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OMEGA-3 POLYUNSATURATED FATTY ACID SUPPLEMENTATION VS. A MEDITERRANEAN DIET AS A TREATMENT FOR NONALCOHOLIC FATTY LIVER DISEASE

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Summary. Introduction: Non-alcoholic fatty liver disease (NAFLD) is becoming increasingly prevalent and is the leading liver disease worldwide. The aim is to compare new dietary-nutritional strategies, such as the Mediterranean diet and omega-3 polyunsaturated fatty acids, to determine which is more effective as a treatment for this disease. Objective: To evaluate which nutritional management is more effective as a treatment for nonalcoholic fatty liver disease, omega-3 supplementation or a Mediterranean diet. Method: A bibliographic review was carried out, for which several scientific articles were consulted and selected from various databases, documents and the online information service provided by the National Library of Medicine of the United States (MedlinePlus), thus obtaining a total of 17 studies belonging to the PubMed database, which were analyzed in depth. Results and discussion: Both the Mediterranean diet and supplementation with omega-3 polyunsaturated fatty acids promote benefits on the clinical characteristics of patients with fatty liver disease. Following a Mediterranean diet seems to have greater benefits in the treatment of NASH by improving the clinical features of the disease such as hepatic steatosis, inflammation, fibrosis and non-alcoholic steatohepatitis, in addition to the metabolic syndrome.

Key words: omega-3 , NASH, Mediterranean diet, metabolic syndrome, NASH.

SUPLEMENTACIÓN CON ÁCIDOS GRASOS POLIINSATURADOS OMEGA 3 FRENTE A UNA DIETA MEDITERRÁNEA COMO TRATAMIENTO PARA LA ENFERMEDAD DEL HÍGADO GRASO NO ALCOHÓLICO

Resumen. Introducción: La enfermedad del hígado graso no alcohólico (EHGNA) cada vez es más prevalente y es la principal enfermedad hepática a nivel mundial. Se quiere comparar nuevas estrategias dietético-nutricionales, como la dieta mediterránea y los ácidos grasos poliinsaturados omega-3, para determinar cuál es más efectiva como tratamiento para esta enfermedad. Objetivo: Evaluar que manejo nutricional es más efectivo como tratamiento del hígado graso no alcohólico, si la suplementación con omega 3 o una dieta mediterránea. Método: Se realizó una revisión bibliográfica, para la cual se consultaron y seleccionaron varios artículos científicos de diversas bases de datos, documentos y el servicio de

información en línea provisto por la Biblioteca Nacional de Medicina de los Estados Unidos (MedlinePlus), obteniendo asi un total de 17 estudios pertenecientes a la base de datos PubMed, los cuales fueron analizados en profundidad. Resultados y discusión: Tanto la dieta mediterránea como la suplementación con ácidos grasos poliinsaturados omega-3 promueven beneficios sobre las características clínicas de los pacientes con hígado graso. La realización de una dieta mediterránea parece tener mayores beneficios en el tratamiento de la EHGNA al mejorar las características clínicas de la enfermedad como la esteatosis hepática, la inflamación, la fibrosis y la esteatohepatitis no alcohólica, además, del síndrome metabólico.

Palabras clave: omega 3, EHGNA, dieta mediterránea, síndrome metabólico, EHNA.

Introduction

The National Library of Medicine (1) defines non-alcoholic fatty liver disease (NAFLD) as "the accumulation of fat in the liver that is NOT caused by consuming too much alcohol." It is characterized by an excessive accumulation of triglycerides (TG) and cholesterol in the form of lipid droplets in hepatocytes (2). NASH has different stages and can be divided into simple nonalcoholic fatty liver disease (NAFLD) or simple hepatic steatosis (NASH), which can be reversible through adequate nutritional treatment together with physical exercise for weight loss, or if it progresses it can become nonalcoholic steatohepatitis (NASH), with inflammation and cell damage. NASH can develop different stages of fibrosis, which can eventually lead to cirrhosis or liver cancer. Both NASH and cirrhosis are irreversible and the only existing treatment for them is liver transplantation. Therefore, it is necessary to find out more about the appropriate treatment for this disease (1,3–8).

