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Editorial OMICS International

Omega-3 Polyunsaturated Fatty Acids in the Treatment of Non-Alcoholic Fatty Liver Disease: Are They So Good?

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Editorial

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent hepatic problem in Western and Asian countries where it can affect more than 30% of people [1]. NAFLD pathological characteristic is a fat infiltration of the hepatocytes (hepatic steatosis) in subjects who are mild or no alcohol drinkers and do not have other secondary causes of hepatic lipid accumulation. In one fifth of affected patients, NAFLD can evolve in a liver inflammatory damage, which is associated with oxidative stress, cytolysis, and fibrosis (steatohepatitis) [2]. Of these patients, more than one-third progress to liver cirrhosis and a small part can develop hepatocarcinoma along years. It's not clear why some patients with NAFLD evolve to non-alcoholic steatohepatitis (NASH) while others remain stable over years, though a role of intestinal inflammation, gut dysbiosis, and hypovitaminosis D has been recently proposed [3]. Consistently, subjects at high risk to develop NAFLD are those affected by obesity, type 2 diabetes mellitus, and other conditions associated with insulin resistance or hyperinsulinemia such as hypertension, dyslipidemia, polycystic ovary disease, and metabolic syndrome, as well as patients with chronic inflammatory bowel diseases [4]. Patients with NAFLD are characterized by increased circulatory levels of triglycerides and free fatty acids (FFAs) that come from the adipose tissue through the lipolytic process, from the hepatic lipid de-novo synthesis, and to a minor extent from food intake. Both insulin resistance and hyperinsulinemia in predisposed subjects are associated with a visceral fat distribution and are responsible for the high level of circulatory FFAs [5]. FFAs enter and accumulate in insulin-resistant hepatocytes and by esterification with glycerol increase hepatic triglycerides synthesis and very low-density lipoproteins (VLDL) production; thus, favoring hypertriglyceridemia. The overflow of plasma lipids and lipid metabolites in non-adipose tissues induces "lipotoxicity", a pathological process characterized by lipids accumulation in liver and in other organs such as heart, kidney, pancreas, and skeletal muscle [6]. This process is responsible for the development and progression of heart and kidney failure, obesity, and diabetes, as well as for the systemic release of inflammatory cytokines. System cytokines maintain chronic subclinical inflammation, induce oxidative stress and endothelial dysfunction, and predispose to the atherosclerotic process [7]. Although NAFLD has been considered as the hepatic manifestation of the metabolic syndrome, evidence has shown that NAFLD is associated with cardiovascular morbidity and mortality independently of metabolic syndrome. Therefore, other than pro-cirrhotic, NAFLD had to be considered an important modifiable risk factor for cardiovascular diseases [8].

As a result of the high clinical impact of NAFLD in the general population, treatment of NAFLD is essential. However, despite promising studies have been conducted with several agents, so far no strong evidence supports a specific pharmacological treatment. Weight loss is the first efficacious non-pharmacological intervention that should be applied to all patients with NAFLD and avoid even mild alcohol consumption in these patients could be a good rule of reason, as well. Hypocaloric diet and regular physical activity in overweight and obese patients should induce at least 7 to 10% of weight reduction to exert their beneficial effect on liver steatosis and steatohepatitis. Consistently, bariatric surgery has shown to be highly efficacious in severe obese patients with NAFLD/NASH [9]. Thiazolidinediones (pioglitazone) and antioxidant (especially vitamin E) are those pharmacological treatments that are more frequently used. However, positive effects of the insulin-sensitizer pioglitazone are counterbalanced by a significant weight gain and results with antioxidants are discordant mostly because they have been used in different formulations and dosages or associated with different lifestyle modifications. Other pharmacological treatments may include the angiotensin-II receptor blocker telmisartan, L-carnitine, and the promising omega-3 polyunsaturated fatty acids (PUFA) [10].

