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Review Article

# Practical approaches to the nutritional management of nonalcoholic fatty liver disease

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome and a serious health burden worldwide which increases risk of cirrhosis, type 2 diabetes mellitus (T2DM), and cardiovascular complications. Current epidemics of obesity, unhealthy dietary patterns, and sedentary lifestyles, all contribute to the high prevalence of NAFLD. Dietary patterns and nutrients are important contributors to the development, progression, and treatment of NAFLD. A healthy diet is beneficial for all NAFLD patients beyond weight reduction. Generally, hypercaloric diets, especially rich in trans/saturated fat and cholesterol, high consumption of red and processed meat, and fructose-sweetened beverages seem to increase the risk of progression toward nonalcoholic steatohepatitis (NASH), whereas reducing caloric intake and high-glycemic index (GI) foods, increasing consumption of monounsaturated fatty acids, omega-3 fatty acids, fibers, and specific protein sources such as fish and poultry have preventive and therapeutic effects. Therefore, nutrition serves as a major route of prevention and treatment of NAFLD, and patients with NAFLD should have an individualized diet recommendation. In this review, the evidence linking macronutrients to NAFLD are discussed.



## 1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a metabolic stress-related liver disease defined as the hepatic accumulation of lipids, mainly triglyceride, in the absence of substantial alcohol consumption (< 20 g/day) or other secondary causes. It encompasses a spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), which increases the risk of cirrhosis and hepatocellular carcinoma. Currently, NAFLD is the main cause of chronic liver disease worldwide. Its prevalence is much higher in diabetic or obese individuals. Patients with NAFLD should be treated for steatohepatitis and the associated metabolic comorbidities, whereas patients with simple steatosis only need to treat the associated conditions to prevent hepatic and metabolic complications.[1,2]

As pharmacotherapy is not effective and safe enough, and obesity is intimately associated with hepatic steatosis, lifestyle modification is the first line of treatment. The usual steps for the management of NAFLD are gradual weight loss,

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adopting a healthy diet which has benefits beyond weight reduction, and increased physical activity. Several studies have demonstrated the beneficial impacts of dietary interventions in treating obesity, insulin resistance, and NAFLD and that specific macronutrients might benefit NAFLD independent of weight loss.[3–8] This review summarizes the evidence for the macronutrient effects including carbohydrates, lipids, and proteins in the management of patients with NAFLD.

## 2. Macronutrient effects on NAFLD carbohydrates

Carbohydrates (CHO) are the main source of body energy for both children and adults. Based on the level of polymerization, they are categorized as sugars (monosaccharides and disaccharides), oligosaccharides, and polysaccharides. Although studies have shown that several carbohydrates may be linked to NAFLD, the main focus has been on glycemic index, fructose, and fiber.[9]

Several studies suggest that CHO restriction can improve insulin resistance through reducing glycemic load and beta-cell insulin secretion.[10] Low-CHO diets could also reduce serum triglycerides, insulin, and glucose and increase high-density lipoprotein (HDL).[11] Concerning NAFLD, a recent cross-sectional study showed a positive correlation between aminotransferase levels (a surrogate measure of NAFLD at population level) and CHO intake after adjusting for age, body mass index (BMI), and energy intake.[12] In another report, a *post hoc* analysis showed that of 52 obese insulin-resistant patients subjected to a hypocaloric diet based on a low-CHO/high-fat diet (40% and 45% total calories per day, respectively) or a high-CHO/low-fat diet (60% and 25%, respectively), reduction of alanine transaminase (ALT) and serum insulin was significantly greater in the patients allocated to the low CHO diet.[13] Similarly, a randomized study of 22 obese patients comparing a low-CHO (< 50 g/day) versus a high-CHO (> 180 g/day) hypocaloric diet, showed a greater reduction of liver glucose production and hepatic steatosis at 48 hours in patients on the low-CHO diet. Nonetheless, the differences in liver steatosis were insignificant after achieving > 7% weight loss, irrespective of the CHO composition of the diet.[14] This data propose that in spite of an early weight-independent effect of low-CHO diets on liver steatosis and insulin resistance, this effect is surpassed by significant weight loss. Congruent with this, another randomized study of 170 obese or overweight patients comparing a hypocaloric low-CHO diet (> 1200 calories restriction per day, < 90 g CHO per day, and > 30% calories per day from fat) versus a hypocaloric low-fat diet (< 20% of total calorie intake), showed a similar reduction in weight (7.4%), fat mass, visceral adipose mass, insulin resistance, and liver fat after a 6-month follow-up.[15] Histology assessments were not provided by any of these studies. Therefore, although moderate CHO restriction seems to have no further effect on liver steatosis in patients with significant weight loss (≥ 7%), its impact on liver inflammation and fibrosis and its utility in patients without significant weight loss have not yet been elucidated.