NASH is the most prevalent chronic liver disease in the world, especially in Western countries, affecting both children and adults. Its prevalence increases along with that of obesity, approximately 20-30% of the general population suffers from it, being 2 times higher in men than in women. Of patients with NASH, approximately 20-25% have NASH, within this percentage, 20% will progress and develop liver cirrhosis (5,6,9–12). Within patients with NASH, those with NAFLD have a life expectancy similar to that of the general population, whereas patients with its more severe form, NASH, have a lower survival, due to cardiovascular problems and progression of liver damage (5,6,9,12).

Certain metabolic risk factors, genetic polymorphisms, an inadequate diet consisting of excess energy or changes in the composition of the intestinal microbiota (IM), which causes an increase in body fat and IR in peripheral tissues, are involved in the onset and progression of this pathology (13,14). It is mainly associated with metabolic syndrome (MS), which includes type 2 diabetes mellitus (DM2), dyslipidemia, arterial hypertension (AHT) and obesity. Often patients do not present with symptoms; if they do, they may present with ascites and fluid retention in the lower extremities, among others (1,6,15).

According to several publications, a change in lifestyle through the control and reduction of risk factors, especially associated metabolic comorbidities, is the current treatment for this disease. Weight loss is important in the case of overweight or obesity, along with physical exercise and a diet appropriate for the pathology. In addition, to reduce liver fat it is necessary to lower cholesterol and TG levels. Hepatitis A and hepatitis B vaccines need to be given to NASH patients (1,5,10,16,17). As for pharmacological treatment, its use is not very clear and further studies would be necessary. If used, these vary depending on the stage of the disease, comorbidities, grade

and phenotype. They are usually used for people with worse prognosis such as patients with NASH and fibrosis (5,10).

Linked to all this, in recent years new lines of research have emerged regarding nutritional treatments for this disease. On the one hand, the Mediterranean diet (DietMed) generally combined with physical activity and, on the other hand, supplementation with omega-3 polyunsaturated fatty acids (PUFA ω-3) are investigated. Both nutritional treatments are currently being studied and considered a suitable course of action due to their numerous beneficial effects as a treatment for this disease (15,18–20).

The main objective of this review is to evaluate which nutritional management is more effective as a treatment for NASH, whether ω-3 PUFA supplementation or a DietMed.

Methodology

A search for scientific articles related to the topic was conducted, giving priority to relevant human studies and clinical trials, systematic reviews and meta-analyses using the databases of: Pubmed, Scielo and Science Direct.

The literature search for articles began in January 2022 and ended in April 2022.

To locate the articles used in this review, inclusion criteria of 5 years old were applied, with the exception of relevant articles from previous years; articles with a significant sample and journals indexed with an impact factor greater than 1.5.

The following keywords were used in the databases to search for articles in the different sections:

- Fatty liver: "Fatty liver.
- Non-alcoholic fatty liver disease: "NASH", "gut microbiota", "metabolic syndrome", "NASH", "weight loss", "physical activity", "diet", "developmental mechanism"
- Mediterranean diet: "NASH", "NASH", "Mediterranean diet", "cardiovascular problem".
- Omega 3 polyunsaturated fatty acids: *"EHGNA", "EHNA", "omega-3 PUFA", "EPA", "DHA".*

The exclusion criteria were: articles older than 5 years, that did not fit the topic of interest, that the sample was not significant or that it was impossible to read beyond the title/abstract.

Finally, of all the articles found, a total of 17 were selected and included in the review: 4 studies cover the relationship between DietMed and NAFLD; 4 studies cover the relationship between DietMed, physical activity, and NAFLD; 7 studies cover the relationship between ω-3 PUFA supplementation and NAFLD; and 2 studies cover the relationship between DHA supplementation and NAFLD. All of them were analyzed in depth.

Results

Mediterranean Diet

DietMed is a type of diet characteristic of the Mediterranean region that is mainly composed of monounsaturated fatty acids from olive oil; plant-based foods such as fruits, vegetables, grains, nuts, legumes; and to a lesser extent meats and dairy products. This

diet has been attributed numerous health benefits: it decreases MS and cardiovascular risk by reducing cholesterol and TGs. DietMed is associated with a healthy lifestyle and the practice of physical exercise (18,21–23).

