



Non-alcoholic fatty liver disease and the metabolic syndrome: Effects of weight loss and a review of popular diets. Are low carbohydrate diets the answer?

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Abstract

Non-alcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of fat-induced liver injury, ranging from relatively benign steatosis to cirrhosis and liver failure. The presence of obesity and insulin resistance is strongly associated with non-alcoholic fatty liver and confers on it a greater risk of histologically advanced disease. There is a growing concern in the medical profession as the prevalence of this disease continues to rise in parallel with the rise in obesity and the metabolic syndrome. Treatment options are limited and dietary weight loss is often advised. Low fat diets are difficult to adhere to and recent studies have shown the potential of low carbohydrate diets for weight loss and improving insulin resistance. Thus far, no study has evaluated the effect of low carbohydrate diets on NAFLD. Future studies will be required to address this question and others with regards to the nutritional adequacy and long-term side effects of these diets.

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Key words: Non-alcoholic fatty liver disease; Obesity; Metabolic syndrome; Diet management

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INTRODUCTION

In the 1970s, patients undergoing jejunoileal bypass surgery

for morbid obesity were noted to develop steatohepatitis and even liver failure following rapid weight loss^[1]. Their liver histology was similar to that seen in alcoholics, with macrovesicular steatosis, Mallory hyaline, focal hepatocyte necrosis, mixed lobular inflammation and fibrosis^[2]. Similar findings were later described in obese patients without significant alcohol consumption. In 1980, Ludwig *et al*^[3] coined the term 'non-alcoholic steatohepatitis' (NASH) to describe these findings. Since then, interest in the disease has grown exponentially in keeping with its rising prevalence. NASH was initially thought to be a benign condition largely limited to middle-aged obese women with diabetes. However, recent studies have shown it to be a far more complex disease that is found in men, women and even children. The spectrum of disease ranges from pure steatosis alone to NASH with hepatic fibrosis, cirrhosis, hepatocellular carcinoma, liver failure and even death^[4-6]. Estimates suggest that 20-30% of adults in Western countries may have NAFLD and about 10% of these individuals meet criteria for diagnosis of NASH^[7]. NAFLD is now recognized as the most common cause of chronically elevated liver transaminases^[8,9] and may be the most common liver disorder^[10]. Obesity is the single most common condition found in association with NAFLD. Other features of the metabolic syndrome, such as hyperinsulinemia, hypertriglyceridemia and hypertension, also play a significant pathophysiologic role in its development.

In general, NAFLD in the absence of NASH is an indolent disease with a benign course. However, as noted, end stage liver disease may occur as a consequence of NASH. The seriousness of this condition is demonstrated by the fact that approximately 50% of patients develop fibrosis, 15% develop cirrhosis and 3% may advance to liver failure requiring transplantation^[11]. NASH is now being recognized as the underlying cause of most cases of cryptogenic cirrhosis^[12,13]. The natural history of NAFLD is poorly understood, and it is not known why some patients progress to cirrhosis, while others do not. However, obesity and insulin resistance have been shown to be associated with more histological advanced disease.

The aim of this article is to review the role of the metabolic syndrome, especially insulin resistance and obesity in the development of NAFLD, to discuss the effect of weight loss on NAFLD and, finally, to evaluate popular diets and compare them with regard to their effects on the metabolic syndrome and NAFLD.

