Nonalcoholic Fatty Liver Disease and Low-Carbohydrate Diets

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Key Words

metabolic syndrome, insulin resistance, weight loss

Abstract

Nonalcoholic fatty liver disease (NAFLD) is associated with insulin resistance, obesity, and other features of metabolic syndrome and is known to be the most common cause for abnormal liver enzymes. The recent surge in the number of patients with NAFLD has been accompanied by an increase in research on potential treatment options, particularly weight loss and dietary interventions. Given the growing interest on the role of carbohydrates in the prevention and treatment of NAFLD, this review discusses the relationship between the amount of carbohydrates in the diet and effects on NAFLD, with special emphasis on a low-carbohydrate diet. We discuss the role of insulin resistance in the pathophysiology of NAFLD and provide an overview of various popular diets and their role as a treatment option for NAFLD. Additional large, longer-duration trials studying the efficacy of a low-carbohydrate diet in the treatment and prevention of NAFLD are eagerly awaited.

Contents

INTRODUCTION: WHAT IS NONALCOHOLIC FATTY LIVER DISEASE?

Nonalcoholic fatty liver disease (NAFLD): accumulation of lipid in the liver in individuals who do not consume significant amounts of alcohol (<20 g ethanol/d) and in whom other known causes of steatosis, such as certain drugs, viruses, and toxins, have been excluded

Nonalcoholic fatty liver disease (NAFLD) is defined as accumulation of lipid in the liver in individuals who do not consume significant amounts of alcohol (<20 g ethanol/d) and in whom other known causes of steatosis, such as certain drugs, viruses, and toxins, have been excluded (45). Although a variety of terms have been used to describe this entity, including fatty liver hepatitis, nonalcoholic Laennecs's disease, diabetes hepatitis, alcohol-like liver disease, and nonalcoholic steatohepatitis, NAFLD has become the preferred term. The spectrum of NAFLD includes steatosis alone (type 1), steatosis plus inflammation (type 2), steatosis plus hepatocyte injury or ballooning degeneration (type 3), and steatosis plus sinusoidal fibrosis and/or Mallory bodies (type 4), (37, 44, 45). Nonalcoholic steatohepatitis (NASH) is considered to be the most severe form of NAFLD (types 3 and 4) and is associated with an array of adverse clinical outcomes, including cirrhosis, hepatocellular carcinoma, and advanced liver disease, which

leads to liver-related death (14, 17). NASH is now recognized as the underlying cause of most cases of cryptogenic cirrhosis (15, 54).

EPIDEMIOLOGY

Obesity, type 2 diabetes, hyperlipidemia, central obesity, and other conditions associated with insulin resistance are generally present in patients with NAFLD. Obesity is associated strongly with NAFLD and in cross-sectional studies is present in 25% to 93% of patients who have NAFLD (5, 18, 22, 39, 40, 43, 44, 55). In most case series of NAFLD, diabetes is present in 30% to 50% of patients (5, 18, 22, 39, 44, 55). Hyperlipidemia also is associated commonly with NAFLD, found in up to 92% of patients who have NAFLD (5, 18, 22, 24, 44, 55). In addition, NAFLD has been associated with several rare disorders of lipid metabolism and insulin resistance (e.g., abetalipoproteinemia, lipoatrophic diabetes, and Mauriac and Weber-Christian syndrome), as well as with total parenteral nutrition, acute starvation, intravenous glucose therapy, abdominal surgery (e.g., extensive small bowel resection, biliopancreatic diversion, and jejunal bypass), use of several drugs (e.g., amiodarone, tamoxifen, glucocorticoids, and synthetic estrogens), and exposure to several types of chemicals (e.g., organic solvents and dimethylformamide) (14, 37, 44, 45). For this reason, basal insulin levels, oral glucose tolerance test, and a lipid profile should be an integral part of the evaluation of NAFLD patients.

HOW COMMON IS NONALCOHOLIC FATTY LIVER DISEASE?