Glycemic load is defined as the absolute amount of glucose in grams that is provided by the food group concerned. High-glycemic-load foods (including those rich in simple and complex carbohydrates, such as chocolates, candies, cookies, or potato, pasta, bread, and rice) increase postprandial glycemia and insulinemia, especially in patients with insulin resistance.[16] Glycemic index (GI) is defined as the proportion of food converted and absorbed as glucose, and it is expressed as a percentage. A recent meta-analysis of studies on dietary regimens based on GI, concluded that higher glucose and insulin exposure is associated with long-term complications, such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).[17,18] Likewise, a Cochrane meta-analysis of six trials with a follow-up time between 1 month and 6 months concluded that a diet based on low-GI products induces a significantly higher weight loss (−1.1 kg) and fat mass reduction.[19] In a cross-sectional analysis of 257 healthy individuals, Valtueña et al[20] demonstrated that there is an association between high-GI food intake and the presence of liver steatosis (assessed by ultrasound). However, longitudinal prospective studies are needed to explore the effects of such diets on NAFLD and hepatic inflammation.

During the past decades, fructose intake has considerably increased. It is mainly derived from sucrose (table sugar) and corn syrup which is abundantly used in sugar-sweetened beverages.[21] Fructose metabolism increases lipogenesis, free radical oxygen species production, gut permeability, bacterial overgrowth, and serum lipopolysaccharide levels. Furthermore, it reduces lipid oxidation.[9,22] In animal studies, some of these mechanisms have been suggested to play a role in NASH and insulin resistance pathogenesis.

Longitudinal epidemiologic data from an analysis of the Framingham study database ($n = 6039$) demonstrated that the consumption of one or more soft drinks per day increases risk of obesity and metabolic syndrome, including all of its components (impaired fasting glucose, high blood pressure, hypertriglyceridemia, and low HDL).[23] Additionally, a cross-sectional analysis of 427 patients with biopsy-proven NAFLD demonstrated that intake of seven or more sugar-sweetened drinks per week is associated with significantly higher fibrosis, inflammation, and hepatocyte ballooning after adjustment for age, sex, BMI, and total calorie intake.[24] Recently, a study of 47 overweight patients allocated to a daily intake of 1 L of sugar-sweetened soft drinks per day for 6 months showed a significant increase in liver fat (150%), muscle fat (200%), visceral adipose tissue fat (25%), serum triglycerides (32.7%), and cholesterol (11.4%).[25] It is important to note that whether this effect is specific for an excess intake of fructose or is only a consequence of calorie excess, is still under debate. Meta-analyses have not demonstrated significant effects of high fructose intake on weight,[26] and increased fasting triglycerides are only observed in normal individuals with a high intake of fructose.[27] A recent study of 55 healthy individuals who were allocated either to a high-fructose (1.5 g/kg/day, 3.0 g/kg/day, or 4.0 g/kg/day, $n = 7$, $n = 17$, and $n = 11$, respectively), high-glucose (3 g/kg/day, $n = 10$), or high-saturated fat diet (30% of total calorie intake, $n = 10$) showed a significant increase in liver steatosis [assessed by magnetic resonance spectroscopy (MRS))] only in patients exposed to 3 g/kg/day or more of fructose, and this was higher compared with the glucose group (60%, $p < 0.05$) and similar to the saturated-fat exposed groups (90%, $p =$ insignificant).[28] Although a direct role of fructose in human NAFLD pathogenesis remains to be