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A Review of the Effects of Omega-3 and Omega-6 on Alcoholic and Non-Alcoholic Fatty Liver

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is characterized by fat accumulation in the liver not caused by excessive alcohol consumption. In contrast, alcoholic liver disease (ALD) is directly caused by it. Excessive alcohol consumption causes inflammation and liver damage. Specific fatty acids (FAs) may be involved in this liver damage. Anti-inflammatory and blood lipid-lowering effects are the effects of omega-3 unsaturated fatty acids (n-3 PUFAs). NAFLD is the hepatic manifestation of metabolic syndrome because obesity and insulin resistance are the main pathogenic factors of both diseases. NAFLD is a disease associated with metabolic syndrome. Most patients with NAFLD are obese, although the disease can also affect non-obese people. Metabolic and genetic factors play an essential role in the occurrence of this disease. Oxidative stress, lipotoxicity, and inflammation play a key role in the development of NAFLD. There is a lot of evidence for the therapeutic potential of omega-3 polyunsaturated fatty acids (n-3 PUFA), mainly docosahexaenoic acid and eicosapentaenoic acid (EPA), in the treatment of metabolic diseases due to their antioxidant and anti-inflammatory properties. Therefore, in this review article, we examined the effects of omega-3 and omega-6 on alcoholic and non-alcoholic fatty liver disease.

Introduction

The organs of the body suffer from chronic diseases [1-3]. One of these organs is the liver .The largest visceral organ of the human body is the liver, which is the center of many physiological processes. The liver has dual blood supply; the celiac artery, which supplies oxygenated blood directly through the hepatic artery, and the portal vein, which brings nutrient-rich blood from visceral organs, such as the intestines, to the liver [1]. Consumption of simple sugars, inactivity, and obesity are among the underlying factors for a person to suffer from liver diseases, and excessive production of glucose and triglycerides by the liver are known as two key factors in the increase of fatty liver disease [2].

Non-alcoholic steatohepatitis (NAFLD) and alcoholic steatosis (ALD) are the two main categories of steatohepatitis [2,3]. NAFLD is recognized as an emerging health problem in Asia, which is associated with diseases such as diabetes, obesity, cardiovascular disease, and atherosclerosis. According to statistics presented in various studies, the prevalence of NAFLD is high in Asia (15 -20%) and is increasing over time. Far countries such as the Republic of China, Hong Kong, and Japan report a higher prevalence in the population than South Asian countries, including India and Sri Lanka. Among the reasons for the high prevalence of FLD in Asia can be mentioned:

1. Asians are more sensitive to non-communicable metabolic syndrome diseases (atherosclerosis, diabetes, and hepatic steatosis) than other races.
2. Alcohol consumption is higher among Asians

More than a quarter (27-34%) of the general American population has non-alcoholic fatty liver disease. Similar to Asia and North America, the prevalence of fatty liver disease is also very high in Europe. A quarter of Europeans suffer from this disorder, and its prevalence rates vary from 8% in Romania to 45% in Greece. Today, the prevalence of both alcoholic and non-alcoholic fatty liver disease is increasing. Both forms of the disease tend to cause cirrhosis and liver carcinoma [2].

