World Journal of Hepatology

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DOI: 10.4254/wjh.v7.i24.2522

World J Hepatol 2015 October 28; 7(24): 2522-2534
ISSN 1948-5182 (online)

REVIEW

Dietary approach in the treatment of nonalcoholic fatty liver disease

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Supported by The Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG).

Conflict-of-interest statement: None of the authors have any potential financial conflict of interest related to this paper.

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Received: April 20, 2015
Peer-review started: April 21, 2015
First decision: August 10, 2015
Revised: September 2, 2015
Accepted: October 1, 2015
Article in press: October 8, 2015
Published online: October 28, 2015

Abstract

Nonalcoholic fatty liver disease (NAFLD) has been identified as one of the most prevalent chronic liver disease in adults and children populations. NAFLD is usually associated with the metabolic syndrome (MS), which is chiefly related to insulin resistance and its consequences. Insulin resistance has a crucial role in the pathogenesis of hepatic steatosis and potentially nonalcoholic steatohepatitis (NASH). Because of the contemporary epidemics of MS and obesity, the burden of NAFLD is also expected to rise. Unhealthy diets, such as the so-called western diet, are enriched in fructose, trans-fatty acids and saturated fat and seem to be associated with the development of NAFLD. In human studies, certain dietary sugars, particularly fructose, are used as a substrate for lipogenesis leading to hepatic fatty infiltration, inflammation, and possibly fibrosis. Other investigations have shown that fat consumption especially cholesterol and trans/saturated fatty acids are also steatogenic and seem to increase visceral adiposity. The identification of specific dietary components that favor the development of NASH could be important for the management of this disorder. This review focuses on the effects of different dietary approaches to prevent and treat NAFLD emphasizing the macronutrients and energy composition.

Key words: Fatty liver; Dietary carbohydrates; Dietary

fats; Dietary fructose; Energy intake

Core tip: Nonalcoholic fatty liver disease (NAFLD) has been identified as one of the most prevalent chronic liver disease. Its pathogenesis is not fully elucidated, and until now there is no effective treatment for this condition. Evidence supports that dietary pattern may be related to the development of NAFLD. Furthermore, dietary intervention could be beneficial in NAFLD treatment. However, there is no consensus regarding the best dietary intervention to treat NAFLD. In this context, we conducted a systematic review about recent advances in the effects of different diets in the development of NAFLD in humans, and also in the dietary treatment approach of this disorder.

Ferolla SM, Silva LC, Ferrari MLA, da Cunha AS, Martins FS, Couto CA, Ferrari TCA. Dietary approach in the treatment of nonalcoholic fatty liver disease. *World J Hepatol* 2015; 7(24): 2522-2534 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i24/2522.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i24.2522

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has been considered the most common chronic liver disease in the Western World[1]. NAFLD defines a spectrum of liver diseases that can progress from steatosis (nonalcoholic fat liver) to nonalcoholic steatohepatitis (NASH), hepatic fibrosis/cirrhosis, and also to hepatocellular carcinoma[2]. The prevalence of NAFLD is growing fast because of the increasing prevalence of obesity and diabetes[1,2]. It is expected, by this year, 2015, that the number of overweight subjects exceeds 2.3 billion. More than 20%, 60% and 90% of the Western population, diabetic individuals, and morbidly obese patients, respectively, will present steatosis. Furthermore, up to 15% of the Western population, 25%-30% of subjects with either obesity or type-2 diabetes mellitus, and over 35% of the severely obese individuals will develop NASH[2].

NAFLD is strongly associated with insulin resistance (IR), visceral obesity, and dyslipidemia; therefore, it was early recognized as the hepatic manifestation of the metabolic syndrome (MS). Currently, NAFLD is considered a multifactorial condition that causes a rise in the rate of complications and death due to liver disorders, and increases the chances of becoming type-2 diabetic and developing cardiovascular diseases[3].

The pathophysiology of NAFLD is complex involving mechanisms not completely understood. However, based on the theory proposed by Day, in 2002, which is widely accepted, IR is crucial element in initiating lipid accumulation in the liver and, possibly, NASH[4]. Several metabolic pathways are involved in the development of NAFLD such as high flux of free fatty acids (FFA) from adipose tissue to the liver due to increased lipolysis in visceral and subcutaneous adipose tissue; enhanced FFA supply to the liver as a consequence of a high-fat diet (HFD); the impairment of the β-oxidation of FFA in the liver; high hepatic *de novo* lipogenesis (DNL); and diminished export of FFA from the liver due to reduced synthesis or secretion of very low density lipoprotein (VLDL)[5-7].

In this context, it seems that the dietary composition is related to NAFLD pathogenesis since it can influence IR, FFA cell influx, DNL, and oxidative stress in the liver[8,9]. Furthermore, the NAFLD/NASH patients seem to have a dietary pattern characterized by a higher consumption of saturated fats (SF) and cholesterol, and lower ingestion of polyunsaturated fats (PUFA), fibers and antioxidants (vitamin C and E)[10,11]. Fructose consumption is likely to be more elevated in subjects with NAFLD than in control patients without NAFLD[12-14]. In subjects with NAFLD, the consumption of fructose per day was associated with more extensive fibrosis[15].

Non-pharmacological interventions are the first clinical approaches aiming at correcting unhealthy life-style, treat the clinical manifestations of the MS, and therefore, are an effective therapeutic option for patients with NAFLD[16]. Lifestyle changes include acquiring healthy dietary pattern, increasing physical exercise and losing weight[1,16]. Although weight loss is recommended in NAFLD treatment, certain diets such as very low-carbohydrate diet (VLCD) or HFD in spite of causing weight loss, can induce IR and, thus, may cause or exacerbate the hepatic disorder. Indeed, modifications of the macronutrient composition of the diet, such as reducing fat or carbohydrate intake, can improve NAFLD without any changes in body weight[8].