Nonalcoholic fatty liver disease is the most common cause of abnormal liver enzyme test results among adults in the United States (20). Data from the Third National Health and Nutrition Examination Survey (NHANES III) showed that as many as 23% of Americans have unexplained elevations in liver enzymes (21, 57). These persons are presumed to have NAFLD. Although fatty liver and NASH have been reported in all age groups, including children (7, 69), the prevalence increases with increasing body weight (1, 9). Fatty liver has been documented in up to 10% to 15% of normal-weight individuals and 70% to 80% of obese individuals. Correspondingly, about 3% of normal-weight individuals and 15% to 20% of morbidly obese subjects (body mass index >35 kg/m^2) have steatohepatitis (1, 75, 65). NAFLD is extremely common among patients who have undergone bariatric surgery, ranging from 84% to 96% (19). Taken together, these findings are of particular concern given the increasing prevalence of obesity in virtually all age groups. The highest prevalence of NAFLD currently is in the age group of 40 to 60 years (6, 55, 70). Approximately half of the patients with NASH develop liver fibrosis, 15% develop cirrhosis, and 3% may progress to liver failure or liver transplantation. Interestingly, patients who have undergone liver transplantation for end-stage liver disease secondary to NASH have frequent recurrence of steatosis and NASH even after transplantation (16).

Angulo and colleagues (4) have demonstrated that old age, obesity, and diabetes mellitus are independent predictors of liver fibrosis in patients with NASH. Although earlier studies found a higher prevalence of NASH in women (65% to 85% of all patients), more recent studies have shown that NASH occurs with equal frequency in both sexes (6, 41, 70). In the United States, there appear to be ethnic differences in the prevalence of NASH. A higher prevalence of hepatic steatosis was found in Hispanics (45%) compared with Caucasians (33%) or African Americans (24%) (13).

WHAT CAUSES NONALCOHOLIC FATTY LIVER DISEASE? THE TALE OF TWO HITS

The pathophysiology of NAFLD is not fully understood. One hypothesis, the "two-hit" model of the pathogenesis of NAFLD, is widely accepted.

NASH: nonalcoholic steatohepatitis

Insulin resistance: the reduced ability of cells to respond to insulin in transporting glucose from the bloodstream to muscle and other tissues. It develops in conjunction with obesity and often predates type II diabetes

Metabolic syndrome: a clustering of three or more risk factors for cardiovascular disease as identified by the National Cholesterol Education Program's Adult Treatment Panel III

First Hit

In the two-hit model, liver fat accumulation is the suggested first hit, or first step. It is a consequence of excessive triglyceride accumulation caused by imbalance between influx and synthesis of hepatic lipids on one side and their β-oxidation and export on the other (25).

The most widely supported theory implicates insulin resistance as the key mechanism in NAFLD, leading to hepatic steatosis and perhaps also to steatohepatitis. A recent study has demonstrated that insulin resistance is directly proportional to severity of steatosis (3). Alterations in lipid metabolism associated with insulin resistance result from the interaction between the effects of insulin resistance located primarily in muscles and adipose tissue and the impact of compensatory hyperinsulinemia on tissues that remain insulin sensitive. These alterations include enhanced peripheral lipolysis, increased hepatic uptake of free fatty acids (FFAs), and increased hepatic triglyceride synthesis. FFA influx and neogenesis exceed FFA oxidation and triglyceride secretion, resulting in the net effect of hepatic fat accumulation. The resulting accumulation of fat within the hepatocytes initiates further damage, causing hepatic insulin resistance and reactive oxygen species production. This can explain a key role of insulin resistance in the development of hepatic steatosis and, potentially, steatohepatitis (17, 38, 42, 48, 50, 59). Insulin stimulates lipogenic enzymes via sterol receptor binding protein 1-c (SREBP-1c) even in the insulin-resistant state (68).

Second Hit

NASH is thought to occur when the steatotic liver subsequently becomes vulnerable to presumed second hits, leading to hepatocyte injury, inflammation, and fibrosis. The presumed factors initiating second hits are oxidative stress and subsequent lipid peroxidation, proinflammatory cytokines (principally tumor necrosis factor-α), and hormones derived from adipose tissue (adipocytokines). This oxidative stress (23) may occur via increased mitochondrial beta-oxidation of the FFAs, production of reactive oxygen species, and depletion of antioxidants glutathione and vitamin E. This depletion of antioxidants hampers reactive oxygen species inactivation and increases the deleterious effects on the mitochondria. This combination of lipid peroxidation and cytokine production results in hepatocyte death.