The following sections will discuss the side effects and beneficial effects of this dietary pattern on NASH.

Adverse effects of the Mediterranean diet

Caution should be exercised when following a DietMed since, being composed mainly of fats, there is a risk of weight gain. Low levels of iron, vitamin C and calcium may also result from consuming fewer foods that contain them (23).

Beneficial effects of the Mediterranean diet

This type of diet is characterized by its reduced content of refined sugars and fructose. Corn syrup is a refined sugar with high amounts of fructose, and its consumption has been shown to increase the risk of NASH, since high fructose consumption produces an accumulation of lipids in the liver, therefore, this low-fructose dietary pattern reduces the probability of suffering from this disease. It is also characterized by the absence of processed foods, such as soft drinks, which are rich in fructose and added sugars. This type of food promotes fat accumulation in the liver through de *novo* lipogenesis of fructose in the liver (24,25). In patients with NASH this mechanism is altered. Therefore, the absence of processed foods, rich in fructose and refined sugars in the diet, prevents the accumulation of fat in the liver and the development of liver disease (4,7,24,26).

Unlike other types of diets, DietMed is rich in complex carbohydrates, especially whole grains, and fiber. This type of food has a lower energy density than refined carbohydrates and is very satiating, which favors a lower accumulation of fat in the liver due to excessive energy intake. In addition, high fiber intake can favor the enrichment of certain bacteria in the intestine, such as *Firmicutes*, which are responsible for degrading fiber, leading to an increase in SCFAs such as butyrate, which is responsible for eliminating inflammation in the liver (27). It should be noted that whole grains improve postprandial glycemic control, which has a protective effect against associated problems such as MS (obesity and DM2) and cardiovascular risk (18,24,27–29).

Reducing meat consumption is beneficial, especially red meat, because meat contains cholesterol and saturated fatty acids that are deposited in the liver in the form of fat, increasing the risk of MS and cardiovascular problems. Therefore, the performance of the DietMed has an inverse association with this pathology (21,24,28).

DietMed does not speak of a specific consumption of coffee, therefore, based on current scientific evidence, it is possible to consume 2-3 cups per day. Coffee has cardioprotective effects, reducing the appearance of MS due to its caffeine and polyphenol content. It also has a hepatoprotective effect by reducing liver fibrosis (24,26,30).

This diet is characterized by the consumption of large quantities of foods with antioxidant and anti-inflammatory properties such as fruits, vegetables, nuts, whole grains, olive oil and fish rich in omega 3. These foods, thanks to their characteristics, prevent cell damage, oxidative stress and delay the development of hepatic steatosis, in addition to improving metabolic diseases (18,21,28). In addition, high nut consumption is associated with health benefits such as reduced cardiovascular risk, DM2, MS and insulin resistance, all of which are characteristic of NASH (31).

Therefore, this dietary pattern based on fats, fruits, vegetables, legumes, complex carbohydrates, fiber and to a lesser extent simple carbohydrates, refined sugars and meats,

especially processed and red meats; is a type of diet that manages to reduce cardiometabolic risk factors, such as cholesterol and TG, and clinical events *(Figure 1)*, which is very important for the loss of fat in the liver and therefore, for the treatment of NAFLD (18,23,24,28,31,32). The combination of DietMed with physical exercise improves hepatic fat accumulation, increases lipid oxidation and insulin sensitivity. In addition, when combined with probiotics *(Lactobacillus)* , it provides better liver health by controlling dysbiosis and restoring altered IM(33–35,31,26,18).