This comprehensive review aims to analyze the available clinical trials that evaluated different dietary approaches in NAFLD treatment, and their relationship with intra hepatocellular lipids, hepatic DNL and serum levels of liver enzymes. We also discuss the chief aspects on the role of diet in NAFLD development.

RESEARCH

The systematic review was conducted in the PubMed database using the following terms: "Fatty Liver" AND "Dietary Carbohydrates" OR "Dietary Fats" OR "Diet, Fat-Restricted" OR "Dietary Sucrose" OR "Diet, Mediterranean" OR "Energy Intake" OR "Ketogenic Diet" OR "Diet, High-Fat" OR "Diet, Carbohydrate-Restricted" OR "Feeding" OR "Hyperphagia" OR "Food Consumption" OR "Eating" OR "Food Composition" OR "Portion Size" OR "Food" AND "non-alcoholic".

From the 1422 articles initially selected, the publication date 2004-2015; the English, Portuguese and Spanish languages; and adult age (adult, mild aged and

elderly) were added as filters. The search brought up 147 articles; then, we selected the clinical trials. From the 48 clinical trials, we selected those that evaluated dietary intervention as the unique NAFLD treatment, excluding the studies in which the diet was associated with physical exercises, drugs, herbal medicines, supplements as probiotics, multivitamins or whey protein. The only supplements that we included in the review were n-3 PUFA and fibers. Twenty-five clinical trials were considered for the present review. Additional articles were manually selected from the reference lists of the published systematic reviews and some cross sectional studies, based on their relevance.

Thus, we selected controlled clinical trials in which different dietary approaches were used for treating NAFLD or NASH diagnosed by imaging methods and/or histological evaluation, regardless of sex and ethnic origin of the participants.

THE ROLE OF DIET IN THE DEVELOPMENT OF NAFLD

It is increasingly recognized that hepatic steatosis occurs when there is a combination of IR and permanent excess of fatty acids delivered to the liver[9]. The sources that supply fatty acids to the liver are the endogenous fat deposits, hepatic DNL, and dietary fat intake. Approximately 90% of the FFA originate from adipocyte lipolysis and are released by the action of lipoprotein lipase on adipose tissue and other tissues being transported such as circulating triglyceride (TG)-containing lipoproteins. The second major source of liver fatty acids is their synthesis inside the hepatocytes through DNL, which uses carbohydrates as the major substrate. Although DNL usually represents only 5% of fatty acid in the liver, this percentage can reach 30% in patients with NAFLD[17].

The mechanism involving fat-induced hepatic IR is not fully understood. It is likely that as a consequence of a HFD, there is an accumulation of fat metabolites, which in turn stimulate the secretion of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines trigger several signal transduction pathways, for example the serine/threonine kinases [protein kinase-C (PKC)], c-JUN NH2-terminal kinase-1 (JNK), and kappa B-kinase inhibitor, causing hepatic IR[6]. The PKC binds to the insulin receptor, inhibits its tyrosine kinase activity and interfere with the ability of insulin to phosphorylate the insulin receptor substrate-2[18,19]. Furthermore, abundant dietary fat consumption increases FFAs delivered to the liver. FFAs stimulate the hepatocytes, leading to intracellular translocation of the protein Bax to the lysosome and as a consequence release cathepsin B. Capthepsin B induces the nuclear factor-κB translocation which enhanced the secretion of TNF-α inhibiting the action of insulin. Indeed, cathepsin B causes alteration in the mitochondrial function culminating in death of the liver cells and evolution from hepatic steatosis to NASH[20]. Evidence suggests that patients with NASH present impaired postprandial TG response, which may increase TG uptake by the liver, promoting hepatic fatty accumulation[19]. Patients with NASH show an abnormality of hepatic fatty metabolism, which increases lipogenesis. Compared to healthy controls, these patients produce 3 times more TG by hepatic lipogenesis[21].

The intake of simple carbohydrates such as fructose and sucrose has increased over the past decades. Fructose is a monosaccharide that exists in natural foods such as fruits, some vegetables and honey. These natural foods contain small amounts fructose, which are absorbed slowly. However, nowadays, fructose is mostly consumed through commercial and industrial products such as sweetened beverages, soft drinks, and high-fructose corn syrup (HFCS). A high fructose diet decreases the hepatic lipid oxidation by reducing the function of the peroxisome proliferator-activated receptor α (PPARα) leading to hepatic steatosis in experimental models[22]. Furthermore, not only fructose, but also glucose stimulates lipogenic genes in the liver. Diets with high content of fructose or sucrose lead to metabolic alterations related to endoplasmic reticulum stress in the liver by activating JNK, which contributes to liver fat deposition and posterior inflammation[23]. Fructose could affect the metabolism in the liver at the transcriptional level, increasing the proinflammatory transcription factor NFkB and oxidative stress[22]. A high-fructose diet decreases PPARs protein in the liver and increases forkhead boxO1, a transcription factor that stimulates the apolipoprotein apoCIII production, which results in increased VLDL-TG production[24]. The carbohydrate responsive element-binding protein, another transcription factor, participates in the regulation of lipid metabolism in the liver, as carbohydrates bind to it stimulating lipogenic gene expression[25].