Yang et al. (76) have demonstrated that obesity itself may cause progression to steatohepatitis by causing Kupffer cell dysfunction and sensitization of hepatocytes to endotoxin. This suggests that the progression of liver disease may depend on the extent of fatty infiltration. Iron, a strong oxidative agent, has also been proposed as a factor causing the second hit. Elevated serum ferritin levels and insulin resistance have been noted in patients with NASH, as well as increased prevalence of C282Y and H63D mutations in the HFE gene (10, 28).

Sanyal et al. (59) have proposed that another mechanism of development of NASH is a primary mitochondrial abnormality. This defect, otherwise clinically silent, leads to increased mitochondrial beta oxidation and production of reactive oxygen species in the presence of insulin resistance.

SHOULD NONALCOHOLIC FATTY LIVER DISEASE BE CONSIDERED PART OF THE METABOLIC SYNDROME?

There is increasing evidence that NAFLD represents a hepatic component of the metabolic syndrome, which includes central obesity, hyperglycemia, low HDL (high-density lipoprotein) cholesterol, hypertension, and hypertriglyceridemia (**Table 1**). Although overall obesity is clearly associated with NAFLD, body fat distribution, namely central obesity, appears to play an important role in the pathogenesis of NAFLD through its strong association with insulin resistance and possibly as a source of FFAs (36, 49). A recent study conducted by Marchesini and coworkers (43) involving 304 NAFLD patients without overt diabetes found that the prevalence of the metabolic syndrome

increased with increasing body mass index, from 18% in normal-weight subjects to 67% in those with obesity. In the same study, out of 163 patients (54%) biopsied, 120 patients (73.6%) were classified as having NASH; 88% of them had metabolic syndrome versus 53% of patients with pure fatty liver. The authors concluded that the presence of metabolic syndrome carried a high risk of NASH among NAFLD subjects after correction for sex, age, and body mass. The authors also found that there was significant association between metabolic syndrome, insulin resistance, and the degree of fibrosis. Several other studies (56) have confirmed the correlation between insulin resistance and the degree of steatosis (by ultrasonography) in patients without diabetes. With increases in steatosis and insulin resistance, clustering of the five clinical and biochemical ATPIII features of the metabolic syndrome was observed.

Table 1 Criteria for diagnosing metabolic syndrome (three or more risk factors required)[a]

Risk factor		Defining level
Abdominal obesity	Men	Waist circumference >102 cm
	Women	Waist circumference >88 cm
Triglycerides	–	≥150 mg/dl
HDL cholesterol	Men	<40 mg/dl
	Women	<50 mg/dl
Blood pressure	–	≥130/85 mm of Hg
Fasting blood glucose	–	≥110 mg/dl

[a]Adapted from the National Cholesterol Education Program's Adult Treatment Panel 111 criteria. HDL, high-density lipoprotein.

NONALCOHOLIC FATTY LIVER DISEASE AND INSULIN RESISTANCE IN THE ABSENCE OF METABOLIC SYNDROME RISK FACTORS

NAFLD is associated with central adiposity and with insulin resistance in overweight individuals lacking the other complications of metabolic syndrome. Overweight subjects with insulin resistance or central adiposity were at more risk of NAFLD than were those subjects with less insulin resistance or central adiposity (52). Some patients who have NAFLD and who did not present with any of the risk factors of metabolic syndrome described above have been shown in several studies to have insulin resistance when formal testing was done (18, 42, 50). In a controlled trial conducted by Marchesini et al. (42), 46 normal-weight patients with chronically elevated serum aminotransferase levels, "bright liver" (fatty liver) on ultrasound scan, and normal glucose tolerance were compared with 92 normal subjects who were matched for age and sex. The authors found that insulin resistance, fasting triglyceride level, and average insulin concentration in response to oral glucose were independently associated with the presence of NAFLD. This study result suggests that there is an association between NAFLD and insulin resistance that is independent of diabetes and obesity and supports the view that patients with NAFLD should be checked for insulin resistance even in the absence of other metabolic risk factors.

WEIGHT LOSS AS A TREATMENT FOR NONALCOHOLIC FATTY LIVER DISEASE: IS THAT ALL THERE IS?