When histological observations confirm more than 5% of liver cells containing lipid droplets, the person has NAFLD [4]. NAFLD is related to obesity, diabetes, and insulin resistance and is considered a hepatic manifestation of the metabolic syndrome [3,4]. This syndrome, by creating metabolic complications such as increased blood glucose, VLDLs, and CRP, has a negative effect on the patient's survival and causes type 2 diabetes, cardiovascular diseases, and advanced liver disease [5, 6]. Although obesity seems to be an essential factor in the creation of NAFLD disease, not all obese people are affected by this disease, and observations have confirmed that thin people are affected [6]. On the other hand, alcohol consumption can cause ALD. This disease is associated with the fat accumulation in the liver, causing complications such as weakness, anorexia, weight loss, abdominal discomfort, and jaundice, although sometimes it is asymptomatic. The International Classification of Diseases has classified ALD into different types of fatty liver, alcoholic hepatitis, liver fibrosis and sclerosis, alcoholic liver cirrhosis, and liver failure [7]. In case of conversion of alcoholic fatty liver disease to cirrhosis, the disease may remain silent for years, and it can be diagnosed only by imaging; also, Liver biopsy can help diagnose the disease in some instances. Imaging of alcoholic cirrhosis with symptoms such as nodular appearance of the liver and a higher volume index of the caudate lobe. In this case, cirrhosis may cause weakness, peripheral edema, jaundice, symptoms of gastrointestinal bleeding, or abdominal distension. Megaloblastic anemia is common in these patients. Steatosis is a characteristic of the tissue that is seen in all patients with NAFLD. This condition causes the accumulation of lipids in 5% of the hepatocytes. Vacuoles of hepatocytes can be seen in large and medium sizes using the light of a microscope and without the need for special techniques [8]. So far, no particular drug therapy has been discovered to treat this disease. Still, actions that reduce alcoholic fatty liver disease include: dietary modification, regular exercise, stopping alcohol consumption for more than 3 to 12 months, and drug treatments such as acamprosate, naltrexone, disulfiram, and baclofen. On the other hand, to improve non-alcoholic fatty liver disease, doing things such as reducing 3 to 5 percent of the initial weight, doing exercise and fitness, taking vitamin E for 4 to 96 weeks, Increasing the use of Rosiglitazone and Metformin to increase insulin sensitivity, Statins and Fibrates to treat hypertriglyceridemia, Long-Chain Polyunsaturated Fatty Acids such as omega-3 and omega-6, Pentoxifylline and Exenatide and finally surgery are recommended as suggested and not definitive treatments.

Progression of alcoholic fatty liver disease: Normal ↔ Increased risk ↔ Fatty liver ↔ NASH ↔ Fibrosis → Cirrhosis → Death

Deficiency of vitamin A, B_{12} and zinc is associated with alcoholic fatty liver, however, the data shows that increased intake of vitamin A can also be toxic to the liver and is a predisposing factor for alcoholic fatty liver, as well as excessive iron levels can cause an increase in mortality in people with alcoholic fatty liver Although there are data that suggest the effective role of some fatty acids in the therapy of hepatic steatosis and related metabolic disorders [5, 7]. Fatty acids omega-3 (a-linolenic acid) and omega-6 (linoleic acid)

are part of polyunsaturated fatty acids (PUFAs) and are essential, which are not made in the body of mammals and are obtained through diet. The most important biologically active fatty acids are Arachidonic acid from the Omega-6 family, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) from the Omega-3 family. Fish, seafood, and nuts have a high content of omega-3 fatty acids, whereas omega-6 fatty acids are found in animal foods and plant oils [9, 10]. Diets that have a very high content of omega-6 to omega-3 cause many diseases, including cardiovascular disease, inflammatory diseases, cancer, and autoimmunity. This is because enhancing the level of omega-3 to omega-6 has an inhibitory effect on the occurrence of many diseases [11-15]. Some fatty acids can affect inflammation through different mechanisms; they can change the signaling of inflammatory cells by affecting the fluidity of the cell membrane and the receptors inside the cell, and they can also control the gene expression patterns. Cells involved in the inflammatory response are usually rich in arachidonic acid, an omega-6 fatty acid, and eicosanoids derived from arachidonic acid are involved in inflammation. Meanwhile, EPA and DHA cause the production of resolvins, which have anti-inflammatory effects [16]. In general, there are data based on the decrease in EPA and DHA levels in patients with fatty liver disease compared to healthy people, such that the administration of omega-3 increases the amount of EPA and DHA in the blood and decreases omega-6. These changes cause positive effects, resulting in hepatic steatosis [4, 17]. In Table 1, you can see the mechanism of action and how these two fatty acids affect the human body.

Methods

Literature Search and Selection Criteria

In this review study, Embase, Magiran, SID, Web of Science, Scopus, PubMed, and Google Scholar databases were searched using the keywords "Omega-3; Omega-6, alcoholic and non-alcoholic fatty liver". For each Case, selected published clinical trials and review articles were used. Inclusion criteria included articles related to keywords, and exclusion criteria included articles with only abstracts and articles in languages other than English.

