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Review

Diets and nonalcoholic fatty liver disease: The good and the bad

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SUMMARY

Nonalcoholic fatty liver disease (NAFLD) is now described as the hepatic manifestation of the metabolic syndrome and is the most frequent chronic liver disease, affecting about one out of three people in the western world. NAFLD is strongly linked to insulin resistance, which represents a key risk factor for the development of type 2 diabetes. To date, there are no reliable and efficient pharmacotherapies in the treatment of NAFLD. However, obesity, which represents one of the main features of the metabolic syndrome, is strongly associated with NAFLD. Therefore, lifestyle modifications, i.e. weight loss and increased physical activity, are the very first clinical approaches aiming at treating NAFLD. However, although weight loss is beneficial in NAFLD, certain diets known to induce weight loss can actually cause or exacerbate this disease, and therefore induce insulin resistance, such as very low carbohydrate, high fat diets. Moreover, macronutrient diet composition can impact NAFLD without any change in body weight. Indeed, diets rich in fatty acids, particularly saturated, or in refined carbohydrates such as those found in soft drinks, can actually exacerbate NAFLD. The aim of this review is to discuss the role of weight loss and macronutrients modifications, particularly the role of fat and carbohydrate diet composition, in the treatment of NAFLD.

1. Introduction

The prevalence of nonalcoholic fatty liver disease (NAFLD) is rapidly increasing in the western countries and now affects about a third of the population.[1] NAFLD is a spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) that occur mainly due to fat accumulation in the liver, but can ultimately lead to cirrhosis, which is not reversible and may progress to hepatocellular carcinoma. Therefore, NAFLD can be considered as a risk factor for cancer, but is now also recognized as a risk factor for cardiovascular diseases.[2] Moreover, NAFLD is now considered to be the hepatic manifestation of the metabolic syndrome, which is characterized by insulin resistance, dyslipidemia, hypertension, type 2 diabetes and excess body weight.[3,4] In particular, patients presenting one of the metabolic syndrome features are at increased risk for the development of NAFLD compared to the unaffected ones. For instance, among morbidly obese patients, approximately 90% have NAFLD.[5] The diagnosis of NAFLD is beyond the scope of this review and is discussed elsewhere.[6] Because obesity strongly influences the development of NAFLD, weight loss appears as the main rational target to treat NAFLD. Indeed, to date no pharmacological therapy is approved for NAFLD, and lifestyle modifications are strongly recommended for patients with NAFLD.[7] An important aspect of lifestyle is diet. The aim of this review is therefore to discuss the role of dietary interventions in the treatment, but also in the pathogenesis of NAFLD. We will first precise the pathophysiology of NAFLD and its nutritional implications will be summarized. Secondly, the potential role of some diets in the development of NAFLD will be outlined. Finally, we will examine the nutritional/dietary therapeutic approaches in the treatment of NAFLD.

2. Pathophysiology of NAFLD and nutritional implications

The pathophysiology of NAFLD is complex and multifactorial. It is mainly characterized by the accumulation of lipids. The latter may be due: 1) to excessive influx of fatty acids from endogenous fat depots (mostly white adipose tissue); 2) from excess dietary fat intake and 3) from *de novo* hepatic lipogenesis (Fig. 1). In animals, this net accumulation of fat in the liver, i.e. NAFLD, has been clearly linked to the development of hepatic insulin resistance.[8–17] Genetic and dietary animal models of NAFLD have been reviewed by Hebbard and co-workers.[18] Hepatic insulin resistance is therefore secondary to hepatic fat accumulation, but actually specific lipid intermediates are more prone to induce insulin resistance than others. Specifically, diacylglycerols and ceramides, to the opposite of triglycerides, are known to activate different effectors, finally inhibiting the insulin signaling. These mechanisms have been

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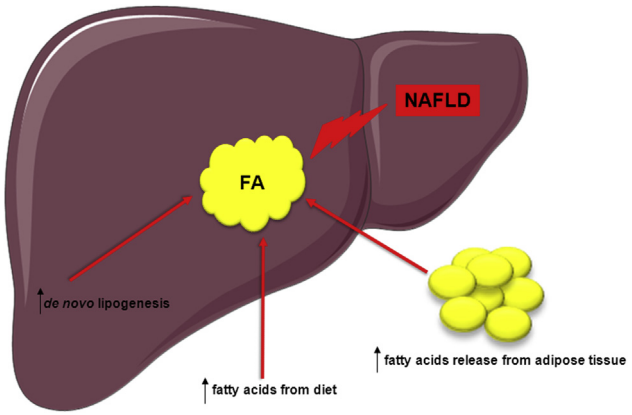