At present, weight loss is the general recommendation of treatment for NAFLD. Moderate amounts of weight loss as well as exercise are associated with improvement in insulin sensitivity and, therefore, are logical treatment modalities for patients with NAFLD who are overweight or obese. Weight reduction may be achieved by caloric restriction from dieting, physical exercise, and/or pharmacotherapeutic agents (orlistat, sibutramine) as well as bariatric surgery in those patients with morbid obesity who are candidates. In recent trials with modest weight loss and less malnutrition, bariatric surgery reduced the fat, inflammation, and even the fibrosis in well-documented NASH (63). However, rapid weight loss has been associated with improvement in hepatic steatosis, but deterioration of inflammation and fibrosis (2). In a study by Wang et al. (73), 76 obese children were

divided into three groups: an untreated control group, a weight loss/exercise group, or an oral vitamin E therapy group. Results showed that lifestyle had the most positive effect on NAFLD. Reducing weight by at least 5% with subsequent weight control and exercising regularly may be beneficial in treating NAFLD. Exercise is of great value as it reduces weight by preferentially decreasing visceral obesity while preventing the loss of muscle mass. It also enhances muscle insulin sensitivity even in the absence of weight loss (29). Prediabetics and diabetics experience better glucose control with exercise due to improvement in insulin sensitivity. Thus, exercise coupled with behavior modification is imperative for any weight-loss program to ensure adherence and long-term compliance.

DOES THE GLYCEMIC INDEX PLAY A ROLE IN NONALCOHOLIC FATTY LIVER DISEASE?

Not only the percentage of carbohydrate (CHO) in the diet but also the glycemic index of the carbohydrates in the diet should be reviewed. Scribner et al. (60) studied whether a diet high in rapidly absorbed CHO versus slowly absorbed CHO caused NAFLD in mice controlled for dietary factors and with similar body weight. Triacylglyerol and body adiposity increased twice as much in the rapidly absorbed CHO group. Plasma insulin and triacyglycerol concentration were higher in the rapidly absorbed carbohydrate group as well.

WHAT ARE THE EFFECTS OF LOW-CARBOHYDRATE DIETS (∼<40%) ON NONALCOHOLIC FATTY LIVER DISEASE?

For more than a century, low-carbohydrate diets have been in and out of fashion, and each time they return, it is with the promise of quick and easy weight loss. There is no clear consensus on the percentage of calories from carbohydrate that would constitute a low-, moderate-, or high-carbohydrate diet. In the current review, low-carbohydrate diet is taken to be ∼<40% calories from carbohydrate, moderate-carbohydrate diet is ∼40%–50% calories from carbohydrate, and high-carbohydrate diet is ∼50%–65% calories from carbohydrate.

The first low-carbohydrate diet to have enjoyed popular success was that described by William Banting in the 1860s (8). On this diet, Banting claimed that he was never hungry, and at the age of 66, in a period of a year, lost 46 of his initial 202 pounds. He wrote, "The great charms and comfort of the system are that its effects are palpable within a week of trial and create a natural stimulus to persevere for a few weeks more" (8). Advocates of low-carbohydrate diets claim that diets higher in protein and lower in carbohydrates promote the metabolism of adipose tissue in the absence of available dietary carbohydrate and result in rapid weight loss.

Low-carbohydrate diets have recently resurged in popularity as a means of rapid weight loss and improvement in insulin resistance along with other parameters of metabolic syndrome, potentially offering a treatment option for NAFLD. A recent systematic review by Bravata et al. (11) that included 107 studies concluded that participant weight loss while using low-carbohydrate diets was principally associated with decreased caloric intake and increased diet duration, but not with reduced carbohydrate content. On the contrary, a quasi-randomized controlled study by Fraser et al. (27) found that alanine aminotransferase levels significantly decreased in a group on a low-carbohydrate/low-glycemic-index diet (35%) in comparison to groups on high-carbohydrate and high-carbohydrate/low-glycemic-index diets. Because clinical trials studying the effects of a low-carbohydrate diet on NAFLD are lacking, we discuss the effects of a low-carbohydrate diet on body weight and metabolic syndrome, which are strongly associated with NAFLD.