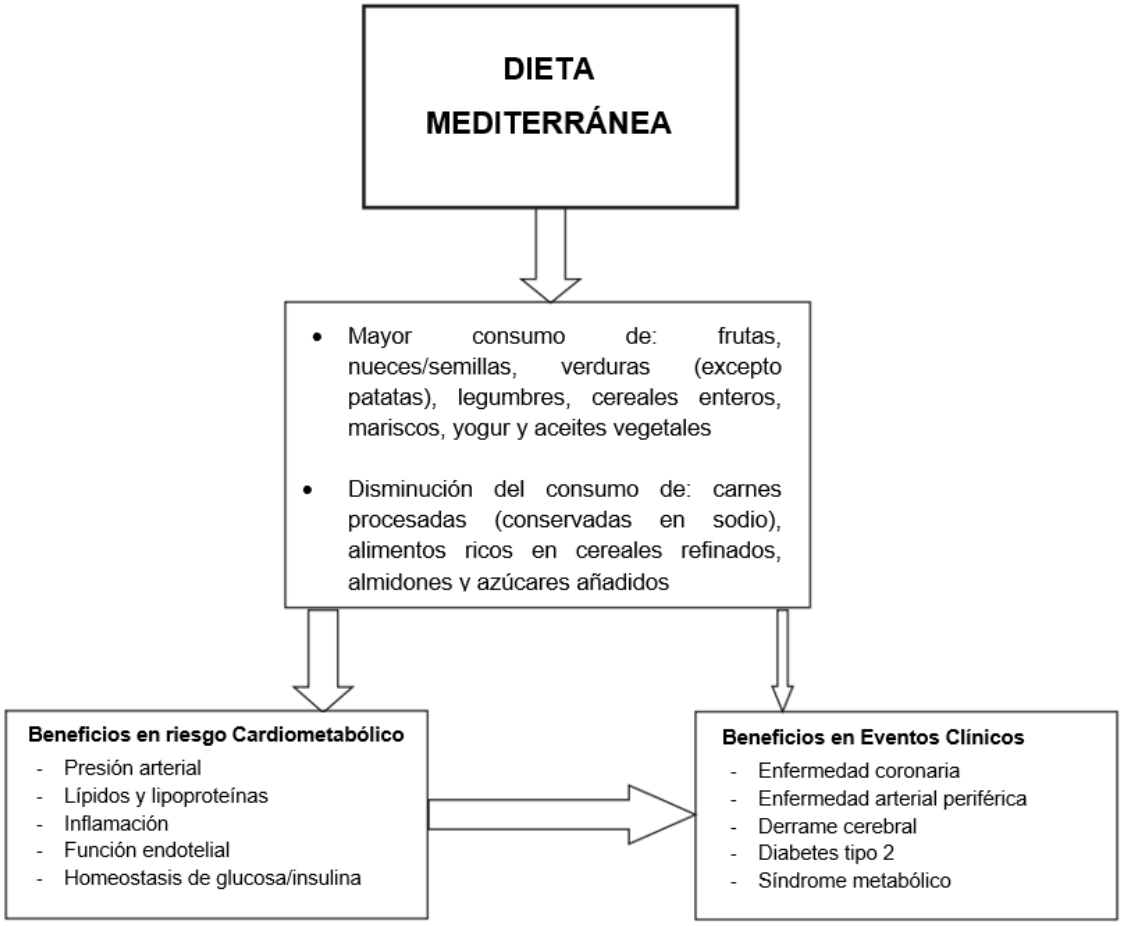

Figure 1. Characteristics of the DietMed and its benefits at the cardiometabolic and clinical event level. Improving cardiometabolic risk factors associated with DietMed consumption may lead to the prevention of clinical events. The thickness of the arrows is not proportional to the observed benefits (cardiometabolic or clinical), but may indicate a different hierarchy of effects (34).

Polyunsaturated omega-3 fatty acids

The PUFA ω-3, are a type of polyunsaturated fat essential for different processes in our body, such as maintaining stable cholesterol levels. These are of the essential type, i.e., the body cannot synthesize them, so they have to be obtained through the diet. These ω-3 PUFA are found in few foods, therefore, habitual intake is often deficient, which is associated with increased hepatic fat (HD) (36). Omega-3s have been shown to be beneficial in preventing cardiovascular problems due to their anti-inflammatory effect, improving insulin sensitivity and reducing oxidative stress (16,19,24,37,38).

Within PUFA ω-3, there are different types of long-chain fatty acids: α-linolenic acid (ALA), stearidonic acid (SDA), docosapentaenoic acid (DPA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). In the case of NASH treatment, we are only interested in the last two, DHA and EPA, modulators of hepatic gene expression. Both reduce TG and very low density lipoprotein (VLDL) levels, converting them into low density lipoproteins (LDL) and intermediate density lipoproteins (IDL) (16,19,39).