Discussion

Effective factors in the occurrence of fatty liver disease

Owing to the high outbreak of this disease, it is necessary to know the factors affecting the development of this disease. These factors include: non-modifiable risk parameters, for example: sex, age, ethnicity, some genes, and modifiable risk factors include: obesity, low physical activity, and daily diet, which affect the process of people getting NAFLD [19]. In general, 90% of people with non-alcoholic fatty liver disease are obese or overweight. Two studies aimed at the effect of age on this disease were conducted. The results of these studies showed that the average age of people with non-alcoholic fatty liver disease in America and Europe is between 40 and 50 years [20, 21]. In general, being male, being younger (less than 50 years old), and being Hispanic increase the risk of NAFLD in the United States [22]. In Europe, similar risk factors for type 2 diabetes, obesity, hypertension, and dyslipidemia increase the risk of NAFLD. In Asia, NAFLD begins to increase after the age of 30, and this rate is reported to be higher in men than in women, although the rate of infection in women after menopause is not different from that of men [8].

Agent	The effect	Mechanisms of action
Omega-3 and Omega-6	After being converted into arachidonic acid, Eicosapentaenoic acid and Docosahexaenoic acid contribute to the production of hormones such as prostaglandins, prostacyclins, thromboxanes, or leukotrienes, and then cause decreasing blood cholesterol levels, risk of arthritis, cardiovascular disease, and neurodegenerative diseases, and help the proliferation of lymphocytes. Suppression of inflammatory cytokines and their phagocytosis, as well as controlling the activity of the body's immune system, are among its other functions [18]	-remarkable decrease in plasma levels of TG and TC -Significant increase in HDL -improve the BMI [16]

Table 1: The effects and mechanisms of fatty acids on the human body system

Several studies have stated that lifestyle changes, diet, quality and quantity of exercise, and various drug treatments may have affected fatty liver disease [17, 23, 24]. Fatty liver disease can lead to cirrhosis and liver carcinoma, so lifestyle changes such as daily exercise and proper diet can be an effective step in preventing this process [25]. There are no current FDA-approved therapies for this disease. Still, the use of traditional therapies, including pioglitazone and vitamin E, has been significant for inflammation and steatosis, but has no effect on fibrosis, which is the strongest predictor of mortality in this disease [26]. The incidence rate of hepatic steatosis has increased due to the increase in obesity in societies [27]. On the other hand, the findings show a significant correlation between the decrease in liver fat and weight reduction [28]. In obese patients with NAFLD who do not respond to weight reduction, bariatric surgery can be suggested as a suitable therapeutic solution because it can significantly improve steatosis, inflammation, and fibrosis [29-32]. Many studies emphasized the effects