EFFECTS OF HYPOCALORIC LOW-CARBOHYDRATE DIETS AND WEIGHT LOSS ON NONALCOHOLIC FATTY LIVER DISEASE

Given the intense interest in the possible benefits of low-carbohydrate diets in recent years, it is worth reviewing the findings of recent clinical trials that compared the short-term effects of hypocaloric low-carbohydrate diets with conventional (high-carbohydrate/low-fat) diets on weight loss and metabolic syndrome risk factors with implications for NAFLD.

Foster et al. (26) conducted a one-year randomized, controlled trial involving 63 nondiabetic obese men and women assigned to either a low-carbohydrate (20 g per day, then gradually increased), high-protein, high-fat diet or a low-calorie, high-carbohydrate, conventional (low-fat) diet. At the end of one year, the authors concluded that subjects on the low-carbohydrate diet had significantly more weight loss than had subjects on the conventional diet at both 3 months and 6 months, but there was no difference at 12 months. The authors suggested that the lack of statistically significant difference between the groups at one year was due to greater weight regain in the low-carbohydrate group and to the small sample size. The authors also found that subjects on the low-carbohydrate diet had a favorable outcome on lipid profile (increase in HDL and decrease in triglycerides) when compared to those on the conventional diet throughout most of the study. Similar results were produced in a randomized study conducted by Stern et al. (67), which reported the one-year comparison of weight loss and metabolic changes in 132 obese adults assigned to either a low-carbohydrate diet (<30 g per day) or a conventional (high-carbohydrate/low-fat) weight-loss diet. At one year, no significant difference in weight loss was observed between the two groups. However, for persons on the low-carbohydrate diet, decreases in triglyceride levels and increases in high-density lipoprotein cholesterol levels were observed. This study was limited by a high dropout rate (34%) and by suboptimal dietary adherence of the enrolled persons. The results of the above studies were further confirmed by Yancy and colleagues (75) in a randomized study that included 120 overweight, healthy hyperlipidemic patients assigned to either a low-carbohydrate diet with nutritional supplementation or a low-fat, energy-restricted diet. The study reported greater weight loss, and improvements in triglyceride and HDL cholesterol levels, in the subjects on the low-carbohydrate diet at six months.

In summary, the results of the randomized trials discussed above have shown that subjects on hypocaloric low-carbohydrate diets have statistically significant weight loss over the short term (six months) in comparison to those on the conventional diet. However, there was no significant difference at one year. The lack of statistically significant difference in the long term and high dropout rates suggest that long-term adherence to low-carbohydrate diets may be difficult and leads to reaccumulation of metabolic risk factors, insulin resistance, and NAFLD. It should be mentioned that subjects on the low-carbohydrate diets also had significant improvement in biochemical parameters of metabolic syndrome in comparison to those on the conventional (high-carbohydrate/low-fat) diet.

UNRESTRICTED CALORIE LOW-CARBOHYDRATE DIETS, WEIGHT LOSS, AND NONALCOHOLIC FATTY LIVER DISEASE

In contrast to hypocaloric low-carbohydrate diets, low-carbohydrate diets without restriction on total calorie intake have equally proven to be an effective tool to short-term weight loss. In a six-month uncontrolled study conducted by Westman et al. (74), 51 overweight or obese healthy volunteers were placed on a very-low-carbohydrate diet (<25 g/d), with no limit on caloric intake, and received recommendations about exercise. At the end of study, the authors

concluded that statistically significant differences were seen with weight loss along with all parameters of lipid panel (decrease in total cholesterol, low-density lipoprotein, triglyceride, and increase in HDL). However, this study was confounded by a simultaneous exercise regimen that could have affected the observed weight loss. Similar results were produced in a six-month trial carried out by Brehm and colleagues (12) involving 53 healthy, obese women randomized to either an ad libitum very-low-carbohydrate diet (initially 20 g/day and then gradually increased to 40–60 g/day) or an energy-restricted high-carbohydrate diet with 30% of the energy as fat. At the end of this study, the very-low-carbohydrate group had lost significantly more weight and more body fat than did the high-CHO, low-fat-diet group. There were no significant differences between the groups in blood pressure, lipid, fasting glucose, and insulin levels. However, these studies were limited by the small sample size and short duration. Further trials studying the long-term efficacy, long-term compliance, and safety of ad libitum low-carbohydrate diets are needed.

