The Role of Carbohydrate Related Factors in Pathogenesis of Nonalcoholic Fatty Liver Disease: A Review

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ABSTRACT
Nonalcoholic fatty liver disease (NAFLD) is among the most common causes of chronic liver disease worldwide and its prevalence is increasing nowadays. This review article discusses the role of carbohydrate in NAFLD. We reviewed 57 papers out of which 48 randomized controlled trials and review articles with good quality were collected. The key words used for the search were: “Carbohydrate”, “Fructose”, “Weight”, “Low carbohydrate, ketogenic diet”, in combination with “NAFLD” for searching in “Pubmed”, “Science direct” and “Google Scholar” databases. We limited our search to studies published in English. The available data provided adequate scientific evidence which pointed toward the considerable potential effects between high intake of carbohydrates, fructose, high glycemic index foods and low dietary fiber and incidence of the NAFLD. This review provided sufficient evidence that higher consumption of carbohydrates and fructose sources may exacerbate NAFLD which leads to more accumulation of fat in the liver; while higher intake of fiber and low GI carbohydrate tends to ameliorate NAFLD.

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Introduction
Nonalcoholic fatty liver disease (NAFLD) is recognized as lipid accumulation through consuming less than 20 g ethanol/day and having no other known causes of chronic liver disease such as drugs consumption or exposure to the toxins (1). NAFLD is linked to the spectrum of hepatic diseases from simple steatosis, to inflammatory steatohepatitis (NASH, the most severe form of NAFLD) with developing fibrosis to cirrhosis and end-stage liver disease (2). Furthermore, this disease could emerge with variety of metabolic disorders such as insulin resistance, dyslipidemia, hypertension, hyperglycemia, and central obesity (3).

The prevalence of NAFLD is varying from 2.8% to 24% globally. It is about 10% in developing countries. In western general population, 20–30% prevalence has been reported. According to Iranian Ministry of Health, NAFLD is responsible for 1% of mortality in individuals older than 15 years. Normal
Carbohydrates in nonalcoholic fatty liver

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Complex interactions exist between lipid because of promoting insulin resistance (8, 9), (ii) Higher postprandial hyperglycemia increases associated with higher fat storage in hepatocytes, because of promoting insulin resistance (8, 9). Complex interactions exist between lipid accumulation (lipogenesis, lipolysis, and diet) and lipid disposal (lipoprotein secretion and fatty acid oxidation) which could affect the deposition of triglyceride in the liver. Elevated fatty acid synthesis causes more production of malonyl-CoA which is an inhibitory mediator in lipid oxidation process through carnitine palmitoyl transferase-1 (responsible for the long-chain fatty acids transportation into mitochondria where they undergo β-oxidations in liver) (10).

According to the studies, there is no approved medicinal therapy for treatment of NAFLD. Thus all clinical guidelines come to this point that weight loss together with lifestyle modifications are the first line therapies until now (3, 11). In this review we discuss about the scope of carbohydrate-related factors including amount of carbohydrate, fructose intake, glycemic index, dietary fiber, and low-carbohydrate ketogenic diets affecting NAFLD from biochemical aspect.

Carbohydrate and NAFLD

High dietary carbohydrate intake has been claimed to play an important role in the development of NAFLD. Indeed, several studies suggest that a diet with high amount of carbohydrates may be a major cause of NAFLD, increasing the probabilities of later signs of the disease (12). Both quantity and quality of carbohydrates could play an important role in pathogenesis of NAFLD (1). In 2004, Solga and colleagues. Reported that NAFLD patients consuming more than 54% of total energy from carbohydrates compared with those consuming less than 35% had a 6.5 fold increased risk of hepatic inflammation (13).

High-carbohydrate diets lead to NAFLD through following mechanisms (1): (i) Activation of carbohydrate response element binding protein (ChREBP), a glucose-activated transcription factor involved in the development of metabolic syndrome (9), (ii) Higher postprandial hyperglycemia increases the hepatic levels of phosphorylated intermediates which act as activators of ChREBP and induction of its target genes, (iii) Activation of the glycolysis, lipogenesis, and glucose 6-phosphatase catalytic subunit (G6PC) enzymes, which in turn results in insulin resistance (G6PC catalyses the final step in glucose production. Induction of this enzyme together with high glucose intake will present as hepatic glucose intolerance or insulin resistance) (5), and (iv) Increasing circulating insulin concentrations cause an increase in fasting triglyceride accumulation and inflammation (14, 15).

Fructose Intake and NAFLD

The influences of excess fructose consumption in the pathogenesis of NAFLD has recently received more attention from the researchers, but the mechanisms of this relationship has been only partly clarified (16). We will mention the pathways between fructose intake and risk of NAFLD through the following steps such as; susceptibility to the metabolic syndrome, copper deficiency, iron overload, impairment in liver enzymatic pathways, and altered fat deposition pathway.