The following sections will discuss the side effects and beneficial effects of ω-3 PUFA on NAFLD.

Adverse effects of omega-3 polyunsaturated fatty acids

Supplementation with ω-3 PUFA can produce gastrointestinal problems such as: heartburn, stomach pain, nausea, vomiting, constipation, diarrhea or belching. It can also produce changes in the sense of taste (37).

Beneficial effects of omega-3 polyunsaturated fatty acids

It has been seen that patients with this disease have a low intake of ω-3 PUFA and a high intake of omega-6 PUFA, which may favor lipid production and IR. Therefore, supplementation with ω-3 PUFA would help to compensate for this imbalance and diminish its negative effects (20,39–41). These fatty acids are used for different processes in our organism, such as maintaining stable cholesterol levels, in addition, they decrease the amount of TG in the liver, which would justify their use in NASH for the loss of fat in the liver (37,42).

The use of ω-3 PUFA supplementation produced improvements in MS risk factors, at the hepatic level in fat content, pancreatic enzyme levels, blood lipid levels and degree of steatosis. DHA has greater efficacy in ameliorating both steatosis and liver fibrosis (43) *(Figure 2)*. But in NASH, supplementation with ω-3 PUFA did not result in any improvement (19,20).

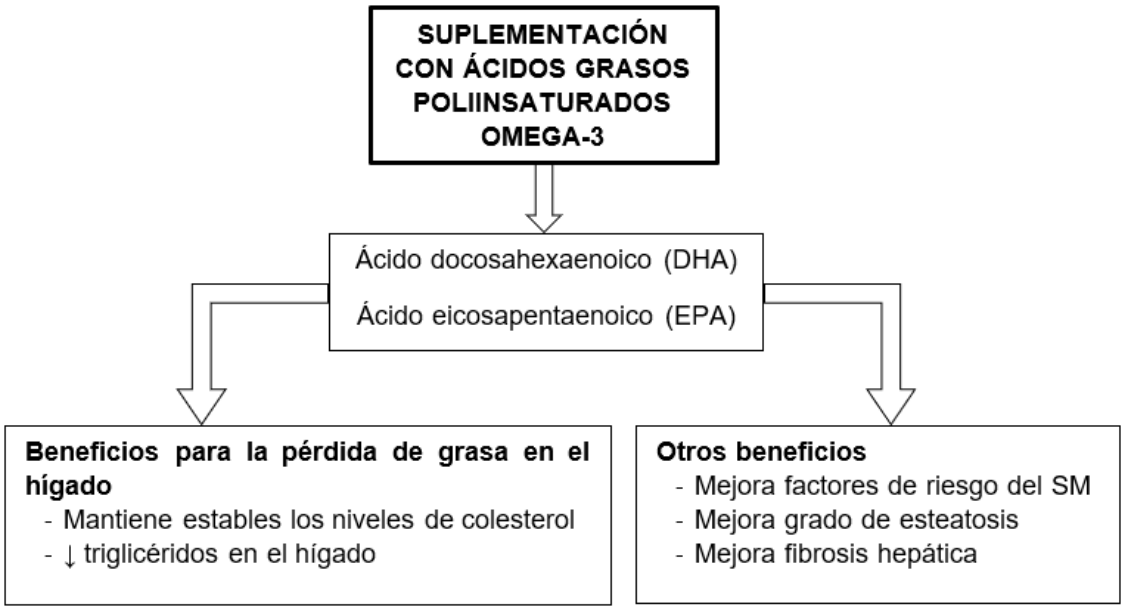

Figure 2. Types of ω-3 PUFA and their benefits for liver fat loss and other risk factors (37,42,43).

Discussion

Regarding DietMed, 3 studies cover the relationship between DietMed and NASH, and 3 other studies cover the relationship between DietMed, physical activity and NASH.

Table 1 shows in more detail the characteristics and results found in each study based on the clinical criteria of the disease. These studies show that the use of DietMed, both on its own and in conjunction with physical activity, improves disease parameters, especially those related to MS (11,15,29,31,32,44).

Table 1

Summary of the characteristics and results of the studies included in the discussion that address the relationship between DietMed alone or in conjunction with physical activity and NASH (11,15,29,31,32,44).