LOW-CARBOHYDRATE DIETS AND THEIR EFFECTS ON METABOLIC SYNDROME

As in the case of weight loss, several other studies have exclusively examined the effects of low-carbohydrate diets on central obesity and other biochemical parameters of metabolic syndrome. In a six-week controlled study conducted by Sharman et al. (64), 12 healthy men switched from their habitual diet (17% protein, 47% carbohydrate, and 32% fat) to a ketogenic diet (30% protein, 8% carbohydrate, and 61% fat) and 8 control subjects consumed their habitual diet. At the end of the study, significant decreases in fasting serum triacylglycerol and fasting serum insulin concentrations along with increases in HDL cholesterol were found in men who consumed the ketogenic diet. There were no significant changes in blood lipids in the control group. Similar results were produced in an uncontrolled study conducted by Hulley et al. (34) involving 13 nonobese men with hypertriglyceridæmia who were followed monthly during a year of dietary treatment where carbohydrate intake was low (30% of total calories), cholesterol intake was low (259 mg daily), total fat intake was high (50% of calories), and the polyunsaturated/saturated ratio was high (3:2). At the conclusion of the study, the modified diet caused significant reductions in the mean levels of triglyceride, cholesterol, pre-β-lipoprotein, and β-lipoprotein. Weight fell significantly (by 2 kg) despite attempts to prevent this, but the triglyceride response appeared to be unrelated to the weight loss.

Accumulation of intra-abdominal fat has also been positively correlated with liver fat (35, 49) and hepatic insulin resistance in both men and women (47). Volek et al. (72) conducted a randomized study with 28 overweight/obese healthy volunteers comparing the effects of an isocaloric, energy-restricted very-low-carbohydrate ketogenic (VLCK) diet and high-carbohydrate (carbohydrate:fat:protein = 60:25:15) diets on weight loss, body composition, trunk fat mass, and resting energy expenditure. This study showed greater weight loss and fat loss preferentially from the trunk region in subjects on a VLCK diet compared to a high-carbohydrate diet. The superiority of the VLCK diet over the high-carbohydrate/low-fat diet was most dramatic for men. However, when individual responses were examined, a group of women clearly showed metabolic advantage as well. Since accumulation of fat in the abdominal area is associated with insulin resistance, diabetes, and dyslipidemias, all features of metabolic syndrome, the VLCK diet might very well help with improvement in fatty liver as well. However, again, long-term adherence to the VLCK diet seems impractical (26, 67).

In summary, the results of the all the studies discussed above indicate that low- and very-low-carbohydrate diets are associated with weight loss in the short term. However, even under similar weight loss conditions, diets that are lower in carbohydrate and relatively higher in fat have greater benefits on insulin sensitivity, triacylglycerol, and HDL cholesterol

concentrations than do similarly hypocaloric, low-fat diets (46). Several other studies (26, 30, 34, 64, 67, 72, 74, 75) on low-carbohydrate diets mentioned above have shown improvement in biochemical parameters of metabolic syndrome, central obesity, and insulin sensitivity in the short term. The studies discussed above are limited by their small sample sizes and short durations. Also, the cardiovascular and renal health effects of relatively higher intake of fat and protein in low-carbohydrate diets is of concern. Direct studies comparing the effects of low-carbohydrate diet on NAFLD are lacking. Large randomized trials studying the efficacy and safety of low-carbohydrate diets in the long term are eagerly awaited.