In addition to role of the monosaccharides, the effects of high glycemic-index carbohydrate have been explored. The high-glycemic index carbohydrate has a close relationship with obesity, IR and increased plasma and hepatic TGs[26,27]. Dietary glycemic index seems to be associated with the grade of hepatic steatosis, regardless of total energy or carbohydrate intake[28]. The underlying mechanism is not fully elucidated, but some hypotheses have been proposed. Foods with high-glycemic index enhance the hepatic influx of glucose. The excess of hepatic glucose exceeds the ability of glycogen production; therefore, this carbohydrate will be used for the synthesis of new TG through DNL within the hepatocytes. An elevated-glycemic index food might augment oxidative stress, which can contribute to NASH development[29].

Based on the exposed data, it is reasonable to conclude that over-consumption of fat and carbohydrates may promote hepatic steatosis. In the following sections, we will discuss the clinical trials on different diets in the development and treatment of NAFLD.

EFFECTS OF DIETARY CARBOHYDRATE INTAKE IN INTRAHEPATOCELLULAR LIPIDS, DNL AND LIVER ENZYMES - EVIDENCE FROM CLINICAL TRIALS OF "HEALTHY" HUMANS

In only a few clinical trials the effects of excessive carbohydrate intake on the liver were investigated in health humans[30-51].

Intrahepatocellular lipids

Evidence from human studies suggests that in a high simple carbohydrate diet the liver quickly accumulates fat. Sevastianova *et al*[46] evaluated 16 overweight subjects that in addition to their usual diet ingested 1000 kcal/d from simple carbohydrate (candy, pineapple juice, sugar-sweetened soft drinks) for 3 wk, and, thereafter, were placed on a hypocaloric diet for 6 mo. It was observed that carbohydrate overfeeding during 3 wk caused a 10-fold higher relative increase in hepatic fat content (27%) than in body weight (2%). The augment in hepatic steatosis was proportional to the rise in *de novo* lipogenesis. When the patients lost weight, they restored liver fat to normal[46].

Considering the simple carbohydrates, the effects of fructose on liver fatty have been explored in many studies. A group of researchers from Switzerland published 5 studies comparing the effects of high fructose and energy diet with a isocaloric diet on intrahepatocellular lipids (IHCLs) in healthy, male adults[39,40,42,49,51]. In the first study, there were no changes in IHCL [measured by magnetic resonance spectroscopy (MRS)] and insulin sensibility in both hepatic and adipose tissue, as well as in the whole body insulin sensitivity, after a 4-wk fructose overfeeding (1.5 g fructose per kilogram body weight per day, which corresponds to the fructose content of 2 L of soda) in 7 lean healthy males. However, it was observed increased plasma concentrations of triacylglycerol, VLDL-triacylglycerol, leptin and fasting glucose after the intervention[39]. The lack of effects on liver fat accumulation after a fructose overfeeding could have been influenced by the reduced sample size of this earliest study. The results of the following 4 studies from the Switzerland group were not consistent with this finding[40,42,49,51]. They were evaluated in a recent random-effects meta-analysis, which leads to the conclusion that short term (1 wk) hypercaloric (35% of energy above the requirement) fructose diets (3 or 3.5 g fructose per kilogram fat free mass per day) compared with an isocaloric diet increased IHCLs by an average of 54% in a total population of 74 healthy adult males[52].

Moreover, in the context of hypercaloric diets, the effects of high-fructose or high-glucose intake were compared in some interventional studies including different healthy populations[36,42,47,48]. In all those studies, the subjects consumed fructose or glucose dissolved in water, 3 or 4 times per day, with the main meals. The results showed that both hypercaloric diets - high-fructose or high-glucose - increased IHCL, and these effects were not different between the 2 monosaccharides[36,42,47,48].

Fructose and glucose are likely to increase IHCL when they are consumed within a hypercaloric diet. However, the studies that examined their effects when they are intake in an isocaloric diet showed controversial results. In the study by Johnston *el al*[36], fructose or glucose were consumed in an isocaloric diet for 2 wk (25% of daily caloric need from glucose or fructose) by healthy, but centrally overweight men, and both monosaccharide diets did not alter IHCLs[36]. In a controlled, randomized double-blinded study, involving 24 adolescents (with hepatic fat > 8% on imaging) received fructose or glucose beverages (with the same energetic value), during 4 wk (3 servings of 8 fluid ounces bottle of study-provided beverage each day, with 33 g of glucose or fructose), no significant changes in hepatic fat (measured by MRS), liver enzymes and body weight were observed[53]. Finally, in a randomized control trial that included 64 healthy subjects, the authors compared the effects on steatosis [measured by computed tomography (CT)] of a HFCS sweetened beverage with sucrose-sweetened low-fat milk at 8%, 18% or 30% of the caloric needs for maintenance of body weight, and observed no significant changes in liver fat despite the kind or quantity of the beverage[32]. These findings support that if monosaccharides are ingested in a normocaloric diet in usually ingested sweeteners, such as sucrose or HFCS, hepatic steatosis is not an expected finding. However, the study by Maersk *et al*[41], which evaluated the results on hepatic fat deposition (measured by MRS) of 47 healthy that consumed 1 L/d of sucrose sweetened regular cola (Coca Cola®; 106 g sucrose/day = 53 g bound fructose/day; 430 kcal), aspartame-sweetened diet cola (Coca Cola®; 4 kcal), semi-skimmed milk (Arla Foods®; 451 kcal), or mineral water (Aqua D'Or®; 0 kcal), during 6 mo, demonstrated significant increase in IHCL in the sucrose sweetened regular cola group, without any changes in whole caloric consumption or body weight[41].