related to the consumption of omega-3 fatty acids on liver metabolism and reducing its inflammation [33-36]. The obtained evidence indicates that omega-3 supplements have an effective role in decreasing TG and LDL levels, improving disease and obesity in NAFLD patients [37 ,17]. Jump *et al*. (2016 also stated the possible role of DHA in avoiding NASH and decreasing the risk of hepatocellular carcinoma [38]. In addition to improving liver function in patients with NAFLD, omega-3 unsaturated fatty acids (PUFA) reduce cardiovascular diseases [39]. Lytle *et al*. (2017 described that DHA supplementation did not affect body weight or blood glucose levels. They also stated that this supplement has the effect of stopping the process of hepatic steatosis, inflammation, fibrosis, or liver damage [40]. Oscarsson *et al*. (2018 stated that omega-3 consumption reduces the amount of serum triglyceride levels but did not significantly reduce the content of liver fat in NAFLD patients without diabetes and hypertriglyceridemia [41]. Masterton *et al*. (2010 admitted that omega-3 fatty acids, in addition to reducing inflammatory markers, cause a decrease in hepatic steatosis and improve insulin sensitivity in patients [42]. The levels of omega-3 fatty acids in the blood serum of patients with type 2 diabetes (T2DM) and non-alcoholic fatty liver disease (NAFLD) are lower than those of healthy people. Feeding these people with omega-3 supplements for 12 weeks showed a significant decrease in serum TG levels [43]. Some studies claimed no support for PUFA supplements in improving the symptoms of diabetics [44]. The process of oxidative stress in combination with inflammation has a significant effect on the progression of NAFLD to NASH among elderly people. Therefore, antioxidant, immuno-modulatory, and anti-inflammatory characteristics of omega-3 polyunsaturated fatty acids make this supplementation an effective option for reducing liver fat in elderly invalids with NAFLD, but the efficacy of this supplement in reducing liver fibrosis is still unclear [45]. In addition to these, other studies also showed the role of omega-3 supplementation in treating hepatic steatosis and improving liver function in children with NAFLD [46, 47]. Shpiro *et al*. (2011 supported the role of omega-3 supplements in improving NAFLD/NASH patients and recommended histopathology evaluation before and after treatment with this supplement, and also stated that two meals a week of oily fish are suitable for these patients [48]. Musa-Veloso *et al*. (2018 stated that omega-3 fatty acids showed their effectiveness in improving the performance of people with NAFLD, but histological characteristics of people with NASH did not improve after taking omega-3; therefore, more trials are needed to better discover the impacts of omega-3 fatty acids on patients with NASH [49]. The study of animal models showed the improving effect of omega-3 fatty acid supplementation in reducing hepatic steatosis in mice [27]. de Castro *et al*. (2018 confirmed reduction of inflammatory markers in NAFLD due to the consumption of n-3 PUFAs and admitted that in cases where we see the ineffectiveness of these supplements, the reason can be sensitivity of the methods used, the short duration of use, patient-specific factors, and poor compliance [50]. Several studies, while confirming the effective effects of omega-3 supplements, stated that the optimal dose of this supplement to produce the desired effects is currently not known [45, 51, 52]. Therefore, it is recommended to conduct clinical trials with a specific duration and a specific endpoint in order to investigate the long-term impacts of these supplements [53, 54]. On the other hand, Cansancao et al. (2020, while confirming the role of DHA supplementation in reducing liver fibrosis, recommended the appropriate dose and duration for the treatment of NAFLD patients, although they emphasized that more experiments are needed to confirm these findings [55]. Sangouni *et al*. (2021 showed that treating patients with omega-3 supplements for 12 weeks improves fatty liver index, visceral obesity index, and lipid accumulation product [56]. Chronic and non-chronic, infectious and non-infectious diseases, such as fatty liver, cancers, etc., are serious health problems and cause pain and suffering to the patient, and finding a treatment solution for them seems essential [57-64]. Chronic diseases are prevalent [65-67]. Today, the desire to use medicinal plants and therapeutic agents in the treatment of diseases has increased because they are rich in secondary medicinal substances and antioxidants, and improve diseases [68-73]. Jump *et al*., 2018 confirmed the effective role of omega-3 in improving liver inflammation, but pointed out several limitations in the way of evaluating the effects of fatty acids on improving the process of liver activity, these limitations include: 1) The low number of participants in clinical trials, 2) Failure to prove the effect of omega-3 fatty acids in increasing the levels of EPA or DHA or reducing the amount of TAG in the blood, 3) Slow healing process of fibrosis compared to hepatic steatosis and 4) Successful reconversion of DHA to its derivatives in tissues and the opposite point, reconverting EPA to derivatives that have the inability to reduce inflammatory markers in fatty liver disease [52].

Conclusion

Epidemiological studies show that metabolic syndrome is a significant concern in public health issues. By examining the studies conducted in the field of metabolic syndrome and fatty liver in this review

article, the close relationship between fatty liver and metabolic syndrome, as well as the undeniable role of nutrition and diet in their prevention and pathogenesis, was shown. Finally, it seems that the reduction of omega-3 and omega-6 intake from food sources due to their association with incorrect eating habits can be the main reasons for the multifactorial nature of this disease. Also, taking the supplement can be helpful in these patients along with modifying the food pattern and lifestyle.

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Conflict of interest

The authors declare no conflict of interest.

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