Fig. 1. Major sources of hepatic fat accumulation. The pathogenesis of nonalcoholic fatty liver disease (NAFLD) is characterized by abnormal accumulation of fatty acids (FA) in the liver. These FA originate mainly from the diet, the adipose tissue lipolysis and from hepatic *de novo* lipogenesis.

discussed elsewhere[4,6,19] and are summarized in Fig. 2. Therefore, as liver fat accumulation can be derived from dietary intake, it is of critical importance to understand how different diets and their macronutrient composition can impact the development of NAFLD.

Despite contradictory results regarding the role of different diets on NAFLD, it is reasonable to propose that over-consumption of either fat or carbohydrates is an important threat that may promote the development of NAFLD. It is also probable that specific fatty acids or carbohydrates are more prone to induce or improve NAFLD. Therefore, in the following sections we will discuss whether the specific subtypes of fat (saturated vs unsaturated) and carbohydrates (complex vs simple) and their relative ratios may be more deleterious than their total amount. These studies are summarized in Table 1. Finally, recent evidence suggests that certain nutrients may also play a role in the development or treatment of NALFD,

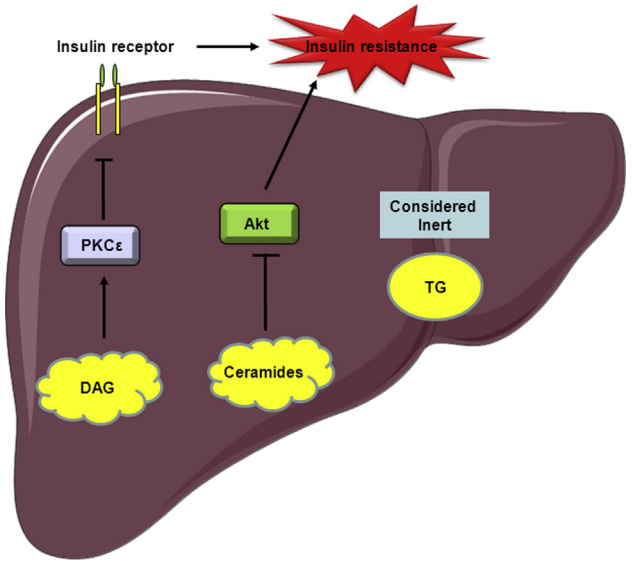

Fig. 2. NAFLD in hepatic insulin resistance. Nonalcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of clinical conditions associated with the accumulation of lipids in the liver. This abnormal lipids accumulation leads to hepatic insulin resistance. However, not all lipids are equal in this process. For instance, diacylglycerols (DAG) by activating the protein kinase Cε (PKCε), which is known to inactivate the proximal insulin signaling, promote insulin resistance. Similarly, ceramides, by inhibiting Akt, induce insulin resistance. On the other hand, triglycerides (TG) are considered inert in the development of insulin resistance.

such as cholesterol, choline, and vitamins D and E. However, these nutrients are beyond the scope of this review and are discussed elsewhere.[20]

3. Influence of fat and carbohydrate diet composition on NAFLD

3.1. Fatty acids

Several epidemiological studies have linked metabolic and cardiovascular diseases to altered lipid metabolism and dietary fat type, but data on the association between dietary type and fatty liver are scarce.[21] A small sample size study has revealed that patients with NASH have an increased intake of saturated fat and cholesterol, and reduced dietary intake of polyunsaturated fatty acids.[22] In line with these results, Toshimitsu and coworkers revealed that patients with fatty liver and NASH present a lower dietary ratio of polyunsaturated/saturated fatty acids compared to the ratio of healthy subjects.[23] This association between fatty acids ratio and the severity of fatty liver disease could be due to several molecular mechanisms. Among these, oxidative stress in NASH has been correlated to the type of dietary fat.[24] When analyzing the dietary intake of 43 patients with NASH and 33 healthy controls, a correlation between saturated fatty acids intake and impaired glutathione metabolism was found, suggesting deleterious pro-oxidant effects of saturated fatty acids. On the other hand, a positive correlation between monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA), specifically n-3 PUFA, and decreased liver fat content was found, indicating a beneficial role of these fatty acids. Recently, it has been reported that MUFA may prevent the development of NAFLD by improving plasma lipid levels, reducing body fat accumulation and decreasing postprandial adiponectin expression. Nevertheless, the authors concluded that further investigations are warranted to ascertain the role of MUFA on NAFLD.[25]