Author, year (Ref.)	Type of study	Sample size	Features	Results
DietMed and EHGNA				
Chen et al., 2019 (31)	Retrospective case-control study	n = 1068 (534 with NASH and 534 without) (31.8% female)	Age 18-70 years old	- No association between nut consumption and NASH risk in the overall sample - Significant inverse association between ↑ nut consumption and EHGNA in the highest quartile of the male sample
Georgoulis et al., 2015 (29)	Retrospective cross-sectional study	n = 73 with NASH (31.5% female)	Age 34-56 years	- 46.5% sample with SM, ↑ waist circumference and ↓ HDL - Positive association between MS and consumption of red meats and refined grains - Negative association between MS and DietMed score (MedDietScore) and consumption of whole grains.
Aller et al., 2018 (11)	Cross-sectional study of adherence to DietMed	n = 203 with biopsy-proven NASH (43.3% female)	Age 44-49 years	- ↑ Serum adiponectin levels and ↓ resistin and leptin concentration in overweight vs obese participants - ↑ Frequency of NASH in obese participants - Adherence to the Mediterranean diet as an independent protective factor for liver fibrosis and NASH in overweight participants.
DietMed, physical activity and EHGNA				
Konerman et al., 2018 (44)	Cohort study	n = 403 who completed the MetFit program at the University of Michigan between 2008 and 2016 (37.5 % female)	Age 45-63 years Duration = 12 and 24 weeks	The main group were men with severe obesity and NASH - 30 % ↓ weight ≥ 5 % - 62 % resolution of hypertriglyceridemia - 33 % low HDL resolution - 27 % resolution of fasting glucose disturbance 43 % ALT normalization
Bullón-Vela et al., 2019 (32)	Cross-sectional study	n = 328 patients with MS participating in the	Age 55-75 (men) and 60-75 (women) years old	- ↓ noninvasive hepatic steatosis index values with ↑ tertiles of physical activity - Adherence to the Mediterranean diet inversely associated with

		PREDIMED-Plus study (45.1% women)		noninvasive hepatic steatosis index values ↑ tertiles of legume consumption inversely associated with the highest tertile of the noninvasive hepatic steatosis index
Gelli et al., 2017 (15)	Observational study	n = 46 with NASH (37% female)	Age 26-71 years Duration = 6 months	- ↓ 93 % to 48 % of the percentage of participants with steatosis grade ≥ 2 - Regression of steatosis in 9 participants - 25 of 46 participants achieved a 7% weight reduction or maintained a normal weight - ↓ Liver enzymes (especially ALT) Improved waist circumference, BMI, waist-to-hip ratio, LDL/HDL, total cholesterol/HDL, triglycerides/HDL, serum glucose, HDL, fatty liver index, HOMA-IR insulin resistance index, Kotronen index, EHGNA liver fat score, visceral adipose index and lipid accumulation product

In the work of Gelli et al (15)the authors demonstrate that DietMed and a more active lifestyle can be considered a safe therapeutic approach to reduce the risk and severity of NASH and related diseases.

In the prospective cohort study (27) comparing DietMed with a healthy diet, it was found that DietMed resulted in a greater loss of liver fat, weight and likelihood of developing NASH than the consumption of a healthy diet. This diet is rich in fruits and vegetables that contain high amounts of water and fiber, contributing to satiety and improved weight control by reducing energy intake. In addition, thanks to fiber, liver inflammation is also reduced. Of note, preliminary evidence suggests that nut consumption may promote fat oxidation and reduce ectopic fat mass in the viscera, although supporting studies are limited.

In the meta-analysis conducted by Akhlaghi et al. (28) on DietMed for NASH patients, we found 7 observational studies and 6 clinical trials. In observational studies there was an inverse association between DietMed and NASH. However, only 4 of the clinical trials proved the positive effect of DietMed on HD, showing a significant drop in BMI, weight, TG and total cholesterol, but no effect was found on LDL and HDL cholesterol, blood pressure, fasting blood glucose and insulin. Overall, the available data from these studies indicate an inverse association between DietMed and HD with a drop in BMI, and plasma TGs, but no significant improvement in waist circumference, cholesterol, glucose or insulin resistance was observed. Although the results are promising, further observational and interventional studies are needed to reach firmer conclusions.