EFFECTS OF MODERATE-CARBOHYDRATE (~40%–50%) DIETS ON NONALCOHOLIC FATTY LIVER DISEASE

Because long-term adherence to a low-carbohydrate diet seems unreasonable, studies on moderate restriction of carbohydrate have been conducted and have shown similar benefits on weight loss. Moderate-carbohydrate diets have also been shown to improve liver enzymes in populations at high risk for NAFLD as well as liver histology in patients with established NAFLD. Golay et al. (31) conducted a study involving 68 patients assigned to one of two groups that received either a 25% carbohydrate (n = 31) or a 45% carbohydrate (n = 37) hypocaloric diet (1200 kcal/d) and were followed for 12 weeks. At the conclusion of the study, the mean weight loss and loss of adipose tissue did not differ significantly between the two groups. Furthermore, waist/hip ratio, glucose/insulin ratio, and fasting blood glucose along with cholesterol and triglyceride concentrations diminished significantly and identically in both groups. The fasting blood insulin decreased more markedly with the 25% CHO diet compared to the 45% CHO diet. The authors concluded that neither diet offered a significant advantage when comparing weight loss or other metabolic parameters over a 12-week period. The results of this study indirectly indicate that moderate carbohydrate restriction might be a favorable option for patients with NAFLD, is more palatable, and produces results similar to those of the low-CHO diet. A six-week study conducted by Golay et al. (30) involved 43 obese adults randomly assigned to receive diets containing 1000 kcal/d composed of either 32% protein, 15% carbohydrate, and 53% fat, or 29% protein, 45% carbohydrate, and 26% fat. The results showed no significant difference in weight loss in response to diets containing either 15% or 45% carbohydrate. These findings showed that energy intake—not nutrient composition—determined weight loss in response to low-energy diets over a short period. Furthermore, fasting plasma glucose, insulin, cholesterol, and triglyceride concentrations decreased significantly in patients eating low-energy diets that contained 15% carbohydrate, but neither plasma insulin nor triglyceride concentrations fell significantly in response to the higher-carbohydrate diet.

The effects of moderate carbohydrate restriction on liver enzymes was studied by Ryan et al. (58) in a 16-week randomized trial in which 52 obese subjects were assigned to hypocaloric diets containing either 60% carbohydrate/25% fat or 40% carbohydrate/45% fat (15% protein). At the conclusion of the study, the 40% carbohydrate diet resulted in a greater decrease in steady-state plasma glucose, circulating insulin, and alanine aminotransferase (ALT) concentrations. ALT changes correlated with improvement in insulin sensitivity and daylong insulin. Given that NAFLD is the most common cause of elevated liver enzymes in high-risk (obese) populations, the decreases in ALT levels observed in this study indirectly indicate that moderate carbohydrate restriction might be a reasonable option for NAFLD patients. Moderate restriction of carbohydrates has also shown to improve liver histology in a recent pilot study conducted by Huang et al. (33) in which 23 patients with biopsy-proven NASH showed stable or histological improvement when they were put on a diet with 40%–45% carbohydrate, 35%–40%

fat, and 15%–20% protein. Compared to those with stable NASH scores, patients with histologic responses had significantly greater decreases in body weight, body mass index, waist circumference, aspartate aminotransferase, and ALT values. There was no patient with histological worsening.

Based on the results of the above studies, we can hypothesize that moderate restriction of carbohydrate is a reasonable option for patients with NAFLD because of the similar benefits in weight loss and improvement in parameters of metabolic syndrome seen with low-carbohydrate diets. Also, long-term adherence with moderate carbohydrate restriction is presumably better. However, with the exception of the Huang et al. study (33) discussed above, the studies have indirectly shown benefits (weight loss, improvement in features of metabolic syndrome, and decreased ALT levels) from moderate carbohydrate restriction in NAFLD patients. Very few studies (33) have shown direct benefits of moderate carbohydrate restriction on NAFLD because liver biopsy, which is the gold standard to diagnose NAFLD, was not performed. Nonetheless, long-term effects of moderate carbohydrate restriction need to be fully investigated. Examples of moderate-carbohydrate diets are the American Diabetic Association diet, the Mediterranean diet, and the Zone diet (53, 61). In particular, the Mediterranean diet has been shown to have a beneficial effect in the development of metabolic syndrome and its components (62, 78).

EFFECTS OF HIGH-CARBOHYDRATE DIETS (~50%–65%) ON NONALCOHOLIC FATTY LIVER DISEASE

A few studies have demonstrated worsening of benign fatty liver to NASH when patients were on a conventional high-carbohydrate diet such as the 2003 American Diabetic Association Diet, which once recommended a 50%- to 65%-CHO diet. In addition, the high-carbohydrate diet recommended for the U.S. population is associated with increased insulin resistance and obesity (32). Solga et al. (66) conducted a retrospective study using a standardized 24-hour food recall with 74 morbidly obese patients presenting for bariatric surgery. Food intake was evaluated for total calories and macronutrients and compared with liver histopathology from biopsies routinely obtained during surgery. The authors concluded that higher carbohydrate intake was significantly associated with higher odds of inflammation in contrast to higher fat intake, which was associated with lower odds of inflammation.