Hepatic de novo lipogenesis

There are few data from human studies about the effects of carbohydrate intake in hepatic DNL. A hypercaloric high-fructose diet (3 g per kilogram body weight plus balanced diet to keep body weight) rose the DNL in the liver by 7.8% (95%CI: 5.8%, 9.8%) in 7 male subjects without any disease[35]. When compared to a hypercaloric high-glucose diet, only the hypercaloric high-fructose (additional 25% of daily energy, during 10 wk) elevated DNL, caused dyslipidemia, reduced insulin sensitivity, and augmented visceral adiposity in subjects who are overweight or obese[50]. On the other hand, the addition of the non-digestible carbohydrate inulin to a diet with 55% of total energy from carbohydrate, for 3 wk, decreased lipogenesis in the liver and blood triglyceride concentrations in 8 healthy subjects examined

in a double-blind, randomized, placebo-controlled cross-over study[54].

Liver enzymes

The liver enzymes outcomes after hypercaloric high-fructose diet are distinct among the studies. After a high-fructose diet (200 g/d) during a 2-wk period, 74 years old male subjects, without any disease, presented increase in all liver enzyme concentrations[43]. In 2 randomized control trials, the authors demonstrated that a diet rich in fructose (3.5 g fructose per kilogram fat free mass daily; 30%-35% of calories above the energy requirement) was associated with increase only in the alanine aminotransferase (ALT) concentrations when compared to the consumption of a weight maintaining diet in healthy people[33,40]. However, in another randomized control trial, the authors did not observe any alteration in this parameter with the same intake of fructose[42]. Sobrecases *et al*[49] assessing the respective effects of high-fructose, high-saturated fat and the association of these diets in young men, without any disease or obesity, verified that the high-fructose diet alone did not change the ALT serum levels; however, the high-fructose associated with high-saturated fat diet increased the concentrations of this enzyme[49].

A random-effects meta-analysis on randomized control trials[30,34,36,42] that compared the outcome of the liver enzymes between hypercaloric high-fructose and hypercaloric high-glucose diets (range 40 g/d to 3.5 g fructose per kilogram fat free mass per day) did not show any significant differences in the ALT and aspartate aminotransferase (AST) levels, regardless of the tested monosaccharide[52]. Only one study demonstrated that high consumption of fructose, but not of glucose, increased gama-glutamyl transpeptidase (GGT) activity[34]. Unexpectedly, an energy balanced diet, with 25% of the caloric need per day from fructose or glucose, was associated with a slight reduction in the liver enzymes concentrations in centrally overweight men[36].

The effects of a hyperenergetic high-sucrose diet on liver function tests have also been investigated. A hyperenergetic (double energy requirement) high-sucrose diet (32% of caloric requirement from sucrose), compared with a standard isocaloric diet in 12 healthy male subjects, increased the blood concentrations of alkaline phosphatase, ALT, AST, GGT, and bilirubin[45]. In agreement with these findings, Porikos *et al*[44] demonstrated that a hypercaloric sucrose containing food-supplemented diet (25%-30% kcal) also raised the ALT and AST levels. However, comparing high-sucrose diet with high-glucose diet, it was not observed any differences in the ALT and AST levels[30,37].

The chief limitations of all intervention studies presented above are the following: (1) small sample size; (2) most studies included only men, and the effects in women may differ due to differences in fructose metabolism mediated by hormonal and anthropometric mechanisms; (3) evaluation of the effects of the disaccharides or monosaccharides on the liver in short term; (4) monosaccharides were provided as their constituent powders as opposed to either incorporated into the matrix of a foodstuff, or as a constituent of sucrose in usual diet; (5) use of large amounts of monosaccharide, which were higher than the levels usually consumed; and (6) fructose or sucrose consumption seems to have been confounded with the excess of caloric ingestion in some studies. Regardless the limitations it is reasonable to conclude that the consequences of fructose consumption on glucose and lipid metabolism seems to be dose-dependent. High-fructose, -glucose and -sucrose diets influence on the amount of fat in the liver, but fructose seems to cause DNL in a higher magnitude. However, the effects of long term dietary intervention on hepatic DNL were not evaluated. Further studies are needed to evaluate if the energy overfeeding changes are monosaccharide specific, and to assess the outcomes of low monosaccharide intakes in patients with NAFLD. Evidence regarding the association between carbohydrate intake and the development of NAFLD comes from observational studies and only a few data result from interventional studies as we will discuss in the following topics.

CARBOHYDRATE INTAKE AND CARBOHYDRATE DIETARY INTERVENTION IN THE TREATMENT OF NAFLD

Some observational studies demonstrated association between high carbohydrate intake or increased simple sugars (sucrose or fructose) consumption and the development of NAFLD[12-14,55-58]. The intake of simple sugars appears to have been associated with the amount of fat in the liver and to the severity of the disease[55,57]. A cross-sectional study demonstrated that high intake of fructose was associated with increased GGT concentrations in 38 subjects under 19 years old who were overweight or obese and presented NAFLD[59]. Based on these findings, some clinical trials were conducted with the aim of understanding the effects of carbohydrate restriction in improving NAFLD.

Intrahepatocellular lipids

In a controlled clinical trial including 18 patients with NAFLD (14 of them biopsy proven), the authors evaluated the effectiveness of a 2-wk administration of VLCD (20 g/d, 9 patients) *vs* calorie restriction (1200-1500 kcal/d, 9 patients) at reducing hepatic TGs measured before and after the intervention by MRS. Weight loss was similar between the groups. Liver TG decreased significantly with weight loss, but the reduction was more intense in the low-carbohydrate subjects compared with in the low-calorie group[60].

In order to evaluate the effects of an even more restricted carbohydrate diet (< 20 g/d of carbohydrate)

on liver histology, a pilot study including 5 NAFLD obese subjects (confirmed by liver biopsy) were instructed to follow a ketogenic diet associated with nutritional supplementation for 6 mo. Post-treatment liver biopsies were performed in 4 of those patients and showed improvement in steatosis, inflammatory grade, and fibrosis. Additionally, after treatment, the patients lost weight (mean weight loss 12.8 kg; range 0-25.9 kg)[61].