Fructose and Susceptibility to the Metabolic Syndrome

Metabolic syndrome (MS), is a clustering of at least three of the five following medical conditions: central obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides and low high-density lipoprotein (HDL) levels (17). Central obesity is a key feature of the syndrome and often contributes to insulin resistance (18). In 2010, Sanchez-Lozada et al. showed that compared with control animals, fructose-fed rats presented early features of the MS (19). Tetri et al. reported the impaired insulin sensitivity and severe hepatic steatosis in mice fed high-fructose corn syrup (20). Therefore, excess fructose intake can play an important role in induction of many features of the metabolic syndrome such as to insulin resistance, hypertension and dyslipidemia which may in turn lead to NAFLD (16).

Fructose and Copper Deficiency

According to the evidences, it has been indicated that one of the probable reasons of copper deficiency in NAFLD, could be high intake of fructose in diet. Aigner et al. have reported that NAFLD patients present less hepatic copper levels than control subjects; hence, copper deficiency should be one of the considerations in treatment of NAFLD (16, 21). High fructose consumption may result in NAFLD due to induction of copper deficiency state as the
probable following mechanisms (22): (i) Reduction of copper absorption by interfering with the copper uptake protein1 (Ctr-1) (the intestinal epithelium mediator for copper absorption), (ii) Downregulating the expression of carnitine palmitoyltransferase I (CPT1) enzyme (the rate limiting enzyme of mitochondrial fatty acid β-oxidation), which in turn reduced mitochondrial fatty acid β-oxidation. Song et al. have been reported the significant reduction of CPT1 protein expression in the livers of marginal copper deficient rats fed with fructose (22), and (iii) Marginal copper deficiency together with high fructose consumption, restrained the hepatic antioxidant defense system and promote the lipid peroxidation, liver injury and fat infiltration, which result in an increased levels of liver enzymes such as aspartate transaminase (AST) and alanine transaminase (ALT) (22).

**Fructose and Iron Overload**

One study reported that borderline copper deficient rats fed with fructose showed remarkably elevated liver iron concentrations compared to the control group (22). Referring to the fenton reaction, in the presence of hydrogen peroxide, ferrous iron generate hydroxyl radical (23). Therefore, it could be assumed that fructose indirectly lead to increased levels of iron in the liver and then result in more production of reactive oxygen species (ROS) through the fenton reaction. Consequently, generated ROSs cause liver damage through lipid peroxidation and oxidative stress, which lead to hepatotoxicity and insulin resistance (24).

**Fructose and Impairment in Liver Enzymatic Pathways**

Long term fructose consumption may cause a metabolic burden on the liver through the induction of fructokinase and fatty acid synthase enzymes. Fructose is metabolized to fructose-1-phosphate by fructokinase, which uses the ATP in the liver (25). Therefore, this possibility exists that excess fructose intake along with higher liver metabolism can lead to high levels of liver metabolic stress via ATP reduction (16). Fatty acid synthase acts a pivotal role in catalysis the last step of the fatty acid biosynthetic pathway and is a key factor of the highest capacity of the liver to synthesis of fatty acids via de novo lipogenesis (26). In 2008, one clinical study demonstrated the liver upregulation of fatty acid synthase due to higher fructose intake in patients with NAFLD, suggesting that molecular imbalances relating to higher fructose intake could play a major roles in induction of NAFLD (27).

**Fructose and Altered Fat Deposition Pathway**

Several studies have been conducted to explicate the comparative importance of the types of visceral and subcutaneous fat mass as one of the main risk factors of NAFLD (16). In 2008, Eguchi et al. indicated that fat mass in visceral area in patients with advanced NASH was higher than that in patients with early NASH (28). Parallel with that, the outcomes of the studies about fructose consumption, showed that a high-fructose diet lead to dyslipidemia, reduced insulin sensitivity, and increased visceral adiposity (29, 30). One cross-sectional study reported that habits about drinking fructose sweetened beverages were associated with increased waist circumference, amount of visceral to subcutaneous abdominal adipose tissue and impaired abdominal fat deposition pattern (31).

**Glycemic index and NAFLD**

Consumption of high-glycemic index (high-GI) foods is linked to the risk of obesity, insulin resistance and higher LDL and total cholesterol concentrations. Immoderate intake of high-GI foods cause hepatic de novo lipogenesis due to rapid and extremely glucose accumulation which overcomes the liver glycogen synthesis capacity. According to the evidences, low glycemic index (low-GI) foods (GI<55); like oats; have potential to lowering the glucose and total cholesterol, and decrease liver fat contents. Thus, one of the consequential factors that should be consider during NAFLD patient’s dietary therapy is glycemic index of the foods. However, there is still no licensed human study investigating the effects of GI precisely in these patients up to now (32-34).

**Dietary Fiber and NAFLD**

All kinds of dietary fibers (insoluble and soluble), have been shown to have positive effects in prevention and control of diabetes with such mechanisms like; decreasing postprandial glucose response and ameliorate lipid parameters. There are just limited studies relating to the impacts of fiber on NAFLD. No randomized studies about the effects of fiber consumptions on NAFLD have been done in humans, and studies including dietary recall in human subjects have delivered contradictory results about the interconnection of fiber consumption and NAFLD (35-37).