Kang et al. (35) conducted a retrospective study of 91 patients with histologically confirmed NAFLD. A food-frequency questionnaire was sent by mail, and results showed that the NAFLD patients with metabolic syndrome consumed more carbohydrate, less fat, and the same amount of calories (1800 calories) and protein (51% carbohydrate, 34% fat, 15% protein) in comparison with those NAFLD patients without metabolic syndrome, who consumed 45% carbohydrate, 40% fat, and 15% protein. Patients with metabolic syndrome also had significantly higher scores for steatosis, NASH activity, and NASH. Toshimitsu et al. (71) analyzed the dietary habits and nutrient intake in patients with NASH and found an excess intake of carbohydrate in patients with NASH compared with patients who had fatty liver. Also, the intake of simple carbohydrates was higher in those patients with NASH. In another study, Zelber-Sagi et al. (77) gave food-frequency questionnaires to 375 people. The results showed that the NAFLD group consumed twice the amount of soft drinks and 27% more meat in comparison with the group with normal liver.

CONCLUSIONS

Weight loss remains the current recommendation for treatment of NAFLD. It can be achieved through exercise and dietary modification. Several studies mentioned above

have shown similar weight loss results with hypocaloric diets varying in macronutrient composition or carbohydrate content. Also, studies on low- and very-low-carbohydrate diets without total calorie restriction have equally proven to be effective in short-term weight loss. Other clinical trials have demonstrated that moderate to severe restriction of carbohydrates resulted in improvement in liver histology, insulin resistance, and other parameters of metabolic syndrome, which are strongly associated with NAFLD.

Although the studies discussed above mark the beginning of meaningful research on low-carbohydrate diets, they have serious limitations, including small sample sizes, short durations, lack of clear consensus on low-carbohydrate diet, high dropout rates, poor or unknown compliance levels, and reliance on self-reported data. Furthermore, they do not provide information on the long-term health effects of low-carbohydrate diets, especially in the face of the relative increase in fat and protein intake, which exacerbates cardiovascular and renal risks, respectively. Also, the long-term effects of repeated use of nutritionally inadequate diets and others that fall far outside the dietary guidelines need to be determined. At present, dietary modification (moderate restriction of carbohydrates and emphasis on high fiber and monounsaturated fatty acids) along with regular exercise and cognitive behavioral therapy to reinforce adherence seems to be a reasonable option for patients with NAFLD. Nonetheless, there is an urgent need for large, longer-duration randomized clinical trials comparing the effects of low-, moderate-, and high-carbohydrate diets on metabolic syndrome, insulin resistance, weight loss, and NAFLD.

SUMMARY POINTS

1. Nonalcoholic fatty liver disease (NAFLD) is associated with insulin resistance, obesity, and other risk factors of the metabolic syndrome.
2. Weight loss is presently the primary treatment for NAFLD.
3. Subjects on low-carbohydrate diets (less than 40% of total calories) had a statistically significant weight loss in the short term when compared to the conventional high-carbohydrate diet, but at one year, no difference in weight loss existed. Adherence to low-carbohydrate diets may be difficult.
4. Subjects on low-carbohydrate diets showed improvement in biochemical parameters of metabolic syndrome in comparison with those on high-carbohydrate diets.
5. Improvement in liver enzymes and liver histology was demonstrated in patients on moderate-carbohydrate diets (approximately 40%–50% total calories).
6. A decrease in metabolic risk factors and ALT concentrations was seen in patients following a moderate-carbohydrate versus a high-carbohydrate diet (approximately 40%–50% total calories).
7. Benefits in weight loss and improvement in metabolic syndrome parameters were seen in both low-carbohydrate and moderate-carbohydrate diets.
8. Some studies showed worsening of fatty liver to NASH in patients who followed a high-carbohydrate diet. More long-term, randomized, clinically controlled studies would be helpful in deciphering the proper carbohydrate percentage in a weight-loss diet for NAFLD patients.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

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Errata

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