Omega-3 PUFA has been studied in patients with NAFLD/NASH because of their potential hypotriglyceridemic, insulin-sensitizer, and anti-inflammatory effects [11]. Observational studied have shown that patients with NAFLD have low plasma levels of omega-3 respect to omega-6 PUFA and other studies founded an association between NAFLD and high consumption of saturated fatty acids respect to omega-3 PUFA. Several preliminary studies on the effect of omega-3 PUFA intake on different aspects of NAFLD/NASH (biomarkers of hepatic damage, liver fat accumulation, and liver fibrosis) have been published with some promising results. Hodson et al. [12] showed that a significant cell enrichment of docosahexaenoic acid after omega-3 PUFA supplementation in patients with NAFLD improved hepatic insulin sensitivity, reduced fasting and post-prandial plasma triglycerides levels and fasting hepatic de-novo lipogenesis, and improved lipid beta-oxidation [12]. Most importantly, omega-3 PUFA treatment can reduce radiological and histological findings of liver steatosis and fibrosis in non-cirrhotic patients [13]. Additionally, omega-3 PUFA intake is inversely related with the risk of hepatocarcinoma [14] and these fatty acids can be beneficial in cardiovascular disease prevention, conditions frequently associated with NAFLD/NASH morbidity and mortality [15]. Very recently, He et al. [16] published an updated meta-analysis of seven randomized controlled trials (RCT) on the effectiveness of omega-3 PUFA in patients with NAFLD/NASH. This study included 442 non-diabetic patients in which omega-3 PUFA significantly improved lipid profile (reduced triglycerides and total cholesterol and increased HDL-cholesterol) and reduced plasma alanine aminotransferase levels, but with unclear effects on signs of liver steatosis and fibrosis and with a significant heterogeneity between studies [16]. Similar findings were showed also in a meta-analysis of 4 RCT that included 263 children and adolescents with NAFLD. Results of this meta-analysis

demonstrated that omega-3 PUFA supplementation reduce the hepatic steatosis grade on ultrasound and liver enzymes plasma levels after at least 1 year of treatment [17]. However, in these patients the treatment does not reduce inflammatory markers and do not modify any metabolic syndrome components.

These results, although encourage the use of omega-3 PUFA for NAFLD prevention, remain too weak to support their routinely use in clinical practice. In some trials of patients with NASH, omega-3 PUFA intake fails to be effective on signs of liver fibrosis. Additionally, some controversies on the use of omega-3 PUFA in metabolic patients could limit their usefulness in the treatment of NAFLD/NASH. In the recent trial of Dasarathy et al. [18] on diabetic patients with NASH, omega-3 PUFA treatment did not show any beneficial effect on histological findings of liver steatohepatitis but, most importantly, the treatment impaired glucose tolerance and insulin sensitivity respect to placebo [18]. Concernedly, similar findings were noted in overweight men in which omega-3 PUFA from krill oil worsened insulin sensitivity [19], and in a stratified analysis of cohort studies where consumption of omega-3 PUFA rich fish/seafood in Caucasian populations were associated with a 38% higher (95% C.I. 13-70%) relative risk to develop a type 2 diabetes [20]. A predisposition to develop type 2 diabetes after omega-3 PUFA intake in Americans but not in Asians was also supported by a meta-analysis of 16 observational studies involving about 700,000 participants [21]. Additionally, results of some experimental studies have raised alarms about the use of omega-3 PUFA in NASH and other hepatic diseases. In a mouse model of steatohepatitis, the effective incorporation of omega-3 PUFA in hepatocytes induced a more severe necro-inflammation and fibrosis of the liver respect to olive oil treatment [22] and a similar pro-fibrotic effect of omega-3 PUFA were demonstrated in mice treated with carbon tetrachloride [23] and in a rat model of biliary atresia [24].

Under the light of these results, the use of omega-3 PUFA in the treatment of NAFLD/NASH is still far from getting an evidence based indication and further well conducted large RCT with histological demonstration of a benefit from omega-3 intake should be performed. Omega-3 PUFA, seem to be effective for reducing liver fat probably for their hypotriglyceridemic effects and they might be useful in early stages of NAFLD. However, doubts persist on their diabetogenic and pro-fibrotic risk in NASH patients. Important questions regarding which source, type, and dose of omega-3 PUFA, how long to treat patients, and which population will benefit more from omega-PUFA intake need to be answered. Fortunately, several ongoing clinical trials with some of these answers will be published soon or in the next few years. Moreover, new encouraging experimental drugs such as the farnesoid X receptor agonist obeticholic acid and the peroxisome proliferator-activated receptors alpha/delta agent elafibranor could became available as specific or combination treatments for patients with NAFLD/NASH, thus increasing the pharmacological armamentarium to treat this widespread disease [25].

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