Among the simple carbohydrates, the effects on IHCLs of a fructose reduction diet were evaluated in a before-after clinical trial including 10 overweight adults with NAFLD. After 6 mo of the intervention, the subjects diminished their fructose intake in approximately 61% associated with significant reduction in total energy consumption per day, total fat, and SF (224%), which resulted in a decreased of IHCL content (236%). In addition, the patients presented a reduction in their body weight and body mass index (BMI)[62].

Liver enzymes

To evaluated the effects on liver enzymes of different proportion of carbohydrates in a hypocaloric diet, Ryan *et al*[63], randomized 52 subjects with obesity and IR (high possibility of developing NAFLD) to receive a normal carbohydrate (60% carbohydrate, 25% fat or both) or moderate restricted carbohydrate (40% carbohydrate, 45% fat) diet during 16 wk. The two dietary interventions lead to a similar decrease in body weight, daily insulin requirement and plasma ALT levels; however, the 40% moderate restricted carbohydrate intervention was associated with more significantly decrease in IR, and in serum levels of insulin and ALT. The reduction of the ALT concentrations was associated with increasing in insulin sensitivity and decreasing in daily insulin requirement[63]. On the other hand, a 2-wk on VLCD (20 g/d) or calorie restriction (1200-1500 kcal/d) correlated with a reduction in the serum levels of AST, but not ALT, in patients with NAFLD[60].

The specific effect of a low-fructose diet was evaluated in both children and adults with NAFLD. Obese children with NAFLD received a restricted-fructose diet (no intake of beverages with sugar neither any type of food sweetened with HFCS) or a restricted-fat diet [according to the American Heart Association (AHA) guidelines] associated with instructions about the diet, during 6 mo. The comparison between the 2 groups demonstrated no improvement in ALT and AST concentrations in either group at the end of the intervention. Likewise, children's BMI Z scores demonstrated no significant improvement[64]. On the other hand, in an adult overweight population with NAFLD, fructose-restricted diet during 6 mo led to weight loss, normalization of AST and ALT levels, and reduction in GGT concentrations in 7 out of 10 patients[62].

Studies using indigestible carbohydrates as dietary fiber supplementation have attracted interest of researchers due to its several physiological benefits. After treatment with soluble fibers (10 g/d) for 3 mo, 75% of the NAFLD patients presented normalization of the liver enzymes (AST, ALT and GGT), and 100% of them showed reduction in BMI, waist circumference and IR index[65]. Corroborating these findings, Daubioul *et al*[66], in a randomized double-blind crossover investigation, studied the effects of daily ingestion of oligofructose (OFS), a kind of soluble fiber, in 7 patients with NASH (biopsy proven). The subjects were randomly assigned to intake 16 g of OFS or maltodextrine (placebo) daily during 8 wk. OFS decreased serum AST after 8 wk, and insulin concentrations after 4 wk[66]. In a randomized controlled trial, the authors evaluated the effects of beta glucan-containing oat cereal (n = 16), another soluble fiber, *vs* placebo (n = 18) in overweight subjects during 12 wk. The consumption of oat reduced the levels of AST and ALT, body weight, BMI, percentage of body fat, and waist-to-hip ratio. However, the anatomic changes were not observed on ultrasound examination[67].

EFFECT OF DIETARY LIPIDS INTAKE IN INTRAHEPATOCELLULAR LIPIDS IN HUMANS WITHOUT FATTY LIVER

HFD is involved in the pathogenesis of IR[68]. Dietary fat and oxidative stress are likely to play a role in NAFLD pathogenesis and its evolution to NASH. The effects of dietary fat content on hepatic TG (assessed by MRS), body fat distribution [evaluated by magnetic resonance imaging (MRI)], biomarkers of inflammation (serum concentrations of IL-6, IL-12, TNF-α, interferon-γ), and oxidative stress (assessed by urinary F2-α isoprostanes) were evaluated in overweight or obesity patients without glucose intolerance. The subjects ingested a control diet (35% fat, 12% saturated fat and 47% carbohydrate) during 10 d, and then, they consumed a low fat [(20% fat wherein 8% as saturated fat) and 62% carbohydrate; n = 10] or a HFD [55% fat (25% saturated fat) and 27% carbohydrates; n = 10] for 4 wk. After the intervention, both groups remained with body weight stable. In the low-fat diet group, compared to the control diet, the hepatic TG decreased, but, in the HFD patients, the hepatic TG presented no alteration. In both diets, intra-abdominal fat did not change; however, the subcutaneous abdominal fat increased in the HFD group. The inflammatory markers, fasting metabolic parameters and urinary F2-α isoprostanes did not demonstrate any changes[69]. Contrary to these findings, the consumption of HFD by 10 healthy subjects, during 4 d, increased IHCLs by approximately 90%[70].

The effects of an isocaloric restricted-fat, restricted-saturated fat (LSAT) and restricted-glycaemic index (GI) diet [LSAT: 23% fat (7% saturated fat), GI < 55; n = 20] on liver fat (without weight loss) were compared with the effects of a high-fat, high-saturated fat (HSAT) and high-GI [HSAT: 43% fat (24% saturated fat) GI > 70; n = 15] diet in an old population. In the LSAT group the IHCL (measured by MRI) decreased significantly while in the HSAT there were no changes in this parameter. The LSAT diet also reduced total cholesterol,

high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) and fasting glucose, and increased TG levels, and the HSAT intervention had no influence on HDL-c or glucose and raised LDL-c and total cholesterol. The Matsuda index of insulin sensitivity got better on the LSAT intervention, but fasting insulin and homeostasis model of insulin resistance (HOMA-IR) did not demonstrated any improvement as a result of both dietary interventions[71].

