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REVIEWS: CURRENT TOPICS

Nutritional therapy for nonalcoholic fatty liver disease

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Abstract

Following the epidemics of obesity, nonalcoholic fatty liver disease (NAFLD) has become the leading cause of liver disease in western countries. NAFLD is the hepatic manifestation of metabolic syndrome and may progress to cirrhosis and hepatocellular carcinoma. To date, there are no approved drugs for the treatment of NAFLD, and the main clinical recommendation is lifestyle modification, including increase of physical activity and the adoption of a healthy eating behavior. In this regard, studies aimed to elucidate the effect of dietary interventions and the mechanisms of action of specific food bioactives are urgently needed.

The present review tries to summarize the most recent data evidencing the effects of nutrients and dietary bioactive compounds intake (*i.e.*, long-chain PUFA, Vitamin E, Vitamin D, minerals and polyphenols) on the modulation of molecular mechanisms leading to fat accumulation, oxidative stress, inflammation and liver fibrosis in NAFLD patients.

Keywords: Nonalcoholic fatty liver disease (NAFLD); Food bioactives; Molecular mechanisms; *In vitro* studies; Animal models; Clinical trials

1. Introduction

Nonalcoholic fatty liver disease (NAFLD), also known as *hepatic steatosis*, is defined by liver fat deposition in the absence of excessive alcohol intake [1]. Following the epidemics of obesity, NAFLD has become the leading cause of liver disease (prevalence, 20–34%) [2,3], and it is epidemiologically associated with the metabolic syndrome and insulin resistance (IR) [4–6]. NAFLD is an umbrella term used to described a histological spectrum ranging from simple steatosis, defined by a concentration of hepatic triglycerides (TGs) exceeding 5% of liver weight, to nonalcoholic steatohepatitis (NASH) characterized by hepatocellular damage, lobular necroinflammation and fibrogenesis [7,8]. NASH may evolve to cirrhosis and then to end-stage liver failure or hepatocellular carcinoma [9,10]. Genetic variants play a major role in disease predisposition [11] by interacting with nutritional and other environmental factors, typically hypercaloric diet and lack of physical activity. To date, there are no approved drugs for the treatment of NAFLD, and the main clinical recommendation as an initial step is lifestyle modification.

Systematic reviews on the role of specific nutrients and phytochemicals on NAFLD and related outcomes have recently been published [12,13]. In this review, we will specifically focus on the mechanism by which selected macro-/micronutrients and food bioactives exert a beneficial effect on the hepatic outcomes of NAFLD.

2. Pathophysiology of NAFLD

Fatty liver results from an unbalance between TG accumulation and removal and represents the safest way to store free fatty acids (FFAs) in the liver [6,14]. Excess hepatocellular TG derives from several sources including dietary fatty acids, increased peripheral lipolysis due to adipose tissue IR and elevated hepatic *de novo lipogenesis* due to hyperinsulinemia. Indeed, the major determinant of NAFLD is systemic IR [4,15]. Reduction of lipid secretion through very low-density lipoproteins (VLDL) and a decreased fatty acids oxidation are also involved in hepatic fat accumulation [5].

The development of NASH has been explained by the occurrence of multiple so-called "second-hits" leading to the activation of inflammation in the context of hepatic steatosis [16,17]. The initial hit leading to the development of fatty liver renders hepatocytes susceptible to other multiple hepatotoxic insults including (a) peroxidation; (b) oxidative stress secondary to free radicals produced during β- and omega-oxidation of FFAs; (c) inflammation triggered by endotoxin engaging Toll-like receptor-4 in Kupffer cells (KCs) and hepatocytes due to increased intestinal permeability; (d) qualitative and quantitative changes in gut microbiota [18,19]; (e) hepatic stellate cells (HSCs) activation; and (f) mitochondrial dysfunction. All these conditions lead in the end to inflammation, cellular damage and activation of fibrogenesis [20].

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3. NAFLD management

The usual management of NAFLD includes lifestyle counseling to achieve a gradual weight reduction and an increase in physical activity. Patients are encouraged to lose ≥8% of their body weight. An intensive lifestyle intervention focused on diet, exercise and behavior modification with a goal of 7–10% weight reduction that leads to significant improvement in liver histology in patients with NASH [21]. Indeed, weight loss improves steatosis [22], reduces hepatic inflammation and hepatocellular injury [21,23] and improves cardiovascular risk profile. However, weight loss through energy restriction is difficult to achieve and sustain [24]. Physical activity and exercise also effectively decrease steatosis. Cross-sectional and prospective studies have shown that physical activity decreases intrahepatic lipids [25,26]. Both aerobic and resistant exercises have been shown to improve liver function, independently of weight loss [27–29].

In addition to total energy intake, the composition of the diet also affects the metabolic and endocrine functions and overall energy balance [30]. Most recommendations encourage the consumption of diets rich in fruits and vegetables for prevention of chronic disease, and NAFLD is not an exception. Such diets would provide significant amount of bioactive components with known beneficial effects due in part to their antiinflammatory properties [31].

General recommendations include a reduction in the intakes of total fat, saturated fatty acids, trans fatty acids and fructose. Indeed, high fructose intake has been associated with increased risk of NAFLD and liver damage [32–34]. Dietary fructose (consumed in the form of soft drinks) has been implicated in the pathogenesis of NAFLD [35]. Mice with *ad libitum* access to fructose solution showed significantly higher levels of hepatic lipid accumulation, lipid peroxidation and endotoxin levels in the portal blood compared to controls and mice fed with glucose solution [36].