In contrast to MUFA, the role of n-3 PUFA on NAFLD has been clearly characterized. Indeed, it has been shown that a diet enriched in n-3 PUFA reduces body weight and hepatic triglycerides accumulation, restores insulin sensitivity and ameliorates liver steatosis.[26–28] Several other studies support the protective role of n-3 PUFA in NAFLD. Among these, a nonrandomized open-label controlled trial analyzed the effect of n-3 PUFA supplementation in 42 patients with NAFLD and revealed that PUFA supplementation significantly reduced the level of NAFLD biomarkers (ALT, AST, and GGT) as well as liver fat content.[29] Confirming these results, another interventional trial conducted in 23 patients with NASH found reduced serum ALT levels and improvement of hepatic steatosis.[30] It is important to note that these dietary modifications did not influence body weight, suggesting that modification of dietary habits rather than weight loss *per se* may improve NAFLD. Therefore, further investigations are required to clarify the association between macronutrient composition and the development of NAFLD in normal weight patients.

3.2. Carbohydrates

During the last decade, dietary habits have evolved to more sweetened and fatty foods.[31] A recent investigation has shown that increased intake of carbohydrate sweetened beverages increases the risk for obesity, type 2 diabetes, the metabolic syndrome, fatty liver, and cardiovascular diseases, possibly due to an excessive caloric intake.[32] In line with these results, Maersk and co-workers found that sucrose-sweetened beverages increase visceral adipose tissue as well as liver fat accumulation but did not impact insulin responsiveness.[33] In addition to sucrose, other studies have shown

Table 1
Role of fats and carbohydrates in NAFLD.

Reference	Type of fat	Type of carbohydrate	Effects on NAFLD
Machado et al.[24]	Saturated fatty acids		Impairs glutathione metabolism and promotes NAFLD
Machado et al.[24]	Unsaturated fatty acids		Reduces fat accumulation
Assy et al.[25]	Monounsaturated fatty acids		Improves plasma lipid levels, reduces body fat accumulation and decreases postprandial adiponectin expression
Masterton et al.; Storlien et al.; Levy et al.; [26–28]	Polyunsaturated fatty acids (n-3 PUFA)		Reduces body weight and hepatic triglycerides accumulation, restores insulin sensitivity and ameliorates liver steatosis.
Capanni et al.; Tanaka et al.[29,30]	Polyunsaturated fatty acids (n-3 PUFA)		Reduces NAFLD biomarkers levels (ALT, AST, and GGT) as well as liver fat content.
Cortez et al.[47]	n-6 fatty acids		Fat intake with an excessive amount of n-6 fatty acids may promote NAFLD
Maersk et al.[33]		Sucrose	Increases visceral adipose tissue as well as liver fat accumulation but does not impact insulin responsiveness
Ouyang et al.; Stanhope et al.; Stanhope et al.[34–36]		Fructose	Increases oxidative stress and insulin resistance. Increases hepatic fibrosis
Jornayvaz et al.; Bisschop et al.; Johnston et al.[8,40,41]		Low carbohydrate diet	Promotes NAFLD risk factors such as insulin resistance and diabetes
Assy et al.; Zelber et al.; Abid et al.[39–41]		Soft drinks	Sugar-sweetened beverage consumption identified as an independent risk factor for NAFLD.

that a high consumption of fructose (notably in the form of high-fructose corn syrup) results in increased oxidative stress and insulin resistance, which are risk factors for NAFLD and type 2 diabetes.[34–36]

Recently, a large-scale study of 427 patients with NAFLD analyzed the role of over-consumption of fructose-containing beverages in the development of this disease. After adjusting for age, sex, BMI, and total caloric intake, the authors found that daily fructose-containing drinks consumption was significantly associated with a higher hepatic fibrosis stage in both younger and older age groups, but also, surprisingly, to a lower steatosis grade in the older group of patients.[37] This lower steatosis grade could be due to a reduction in triglycerides synthesis, as the latter has been linked to improved hepatic steatosis but to exacerbated liver fibrosis.[38] Thus, these studies identified an important avoidable risk factor, i.e. fructose consumption that may ameliorate the severity of NAFLD.