Several important questions about the effects on hepatic steatosis remain unanswered, including the effects of the different types of fat: monounsaturated fatty acids (MUFA), PUFA, and SF acid (SFA). In a randomized, parallel-group study, the authors compared the effects of PUFAs and SFA on hepatic steatosis, systemic inflammation, and metabolic disorders in 61 subjects with abdominal obesity (15% with type-2 diabetes). The subjects received a 10-wk isoenergetic diet (without altering the macronutrient intake), high in vegetable n-6 PUFA (PUFA diet) or in SFA mainly from butter (SFA diet). In the PUFA diet group, hepatic steatosis (measured using MRI and MRS), TNF-α receptor-2, and IL-1 receptor antagonist levels reduced, whereas blood insulin tended to increase in the SFA dietary intervention patients. The n-6 PUFAs diet compared with the SFA diet intake modestly improved the metabolic status and decreased liver fat regardless of weight loss. Indeed, a high n-6 PUFA diet was not associated with any signs of oxidative stress or inflammation[72]. Considering the suppressor action of long-chain PUFAs on DNL in the liver, it could believe that fish oil supplements might be useful in the treatment of NAFLD[35]. This subject will be discussed further.

FAT INTAKE AND FAT DIETARY INTERVENTION IN THE TREATMENT OF NAFLD

Some observational studies were performed to evaluate fat intake by individuals with NAFLD. According to the investigation by Musso *et al*[11], the usual dietary pattern of subjects with NAFLD without hyperlipidemia, diabetes and obesity was rich in SF and cholesterol, and poor in PUFAs. SF intake correlated with insulin sensitive index, features of the MS, and increased postprandial TG[11]. Compared to the healthy controls, patients with NAFLD have been shown to have a lower dietary intake of omega-3 fatty acids and to have an increased n-6/n-3 ratio in their diet[57,73]. The elevated n-6/n-3 ratio in the food has been associated with a pro-inflammatory state[74,75] and increased lipogenesis causing steatosis in animal models[76,77]. On the other hand, it has been demonstrated that omega-3 PUFAs inhibits sterol regulatory element binding protein 1c and upregulates PPARα favoring fatty acid oxidation and improving steatosis[78]. NASH patients seem to have impairment in glutathione metabolism towards an oxidant status, and this alteration has been associated with a high intake of dietary SF and a low consumption of carbohydrates[79]. Based on this finding, some clinical trials were designed to investigate the modulation of dietary fat in the treatment of NAFLD.

Intrahepatocellular lipids

Chan *et al*[80], studied 9 NAFLD subjects who underwent a weight loss program through a low fat diet (LFD) and the results showed a decrease in body weight, BMI, hepatic steatosis, amount of visceral and subcutaneous fat, HOMA-IR score, TGs, VLDL-apoB-100 levels, and VLDL-apoB-100 secretion rate. The amount of steatosis reduction correlated significantly with a decrease in the rate of secretion of VLDL-apoB-100 and visceral fat[80].

The modulation of the different types of fat as a dietary approach of NAFLD has been examined. The effects of the Mediterranean diet (MD), known as a high content in MUFA diet, on IHCL (measured by MRS) and insulin sensitivity were evaluated in 12 biopsy proven NAFLD subjects without diabetes, in a randomized, crossover investigation comprising 6 wk of diet intervention. All participants receive, in a random order, both MD and a control diet [low fat, high-carbohydrate diet (LF/HCD)], with a wash-out period of 6 wk between the dietary interventions. The results demonstrated that although the patients did not present weight loss, the MD was associated with a reduction in the hepatic fat content and also improved insulin sensitivity in the patients with NAFLD and glucose intolerance, in comparison with the subjects from the LF/HCD group[81].

Nigam *et al*[82], compared, in NAFLD patients, the effects of different types of vegetal oil: Canola oil (61% MUFAs, 7% saturated fatty acids and n-6/n-3 ratio nearly 2/1), olive pomace oil (70% MUFAs, 15% saturated fatty acids and n-6/n-3 ratio nearly 9/1), and control oil group - soybean or safflower (15%-24% MUFAs, 12%-16% saturated fatty acids, 50%-60% PUFAs and n-6/n-3 of 7/1 for soya oil and higher than 100 for safflower oil). Ninety-three patients, matched by age and BMI, were randomly assigned into 3 groups to intake not more than 20 g daily of olive oil, canola oil, or soyabean/safflower oil (control; n = 30) and lifestyle counseling, for 6 mo. Compared to the control oil group, the olive oil patients decreased weight and BMI. Furthermore, these subjects presented reduction in fasting insulin level, HOMA-IR, HOMA denoting b-cell function, and disposition index, when compared to the canola oil individuals. Pre- and post-intervention analysis demonstrated that the olive oil group presented increase in HDL-c levels; the canola oil group presented reduction in fasting blood glucose and TG; and both groups (olive and canola oils) presented improvement in the grade of fatty liver and liver span[82].