Conversely, an increase in the intakes of polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids is advised. Moreover, there is recommendation to include long-chain n-3 fatty acids to reduce the risk of NAFLD.

A few trials were conducted to evaluate the impact of specific dietary patterns on liver damage in patients with NAFLD. In this regard, Mediterranean diet led to similar weight loss but induced a more marked reduction of liver enzymes and of IR compared to a low-fat high carbohydrate diet [30]. Indeed, the diet of patients with NASH is usually enriched in saturated fat and cholesterol, whereas it is poor in polyunsaturated fat, fibers and antioxidant vitamins C and E [31]. In addition to an imbalance in fat intake, higher odds of inflammation were associated with higher carbohydrate intake in NASH patients [37].

Apart from lifestyle modification, statins (lipid-lowering drugs), glitazones (insulin sensitizers), antioxidants and metformin have been used as therapies for NAFLD [38,39]. Glitazones improve steatosis at the expense of an increase of weight, and the long-term safety of their utilization is still not clear. Randomized clinical trials with antioxidants (Vitamin E and N-acetylcysteine) have given conflicting results, suggesting that their effect may be different depending on age, dosage and lifestyle modifications [39]. A few studies have tested metformin in nondiabetic patients but with inconsistent results [40,41].

All these findings emphasize the difficulties to achieve success in NAFLD clinical setting and attract attention to the importance of alternative approaches for the prevention of liver damage progression in NAFLD.

4. Promising food bioactives

In this review, we will focus our attention on the most promising bioactive compounds studied in the last years for their possible beneficial effects on the prevention and treatment of NAFLD. We have selected the compounds that have been most investigated in *in vitro* and *in vivo* studies, especially if there is accompanying evidence of efficacy clinical trials. Evaluated bioactives and their putative mechanisms of action are listed in Table 1. In the following paragraphs, we will review the most important evidence supporting their activity and discuss the evidence supporting the mechanisms of their beneficial effects.

4.1. Omega-3 PUFAs

Long-chain omega-3 (n-3) fatty acids have been proposed as potential treatment for NAFLD. These fatty acids are present in large quantities in fish oil, flaxseed and some nuts. They can be synthesized *in vivo* by the human body from α-linolenic acid and mainly occur as eicosapentaenoic acid (EPA) and decosahexaenoic acid (DHA), which are both antiinflammatory. Omega-3 PUFA supplementation ameliorates hepatic steatosis in animal models and in human studies [42,43].

Clinical trials, investigating the therapeutic effect of omega-3 in patients with NAFLD suggested beneficial effects on hepatic fat accumulation, liver function tests, fasting blood glucose and serum TGs [44–46]. A randomized, double-blind, placebo-controlled trial of DHA, EPA or DHA + EPA supplementation has shown that EPA enrichment in the peripheral blood is linearly associated with decreased liver fat percentage in patients with NAFLD [47]. Two controlled clinical trials performed in NAFLD children also demonstrated that omega-3 supplementation for 6–24 months reduced hepatic steatosis, IR, circulating TG and ALT levels [48,49]. Moreover, a recent meta-analysis confirmed the beneficial effect of omega-3 on steatosis [50]. Conversely, evidence about necroinflammation and fibrosis progression in NASH after omega-3 supplementation is still lacking [51]. However, clinical studies are ongoing, and there is a strong mechanistic rationale for supporting such an effect. Indeed, DHA specifically binds with high affinity to the G protein-coupled receptor 120 (GPR120) that mediates potent insulin-sensitizing effects *in vivo* by repressing macrophage-induced tissue inflammation [52]. In pediatric NAFLD, DHA treatment reduced liver damage, the number of inflammatory macrophages and increased GPR120 expression in hepatocytes. Modulation of GPR120 plays a key role in the regulation of the cell-to-cell cross-talk that drives inflammatory response, hepatic progenitor cell activation and hepatocyte survival [53,54].

In HepG2 hepatoma cells, the expression of fatty acid synthase (FAS) and sterol regulatory element binding protein 1c involved in *de novo* lipogenesis was suppressed by DHA or EPA supplementation [55]. Moreover, PUFA supplementation modulated the antioxidant defense increasing SOD, GST and GPX activity [56].

In high-fat diet (HFD) fed mice, dietary intake of EPA reduced steatosis by reducing hepatic cholesterol, TG and FFAs [57]. Moreover, EPA intake seems to abrogate HFD-induced modulation in genes involved in hepatocellular lipid metabolism. These include up-regulation of Srebp-1c, which induces the lipogenic program, FAS and acyl-coenzymeA-carboxylase-1 and the decrease of expression of carnitinepalmitoyltransferase (CPT1), which transports FFAs to the mitochondria and promotes β-oxidation [58]. Several studies have demonstrated that EPA decreases steatosis and fibrosis progression by reducing TG synthesis and the expression of fibrogenic genes, and indeed, it represents an established treatment for hypertriglyceridemia [59,60]. EPA supplementation is associated with decreased hepatic ROS production and activation of AMP-activated protein kinase (AMPK) and Peroxisome-proliferator activated receptor-α (PPARα), which stimulates lipid catabolism. In mice fed with HFD and steatogenic choline-deficient diets, DHA supplementation reduced hepatic steatosis, inflammation, fibrosis and lipid peroxidation [61,62]. Increased activity of superoxide dismutase (SOD) and down-regulation of Srebp-1c seem to account for the inhibitory effect of DHA.