Wilson AM. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. *J Hepatol* 2013; **59**: 138-143 [PMID: 23485520 DOI: 10.1016/j.jhep.2013.02.012]
- 41 **Kontogianni MD**, Tileli N, Margariti A, Georgoulis M, Deutsch M, Tiniakos D, Fragopoulou E, Zafropoulou R, Manios Y, Papatheodoridis G. Adherence to the Mediterranean diet is associated with the severity of non-alcoholic fatty liver disease. *Clinical Nutrition* 2013; In press [DOI: 10.1016/j.clnu.2013.08.014]
- 42 **Pérez-Guisado J**, Muñoz-Serrano A. The effect of the Spanish Ketogenic Mediterranean Diet on nonalcoholic fatty liver disease: a pilot study. *J Med Food* 2011; **14**: 677-680 [PMID: 21688989 DOI: 10.1089/jmf.2011.0075]

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