In several studies, the effects of the intake of n-3 PUFA supplements were investigated as a complementary treatment of NAFLD[83-89]. In general, these studies demonstrated a reduction in liver fat measured by different imaging methods, with the doses raging from 0.83 to 6 g/d, and duration therapy ranging from

8 wk to 18 mo[83-87]. A supplementation of 2 g of n-3 PUFA 3 times per day, for 24 wk, was associated with a complete fatty liver regression in almost 20% of the NAFLD patients and some reduction in 53% of them. In contrast, in the placebo group, 7% fatty liver completely regressed and 35% presented certain reduction in IHCL (measured by ultrasound)[87]. Similar effects were observed using a supplementation daily dose of 4 g of n-3 fatty acids, for 8 wk, on liver fat (measured by MRS) in women with polycystic ovary syndrome. N-3 PUFA diminished liver steatosis, TGs levels, and systolic and diastolic blood pressures[83] while these effects were not observed in the placebo group. Using the same dose of supplementation (4 g/d) of docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA), NAFLD subjects were randomized in a clinical trial, double blind and placebo-controlled to receive n-3 therapy (n = 51) or placebo (n = 52) during 15-18 mo. Liver fat percentage was measured by MRS in 3 liver zones and liver fibrosis was evaluated by 2 validated scores. The supplementation adherence and the presence of contaminants as DHA and EPA in the placebo group were investigating by verifying erythrocyte percentage of DHA and EPA enrichment. The median liver fat at the beginning was 21.7% in the placebo group and 23% in the intervention group, and they changed to 19.7% and 16.3%, respectively. The adjusted multivariable regression model demonstrated a trend towards a reduction in liver fat following treatment with the DHA + EPA; however, there was variable adherence to the intervention and evidence of contamination in the placebo group. DHA enrichment was independently associated with a reduction in hepatic steatosis in the regression analysis. There was no improvement in the fibrosis scores. According to the results, erythrocyte DHA enrichment with DHA + EPA supplementation could be associated with less hepatic steatosis. The authors concluded that increased percentage of erythrocyte DHA enrichment can cause a reduction in hepatic steatosis in NAFLD subjects[84].

These findings were corroborated by the results of another study, in which a smaller dose (2 g/d) of PUFA associated with AHA recommended diet, for 6 mo, were evaluated. About one third (33.4%) of the NAFLD patients presented a complete fatty liver regression, and 50% demonstrated some reduction. In contrast, no patient achieved complete regression in the group that received only the AHA diet, and only 27.7% of them presented some reduction in the steatosis[86]. Another study employing low dose of n-3 PUFA supplementation (0.83 g/d, of which 0.47 g of EPA and 0.24 g of DHA) in olive oil demonstrated improvement in the liver echo-texture (evaluated by ultrasound) and in the hepatic Doppler perfusion index, after 12 mo of treatment of NAFLD patients, compared to a control group of individuals also with NAFLD[85].

Although the investigations based on imaging methods demonstrated a reduction in liver fat as commented above, the studies that investigated the role of n-3 PUFA in NAFLD treatment using liver histology to evaluate the results have shown controversial results[88,89]. Tanaka *et al*[89] prescribed highly purified EPA (2700 mg/d) to 23 NASH (biopsy-proven) patients during 12 mo and the effects were measured by biochemical parameters and hepatic biopsy. The outcome showed a reduction in AST, FFA, soluble TNF-α receptors 1 and 2, ferritin, and thioredoxin serum concentrations, which may be the result of oxidative stress in the liver. Body weight, blood glucose, insulin and adiponectin concentrations did not changed. Post-treatment liver biopsy was performed in 7 out of the 23 NASH patients and demonstrated improvement in liver fat, fibrosis, ballooning in liver cells, and lobular inflammation in 6 subjects[89]. However, in a larger phase 2b multicenter, placebo-controlled trial, these findings were not confirmed[88]. Sanyal *et al*[88], compared the effects of different doses of EPA-E, a synthetic PUFA, in the liver histology of 243 NASH patients with NAFLD activity score $\geqslant$ 4 (minimum score of 1 for steatosis and inflammation, along with either ballooning or at least stage 1a fibrosis). The patients were randomized into three groups which received low-dosage EPA-E (1800 mg/d; n = 82), high-dosage EPA-E (2700 mg/d; n = 86) or placebo (n = 75) and were followed for 12-mo. Liver biopsy was performed 2 wk after the end of the treatment. The primary efficacy end point was NAFLD activity score $\leqslant$ 3 without fibrosis worsening; or a reduction in NAFLD activity score $\geqslant$ 2 with contribution from at least 2 variables, without worsening of fibrosis, 1 year after the end of the intervention. The percentages of patients in the groups that achieved the main end point were similar: 40% in the placebo group, 37% in the low-dose, and 35.9% the high-dose group. EPA-E was not associated with any improvement in the histological parameters of NASH (liver fat, inflammation, ballooning, or fibrosis scores)[88].

Liver enzymes

In some of the studies the effects of n-3 PUFA supplementation were also assessed by the analysis of the liver enzymes[85,87-89]. In an investigation, patients with NAFLD that consumed olive oil plus 0.83 g of n-3 PUFA, during 1 year, presented reduction in liver enzymes (ALT, AST and GGT) and TGs serum levels, and increased in adiponectin serum concentrations, compared with the control group that received similar package of olive oil without addition of n-3 PUFA[85]. In the study in which the NAFLD subjects consumed a higher dose of n-3 PUFA supplementation (2 g/d) associated with the AHA diet or received solely the AHA regular diet, during 6 mo, it was observed a decrease in the ALT levels after the treatment with the n-3 supplementation plus diet, while the other enzymes remained unchanged. These patients also presented a reduction in the TGs and TNF-α level, and in the HOMA-IR score. No alterations in the evaluated parameters were verified in the control group[86]. Different findings were observed with the use of EPA in a dose of 2.7 g/d in the NASH (biopsy-proven) patients, for 12 mo. Among the liver enzymes, only the AST levels were reduced[89]. Corroborating the results of Tanaka *et al*[89], it was demonstrated that in a higher

EPA dose (6 g/d), the NAFLD subjects demonstrated more expressive reduction in the ALT concentrations and also in total symptom scores and serum TG levels when compared to a placebo group. In both groups there were no changes in body weight, fasting glycemia, renal function and blood cell counts, but there was a tendency toward improvement in AST, GGT, total cholesterol and HDL-c levels, without significant differences between the groups[87].