Moreover, other studies have identified soft drinks as a risk factor for NAFLD. For instance, Assy and coworkers, by comparing patients with NAFLD with age-matched healthy controls, revealed mild fatty liver in 44% of cases ($n = 14$), moderate fatty liver in 38% ($n = 12$), and severe fatty liver in 18% ($n = 5$). After adjustment for dietary composition and physical activity, soft drinks consumption was the only independent variable predictive of NAFLD. Therefore, this cross-sectional study emphasizes an important role of soft drinks in the development of NAFLD and suggests that patients with NAFLD should change their drinking behavior.[39] These results are in accordance with other studies that found a positive association between the risk of NAFLD and an increase in soft drinks intake, even when adjusted for other risk factors.[40,41]

In contrast to high carbohydrate diets, low carbohydrate diets improve obesity related symptoms. For instance, it has been reported that insulin sensitivity is improved in obese patients assigned to a low carbohydrate diet.[42] However, the effect of low carbohydrate diets remains extremely controversial. In fact, in healthy non obese subjects, a high fat, low carbohydrate diet was shown to induce insulin resistance instead of ameliorating the ability of insulin to suppress endogenous glucose production.[43] In line with this study, a high fat, low carbohydrate ketogenic diet has been associated with altered metabolism, by notably altering plasma phospholipids and increasing inflammatory risk.[44] In addition, low carbohydrate, high fat diets enhance the risk of mortality and type 2 diabetes, notably when animal proteins and fats are consumed.[45,46] Finally, a study in mice revealed that a high fat, low carbohydrate ketogenic diet prevented weight gain but caused NAFLD and associated hepatic insulin resistance.[9] In summary, although low carbohydrate, high fat ketogenic diets are effective in achieving weight loss, they can also induce adverse effects on metabolism. Therefore, caution needs to be used before recommending such diets to obese patients. Finally, a study evaluating dietary patterns in patients with nonalcoholic steatohepatitis (NASH) revealed that these patients consumed less carbohydrate, more fat and less fibers than healthy controls. Therefore, the authors suggested that the quality and combination of carbohydrates and fat intake may be more relevant than their isolated amount, and that an increased fat intake with an excessive amount of n-6 fatty acids can be implicated in promoting NASH.[47]

4. Nutritional therapeutic approach: from theory to practice, effects on NAFLD

Dietary intake plays a very important role in the pathogenesis of NAFLD. Weight loss is an essential element in the therapy and treatment of this disease, although macronutrients composition seems to play an important role, as discussed above. To achieve weight loss, various approaches have been used resulting in either rapid and drastic or moderate weight loss. Historically, the very first trials experienced the effect of very low caloric diets and found that this type of diets drastically reduces weight. However, this approach presented an important limitation. Indeed, the effect of changing the food component was not discussed at all. Furthermore, this type of diet increased histological lesions in the liver. Indeed, although such caloric restrictions result in a significant improvement of hepatic steatosis, they cause inflammation or periportal fibrosis.[48] Importantly, this study determined the upper limit for the rate of weight loss in NAFLD patients. The authors recommended to not exceed 1.6 kg/week weight reduction to avoid a worsening of fibrosis and hepatocytes necrosis. Finally, rapid weight loss is usually not successful in the long term, with a weight regain that may even exceed the initial body weight, the so-called yo–yo or weight loss cycling effect.[49] Thereafter, other studies investigated the effect of a more balanced diet combined or not with physical activity. Notably, Lazo and co-workers addressed the effect of a prolonged intensive lifestyle intervention on hepatic steatosis in adult patients with type 2 diabetes. The intervention included a moderate caloric restriction in association with increased physical activity and weekly meetings, whereas the control group received only general information on nutrition and