NASH AND METABOLIC SYNDROME

Fatty liver is commonly associated with obesity and insulin resistance. The increasing incidence of NAFLD closely parallels these conditions. There is abundant data showing a relationship between obesity and NAFLD. Wanless *et al*^[14] in an autopsy study of 351 patients found that 70% of obese patients had liver steatosis, and the degree of steatosis was proportional to the degree of obesity. The authors also found steatohepatitis in 18.5% and severe fibrosis in 13.8% of markedly obese patients, compared to steatohepatitis in 2.7% and severe fibrosis in 6.6% of lean people. A prospective study performed by Klain *et al*^[15] evaluated liver biopsies from 100 consecutive morbidly obese patients undergoing Roux-en-Y gastric bypass. Histological abnormalities were found in 98% of biopsies, and ranged from mild fatty infiltration through inflammatory change to fibrosis and cirrhosis^[15]. Data from 90 patients with NASH demonstrated insulin resistance in 85% of them^[16]. An Italian study evaluated the risk factors associated with hepatic steatosis. A total of 257 participants were assigned to one of four categories: Controls, teetotalers with normal body mass index (BMI); obese teetotalers; heavy drinkers (> 60 g of alcohol per day) with normal BMI; and heavy drinkers with obesity. The prevalence of steatosis on ultrasound increased from 16% in controls to 46% in heavy drinkers, 76% in obese individuals and 95% in patients with both obesity and heavy alcohol intake. Compared with controls, steatosis was more common by 2.8-fold in heavy drinkers, 4.6-fold in obese persons and 5.8 fold in obese heavy drinkers. In heavy drinkers, obesity increased the risk of steatosis 2.0-fold, while heavy drinking was associated with only a 1.0-fold increased risk in obese subjects^[17]. The authors concluded that steatosis was more strongly associated with obesity than with heavy drinking.

Evidence of an etiologic association between NAFLD and metabolic syndrome (hyperglycemia, central obesity, hypertension, hypertriglyceridemia and low HDL-cholesterol) has been shown in both obese and non-obese patients^[18]. Studies also have shown that patients with NASH are more insulin resistant than patients with fatty liver alone^[19]. Given the wealth of data supporting it, many researchers now consider NAFLD to be a hepatic manifestation of the metabolic syndrome, instead of a primary liver disease^[20,21]. Chitturi *et al*^[22] tested the hypothesis that insulin resistance is an essential requirement for the development of NASH, and that a high association between insulin resistance and liver disease is relatively specific for NASH. Sixty-six patients with NASH were studied. Insulin resistance was found in virtually all patients (98%) and was seen in both lean and overweight patients. A subset of 36 patients with less severe NASH were compared to 36 age- and sex-matched patients with chronic hepatitis C. The prevalence of insulin resistance was significantly higher in those with NASH than in comparable cases of HCV (75% *vs* 8.3%)^[22]. Marchesini *et al*^[19] studied liver biopsies in patients with NAFLD. Based on histology, these were classified as having NASH *vs* pure fatty liver. The investigators found that 88% of patients with NASH had metabolic syndrome

compared with 53% in patients with pure fatty liver^[19]. Marceau *et al*^[23] investigated the relationship between liver pathology and the metabolic syndrome. Five hundred fifty one severely obese patients undergoing anti-obesity surgery were studied. Steatosis was found in 86%, fibrosis in 74%, steatohepatitis in 24% and unexpected cirrhosis in 2%. With each addition of the components of metabolic syndrome, the risk of steatosis increased exponentially from 1- to 99-fold^[23]. In a series of 505 severely obese patients evaluated before gastropasty, prevalence of steatosis was significantly higher in patients with impaired glucose tolerance or type II diabetes as compared with non-diabetics. The severity of steatosis was positively correlated with BMI, fasting plasma glucose, insulin and triglyceride concentrations, as well as serum ALT, AST and GGT levels^[24].

Issues regarding the nature of hyperinsulinemia in NASH have been raised. It has been questioned as to whether hyperinsulinemia and insulin resistance occur as part of the metabolic syndrome or whether liver damage itself leads to chronic hyperinsulinemia and insulin resistance from impaired insulin degradation, as is seen in cirrhosis. Chitturi *et al*^[22] compared the patients with NASH and mild or absent fibrosis with age- and sex-matched patients with HCV, and found that the patients with NASH showed more attributes of insulin resistance than the controls. They had much higher levels of insulin resistance, serum insulin and C-peptide levels. However, the serum C-peptide/insulin ratio was similar in both groups^[22]. Pagano *et al*^[25] addressed the same question, comparing 19 patients with histologically mild NASH, who had functionally competent livers with 19 normal subjects. Patients with NASH showed marked hyperinsulinemia and insulin resistance as compared with controls, however, the hepatic insulin extraction was similar in both groups^[25]. These two studies showed that insulin hypersecretion, and not just impaired insulin degradation, was the basis for hyperinsulinemia in NASH.