The possible benefit of EPA supplementation on liver enzymes was not supported in a large population of patients with biopsy proven NASH. Both EPA-E 1800 mg/d and EPA-E 2700 mg/d used for 12 mo in NASH patients had no effects on liver enzymes concentrations, IR, adiponectin, keratin 18, high-sensitivity C-reactive protein, or hyaluronic acid levels, but the elevated dose of EPA-E was associated with a reduction of TG levels, without any serious adverse events[88].

CLINICAL TRIALS COMPARING CARBOHYDRATE *VS* FAT DIETARY INTERVENTIONS

Liver enzymes

The results of the studies comparing the effects of low carbohydrate diet (LCD) with LFD on liver amino-transferases in NAFLD patients, allow concluding that despite of macronutrient restriction both diets lead to favorable results when associated with a reduction in body weight[90,91]. In one of these studies, obese subjects were included in the group Ⅰ (n = 112) if normal levels of ALT, or group Ⅱ (NAFLD, n = 30) if increased ALT concentrations (≥ 43 UI/L); then, they were randomly allocated to receive LFD or LCD, for 3 mo. After outcome analysis, the authors concluded that weight reduction following either hypocaloric diets - LFD or LCD - was associated with improvement in ALT concentrations and IR in subjects with NAFLD[90]. Likewise, Rodríguez-Hernández *et al*[91] randomized 59 obese women with NAFLD to receive either LCD (n = 31) or LFD (n = 28), for 6 mo. At end of the intervention, both groups presented weight loss (5.7% and 5.5% in the LCD and LFD, respectively) and decrease in AST and ALT serum levels, but without differences between the groups[91].

Based on the above data, some authors investigated the effects of energy restriction diet without modulation in the proportion of the macronutrients in the treatment of patients with NAFLD, as will be discussed in the next topic.

ENERGY RESTRICTION ON DIETARY INTERVENTION IN THE TREATMENT OF NAFLD PATIENTS

According to the American guidelines for the diagnosis and management of NAFLD, loss of at least 3%-5% of the initial weight through hypocaloric diet (alone or associated with increased physical activity) reduces liver fat, however more expressive weight loss (up to 10%) might be necessary to determine improvement in necroinflammation[1]. In this context, Elias et *al*[92] evaluated the effects of a 6-mo hypocaloric diet (reduction of 500-1000 calories per day) with 15% protein, 55% carbohydrates and 30% fat, on IR, biochemical parameters of the MS, and grade of liver fat in 31 NAFLD subjects. The participants were called adherent (group 1; n = 17), if they showed weight loss higher than 5% of the initial weight, or non-adherent (group 2; n = 14), if they do not reach 5% weight loss from the initial weight. Group 1 patients improved all the anthropometric parameters, and presented a reduction in ALT and GGT levels, HOMA-IR, visceral fat and hepatic density on computed tomography, along with increase on HDL cholesterol levels. These subjects reduced the total caloric consumption and total and saturated fats intake. Group 2 presented only a significant decrease in BMI and waist circumference. Based on these results, the authors concluded that the dietary intervention as the only therapeutic approach but leading to a weight loss of at least 5% from the initial body weight is effective in improving NAFLD[92].

A group of Taiwanese researchers compared the effects of 2 different VLCDs (450 or 800 kcal/d) in 132 subjects presenting obesity (83 with NAFLD). The patients were randomized to 2 VLCD groups aimed to weight loss in 12 wk. During the 12-wk intervention period, the VLCD-450 group showed a loss of 9.14% of the initial body weight and the VLCD-800 group lost 8.98% of the initial weight as revealed by the intention-to-treat analysis. A total of 40.9% subjects from the VLCD-450 group and 43.9% from the VLCD-800 group lost at least 10% of the body weight at the end of the intervention. In both groups, it was observed improvement in the following parameters: body weight, waist circumference, hip circumference, fat mass, blood pressure, TG and glycemia, without difference between the 2 groups. NAFLD was resolved in 41.5% of the cases in the VLCD-450 group and in 50.0% in the VLCD-800 group[93].

Until nowadays, there is no specific recommendation regarding the amount of calorie restriction necessary to improve NAFLD. As demonstrated by Elias *et al*[92] and Lin *et al*[93], the reduction of 500 to 1000 kcal/d in the usual energy intake or even a more restrictive diet (450 or 800 kcal/d) could be effective and safety to treat obesity and to improve NAFLD; without any additional benefit in recommending a more restrictive dietary intervention.

CONCLUSION

Regardless of weight loss, restriction and modulation of dietary carbohydrate (*e.g.*, restriction of simple carbohydrate and high glycemic carbohydrate) and fat (*e.g.*, restriction of total and saturated fat and

increase in MUFAs and n-3 PUFAs) seem to improve metabolic parameters such as IR, decrease the liver enzymes levels and/or reduce the grade of steatosis in NAFLD patients. Contrary, weight loss, independently of restriction of carbohydrate or fat improves the liver parameters. Therefore, in some studies, the effects of the restriction of one macronutrient *per se* could have been confused with the effects of a restriction of energy from the diet. Finally, data demonstrating improvement in liver histology associated with different dietary approaches are scarce. In this context, long-term studies are needed to elucidate the detailed dietary approach of NAFLD, before getting to clinical practice.

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