physical activity. After 12 months, patients assigned to intensive lifestyle intervention lost more weight (−8.5 vs. −0.05%; $P < 0.01$) than those assigned to diabetes support and education and had a greater decline in hepatic steatosis (−50.8 vs. −22.8%; $P = 0.04$). Moreover, it was found that 26% of controls vs 3% of participants in the intervention group, without NAFLD at baseline, developed NAFLD after 12 months. Therefore, the authors concluded that such an intervention was useful to decrease or prevent the development of NAFLD.[50] Nevertheless, it is important to take into account some limitations of this study. Indeed, the follow up of these participants was short (12 months), hence the authors may have missed long term adverse effects induced by this intervention. In addition, this study reports the efficiency of diet adaptation by measuring biochemical markers such as alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transferase. This allowed evaluating the severity and development of NAFLD. However, it is known that some diets may promote asymptomatic liver enzymes elevation although they induce liver injury. Therefore, the assessment of NAFLD should be done at least noninvasively by imaging or more accurately by the gold standard, i.e. liver biopsy. Another study in type 2 diabetic patients showed that a moderate weight loss of about 8 kg decreased intrahepatic lipid content and improved insulin sensitivity when assessed by a hyperinsulinemic-euglycemic clamp.[51]

Overall, most studies tend to conclude that balanced nutrition and moderate weight loss can improve or prevent NAFLD, and can therefore be considered as a therapeutic approach.

In humans, Sacks and co-worker performed a large, long-term trial for which the purpose was to test the efficacy of weight-loss diets. In this study, patients were assigned to diets that differed in their composition in macronutrients: low or high in fat, average or high in protein, and low or high in carbohydrates, and otherwise followed recommendations for cardiovascular health. Thereafter, several data including body weight, levels of serum lipids, glucose, insulin, and glycated hemoglobin were regularly measured for a period of two years. The authors concluded that behavior rather than dietary composition mainly influence weight loss and that diets that are successful in causing weight loss can encompass a wide range of fat, protein, and carbohydrate ratios that have beneficial effects on risk factors for cardiovascular diseases and diabetes.[52] Nevertheless, the difference in nutrients was not so important; thereby the authors could not reach a firm conclusion. Therefore, it appears that weight loss, which is the first line of treatment of NAFLD, could be challenged by behavior adaptation. Importantly, this study did not characterize the effect of the different diets on liver fat content or liver injury and therefore cannot guide the clinician for this issue. In contrast, another randomized study revealed that liver fat content decreased by 20% on a low fat diet and increased by 35% on a high fat diet. Most importantly, these changes were not related to weight loss,[53] suggesting that macronutrients composition of the diet is as important as weight loss *per se*. Indeed, this study showed that decreasing dietary fat content leads to changes in liver fat content within 2 weeks. These changes occurred without any change in body weight, fatty acids concentration, intra-abdominal or subcutaneous fat mass, or rates of carbohydrate, lipid, or protein oxidation. Changes in liver fat content were paralleled by improvements in fasting serum insulin concentrations. Therefore, exploring the association between dietary macronutrients composition and NAFLD is extremely important and may provide new nutritional approaches to slow the progression of the disease.

However, the best dietary composition in macronutrients for the management of NAFLD, independently of weight loss, remains to be evaluated. Moreover, to date, no dietary intervention has been able to show an improvement in hepatic fibrosis.

5. Conclusion

NAFLD is the most frequent chronic liver disease and is mostly associated with the epidemic of obesity. NAFLD is associated with an increased risk of cardiovascular diseases and liver-related complications, such as liver cirrhosis or hepatocellular carcinoma. NAFLD is clearly associated with insulin resistance, which is a key risk factor for the development of type 2 diabetes. Current pharmacological options for NAFLD are disappointing and warrant further research. Weight loss is efficient and can improve liver histology, although it cannot improve liver fibrosis. However, the exact macronutrient dietary composition to be used to lose weight or specifically improve NAFLD, even without weight loss, remains to be determined. This is of importance as some diets have been linked to the development of NAFLD, notably in animal models, such as high fat and ketogenic diets. Therefore, more long-term clinical trials are needed until definitive recommendations on the dietary management of NAFLD can be given. Nevertheless, based on current evidence, we would recommend a diet low in fat, notably in saturated fatty acids, and low in refined carbohydrates, notably by reducing soft drinks consumption, in patients with NAFLD, as these nutritional factors may play a pivotal role in NAFLD.

Conflict of interest statement and statement of authorship

Each author has participated sufficiently, intellectually or practically, in the work to take public responsibility for the content of the article, including the conception, design, and for data interpretation. All authors have read and approved the final manuscript. MA and FRJ have no conflict of interest.

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