In relation to ω-3 PUFA supplementation, 4 studies cover the relationship between ω-3 PUFA supplementation and NAFLD and 1 study covers the relationship between DHA supplementation and NAFLD. *Table 2* shows in more detail the characteristics and results found in each study based on the clinical criteria of the disease. Three of these studies show that supplementation with ω-3 PUFA improves disease parameters,

especially hepatic fat content, with the exception of the trial by Sangouni et al., 2021 (38)in which no significant effects on any parameter were seen.

Table 2

Summary of the characteristics and results of the studies included in the discussion addressing the relationship between ω-3 PUFA and NASH (38,41,42,45,46).

Author, year (Ref.)	Type of study	Sample size	Features	Results
Scorletti et al., 2014 (46)	WELCOME randomized, double-blind, placebo-controlled trial	n = 103 adults with histologically confirmed NASH or imaging evidence of clinical features	Age >18 years old Duration= 15-18 months Omacor (DHA 380mg+EPA 460mg)= 4 g/day Placebo (olive oil)= 4g/day	Treatment with DHA+EPA: - Enrichment of DHA in erythrocytes - ↓ of mean % liver fat in patients with NASH.
Hodson et al., 2017 (42)	Pilot study, pre-specified substudy of the randomized, double-blind, placebo-controlled WELCOME trial	n = 24 adults with NASH (from the WELCOME study)	Age >18 years old Duration = 15-18 months Omacor (DHA 380mg+EPA 460mg) = 4g/day Placebo (olive oil)= 4g/day	Individuals who achieved a change in erythrocyte DHA enrichment of ⩾2 %: - Favorable changes in hepatic fatty acid metabolism and insulin sensitivity - ↓ hepatic fat content.
Capanni et al., 2006 (45)	Pilot study with ω-3 PUFA and placebo, for a future double-blind randomized controlled trial	n = 56 adults with NASH	Age 32-77 years Duration = 12 months PUFA ω-3 (EPA0,9/DHA1, 5)= 1g/day Placebo = control patients without therapy	- ↓ Serum TG and ALT level - Improved ultrasonographic characteristics (↑ Doppler perfusion index (DPI), ratio of hepatic artery blood flow to total liver blood flow) - Improved hepatic blood flow by ↓ intrahepatic fat accumulation.
Sangouni et al., 2021 (38)	Double-blind, randomized, placebo-controlled trial	n = 60 diabetic patients with NAFLD	Age 18-65 years old Duration = 12 weeks PUFA ω-3 (EPA360mg + DHA 240mg) = 200mg/day	Omega-3 supplementation (2000 mg/d) compared to placebo had no significant effect on cardiometabolic risk: plasma atherogenic index (AIP), Castelli I risk index, Castelli II risk index and atherogenic coefficient (AC).

			Placebo (liquid kerosene) = 200mg/day	
Pacifico et al.,2015 (41)	Double-blind, randomized, placebo-controlled trial	n = 58 children with NASH	Age <18 years old Duration = 6 months PUFA ω-3 (DHA) = 250mg/day Placebo (linoleic acid) = 290 mg	DHA supplementation: - Change in hepatic fat fraction estimated by MRI and visceral MRI. - Changes in visceral adipose tissue, epicardial adipose tissue, ALT, TG and insulin sensitivity. - Improving metabolic abnormalities in children with NASH

The double-blind, randomized, placebo-controlled clinical trial (43) shows evidence that supplementation with ω-3 PUFA, specifically DHA, was effective in reducing steatosis and liver fibrosis, thus the dose and duration of supplementation used were able to ameliorate the liver damage occurring in NASH patients.

Musa-Veloso et al (19) demonstrated according to the meta-analysis performed of several studies that supplementation with ω-3 PUFA resulted in statistically significant improvements in 6 of 13 metabolic risk factors, in the levels of 2 of 3 liver enzymes, in hepatic fat content and in the steatosis score. Although histological disease measures (fibrosis score, hepatocellular ballooning score, steatosis score, lobular inflammation score, and NAFLD activity score) assessed in NASH patients showed no improvement by ω-3 PUFA supplementation, this could be due to a low sample of patients in the study and a very low dose (0.345 g/d) of the supplement provided.