One animal study, attempt to indicate the effects of viscous fibers on the development of fatty liver and fuel flexibility in a model of diet-induced obesity by feeding a high fat diet (60% energy from 

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fat) including 5% fiber as cellulose (as non-viscous) and one of two highly viscous fibers; hydroxypropyl methylcellulose (HPMC) or guar gum. After a period of 10 weeks feeding, the results showed that HPMC and guar groups had lower liver weight and liver cholesterol concentration in comparison with the cellulose group. Furthermore, reduced gluconeogenic enzyme’s gene expression in the liver such as phosphoenolpyruvate carboxykinase (PEPCK, the enzyme used in the metabolic pathway of gluconeogenesis and converts oxaloacetate into phosphoenolpyruvate and carbon dioxide) and G6Pase enzyme were also reported (38, 39).

**Low Carbohydrate Ketogenic Diets and NAFLD**

Weight loss is one of the most recommended pathways that frequently suggested to obese patients with hepatic steatosis, and is often reached through the restriction of total amount of daily calorie intake. In line with this, recent studies have indicated the important role of macronutrient content of the diet on liver healthy status (10, 40). In one study, Ryan *et al.* showed that after 16 weeks, insulin-resistant patients on a lower carbohydrate diet (40% carbohydrate, 45% fat) had lower serum ALT concentrations compared with patients on a higher carbohydrate diet (60% carbohydrate, 25% fat) (41).

Low-carbohydrate ketogenic diets typically contain no more than 20 grams of carbohydrate at the beginning of the diet (e.g., the Atkins diet), with a higher intake of protein and fat (42).

**Low-Carbohydrate Ketogenic Diet Typically Involves Three Phases (42).**

(A). The first phase is called “the induction phase”, the weight loss beginning phase and contains no more than 5% of energy from carbohydrate, 35% from protein, and 60% from fat, (B). The second phase, called “the ongoing phase”, a continuation phase of weight loss, with the distribution of carbohydrate (9%), protein (33%), and fat (58%), and (C). The third phase is “the maintenance phase”, in which carbohydrate intake increments to no more than 20% of total energy follow by 25% to 27% protein and approximately 52% of fat.

According to the evidences, low-carbohydrate diets in patients with obesity are associated with higher weight loss and insulin sensitivity as well as reduced intrahepatic triglyceride concentration (33, 43). Therefore, it could be concluded that decreasing dietary carbohydrate intake would be successful in reducing hepatic triglyceride concentration through the restriction of hepatic lipids accumulation (via lipogenesis) and also increasing lipid availability for excretion in liver (via mitochondrial β-oxidation) in NAFLD patients (10). One study investigate the impact of a low-carbohydrate ketogenic diet with the amount of less than 20 g carbohydrate/day on hepatic steatosis in NAFLD patients. After 6 months, according to the results of repeated liver biopsies, significant reduction in hepatic steatosis, inflammation and fibrosis, and also body weight loss of about 12.8 kg was seen in intervention group (44).

But, according to the evidences, in spite of the fact that low carbohydrate ketogenic diets have benefits in reduction of body weight, there are several concerns about higher fat content of these diets. It assumed that long-term maintenance on these diets may stimulates the development of NAFLD through inducing disorders such as; hepatic insulin resistance, systemic glucose intolerance and increased cardiovascular risk factors (40, 42, 45). In a 6 week trial study, twenty adults [Body Mass Index (BMI): 34.4±1.0] were randomized to the ketogenic low-carbohydrate (KLC) diet (60% of energy as fat, start with about 5% of energy as carbohydrate) and non-ketogenic low carbohydrate (NLC) diet (30% of energy as fat and about 40% of energy as carbohydrate). Results showed that KLC and NLC diets have equal effects in reducing body weight and insulin resistance, but the KLC diet lead the participants to the various harmful metabolic and emotional disorders (46).

Referring to the concerns about the high fat content of low carbohydrate ketogenic diets, some of the researchers believed that these diets should obtain protein and fat from foods other than red and processed meats (47). The results of two cohort studies through 26 years of follow up, revealed that an animal- based low-carbohydrate diet with animal sources of fat and protein have linked to the higher all-cause mortality in both genders; while a vegetable-based low-carbohydrate diet with vegetable sources of fat and protein was associated with lower all-cause and cardiovascular disease mortality rates (48).

**Conclusion**

Dietary management of NAFLD should be highly individualized based on nutritional status, dietary habits, and personal preferences. Higher consumption of carbohydrate and fructose sources may exacerbate NAFLD which leads to more accumulation of fat in the liver; while higher intake of fiber and low GI carbohydrate tends to ameliorate NAFLD. The relationship between low-carbohydrate ketogenic diets and NAFLD remains to be elucidated due to the antithesis results and existing concerns.
Conflict of Interest

None declared.

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