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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.

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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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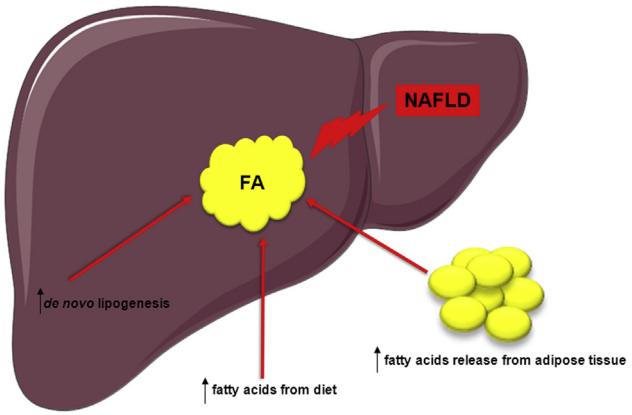

Fig. 1. Major sources of hepatic fat accumulation. The pathogenesis of nonalcoholic fatty liver disease (NAFLD) is characterized by abnormal accumulation of fatty acids (FA) in the liver. These FA originate mainly from the diet, the adipose tissue lipolysis and from hepatic *de novo* lipogenesis.

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,

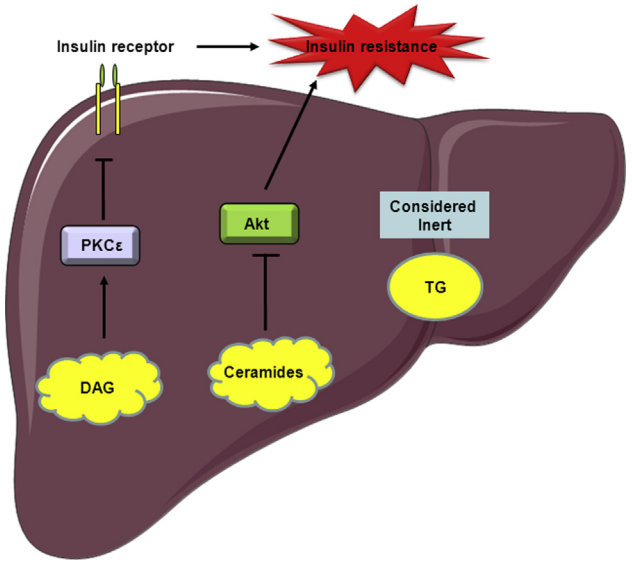

Fig. 2. NAFLD in hepatic insulin resistance. Nonalcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of clinical conditions associated with the accumulation of lipids in the liver. This abnormal lipids accumulation leads to hepatic insulin resistance. However, not all lipids are equal in 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

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