However, in the randomized controlled trial, a significant reduction in liver fat content was observed between the placebo group and the intervention group (40)however, in the randomized controlled trial, a significant reduction in liver fat content was observed between the placebo group and the intervention group, which masked any effect produced by ω-3 PUFA supplementation. Along the same lines Parker et al. (36) found that, using noninvasive techniques for the assessment of intrahepatic lipid concentration and composition, and a dose of ω-3 PUFA that had previously demonstrated reductions in hepatic fat, neither hepatic benefit nor a decrease in hepatic fat could be observed. We also found no effect of ω-3 PUFA supplementation on ALT levels, volume of subcutaneous or abdominal visceral adipose tissue compartments after supplementation. Further studies in which the level of HD is higher in participants are needed in order to observe more significant effects on liver-related outcomes.

Based on the current evidence, when comparing the performance of a DietMed with ω-3 PUFA supplementation for the disease studied, it can be seen that, in the case of DietMed there are a greater number of studies, trials and topical reviews in favor of its use that evidence improvements in the clinical characteristics of NASH. An inverse association can be seen between DietMed and SM; a reduction in weight, TGs, cholesterol, liver fat, visceral fat, liver inflammation, waist-to-hip ratio, BMI and HD index; normalization of some enzymes, including ALT; resolution of impaired fasting glucose. In addition, DietMed has been shown to be a protective factor against liver fibrosis and NASH. However, in the case of ω-3 PUFA, a smaller number of studies, trials and current reviews can be seen that evidence their use in the treatment of this pathology, likewise, the improvements found in the different clinical parameters are

lower. These are the following: reduction in hepatic fat, visceral fat and TG content; normalization of some enzymes, including ALT; improvement of blood flow by reducing hepatic fat, insulin sensitivity, improvement of metabolic risk factors and metabolic abnormalities in children. Therefore, concerning the benefits obtained from the performance of the DietMed versus PUFA ω-3 it can be determined that, in the case of the DietMed multiple improvements in the clinic of the disease have been demonstrated due to its different components, among them the high consumption of foods rich in PUFA ω-3, which would justify the better results of this diet, since it is one of the pillars of this dietary style. The ω-3 PUFA alone as supplements have benefits, although in some studies they are indistinguishable from placebo. At a general level, greater benefits are found with DietMed treatment than with ω-3 PUFA supplementation (11,15,19,27–29,31,32,36,38,40–46).

With respect to limitations, although some of the studies do not have any limitations, in most of them the number of samples in the population is very small and the study time is very short. In addition, some of them lack a control group or are not prospective in nature. It is important to note that each research group uses different markers to assess the progression or improvement of NASH in both the DietMed studies (SM, waist circumference, HDL, serum adiponectin levels, etc) and the ω-3 PUFA studies (hepatic fat content, serum TG level, Doppler perfusion index (DPI), etc), which makes it difficult to compare the results.

With a view to conducting future studies, the following recommendations are proposed: improving the design of future studies with ω-3 PUFA supplementation, extending the study time to a minimum term of 3 months and establishing a higher dose; further investigating the results of these interventions in NASH populations; and the development of future studies on treatment for NASH with a DietMed together with ω-3 PUFA supplementation.

Conclusions

Based on the current literature, we can conclude that in terms of the nutritional approach the best option as a treatment for this disease is the adoption of a DietMed. This diet is usually associated with a Mediterranean lifestyle, which includes physical activity. With this, in addition to obtaining multiple benefits on the clinical characteristics of NASH, especially at the level of the MS, weight loss is achieved, which is important in the treatment of this pathology by achieving an improvement in the liver, decreasing HD and slowing the progression of the disease by reducing inflammation, fibrosis and NASH. Within this diet, it should be noted that one of its fundamental pillars is the consumption of foods rich in PUFA ω-3, which provides better results on the clinic of the disease than with only the supplementation of these fatty acids, this is due to the sum of the benefits of the different components of the diet. Therefore, it would be interesting to conduct future studies in which a Mediterranean diet is evaluated together with omega-3 PUFA supplementation to see if supplementation with these fatty acids could enhance the positive effects of these fatty acids in synergy with those already demonstrated in the Mediterranean diet.

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