The overall incidence of NASH in the severely obese is reported to range from 25-36.4%^[26-28]. The prevalence of obesity in the Western world has shown a large increase in the last 20 years. The data of the National Health and Nutrition Examination Survey (NHANES II, 1976-1980) showed a prevalence of 14.5%. By NHANES III (1988-1994), this number had increased to 22.5%, and the data of NHANES 1999-2000 showed a prevalence of 30.5%^[29]. Significantly, this number could reach 40% by the year 2025^[30]. A similar increase in the number of patients with type 2 diabetes is expected. By some estimates, 29 million people or 7.2% of the population will have type 2 diabetes by the year 2050^[31]. Of grave concern is the increasing incidence of obesity in children and adolescents. Given these statistics, the incidence of NASH will rise significantly in the coming years and so will hepatic complications arising from it.

Factors responsible for the development of NAFLD in obese patients are not clear, and the exact mechanism of its progression to fibrosis and cirrhosis has yet to be elucidated. However, our understanding of disease pathogenesis has advanced significantly. Insulin resistance is thought to be a primary pathophysiologic mechanism

in development of fatty liver. Current understanding of the pathogenesis is as follows: Insulin resistance and visceral obesity lead to a hepatic influx of free fatty acids, resulting in increased triglyceride synthesis and decreased triglyceride export. This leads to hepatic steatosis. At this stage, patients have the relatively benign condition of NAFLD. Some of these patients will go on to steatohepatitis. It is unclear why only a small fraction will advance to NASH and what is the exact impetus for this advance. One proposal is that these lipid-laden hepatocytes are susceptible to a “second-hit”^[32]. The exact mechanism of this second-hit is unknown. In NASH, as in alcoholic hepatitis, oxidative stress and lipid peroxidation have emerged as the most likely candidates. This “hit” occurs via increased mitochondrial beta-oxidation of the free fatty acids, production of reactive oxygen species and depletion of antioxidants glutathione and vitamin E. This depletion of anti-oxidants hampers reactive oxygen species inactivation, and increases the deleterious effects on the mitochondria. Oxidative stress also results in abnormal cytokine production, especially TNF- α through up-regulation of nuclear translocation of transcription factor nuclear factor κ B. This combination of lipid peroxidation and cytokine production results in hepatocyte death.

Another proposed mechanism of development of NASH includes a primary mitochondrial abnormality, as proposed by Sanyal *et al.*^[33]. This defect, otherwise clinically silent, leads to increased mitochondrial beta oxidation and production of reactive oxygen species in the presence of insulin resistance.

Yang *et al.*^[34] have demonstrated that obesity itself may cause progression to steatohepatitis by causing Kupffer cell dysfunction and sensitizing the hepatocytes to endotoxin, suggesting that the progression of liver disease may depend on the extent of fatty infiltration^[34].

Iron, a strong oxidative agent, has also been proposed as a factor causing the second-hit. Elevated serum ferritin and insulin resistance on those levels have been noted in patients with NASH, as well as increased prevalence of C282Y and H63D mutations in the HFE gene^[35,36]. However, evidence that hepatic insulin resistance plays a significant role in fibrosis was found in only one study, and recent studies suggested that increased ferritin levels were likely markers of severe histologic damage and not iron overload^[37]. Leptin production by activated hepatic stellate cells has also been considered an important factor in the progression of fatty liver disease and development of fibrosis^[38]. Supporting evidence is furnished by genetically leptin-deficient ob/ob mice, which do not develop fibrosis even when fed a methionine-choline-deficient diet.

OBESITY AND INSULIN RESISTANCE AS PREDICTORS OF FIBROSIS

The natural history of NAFLD is not well known, but it is known that prognosis varies according to histologic type. Matteoni *et al.*^[39] conducted a retrospective study to compare clinical characteristics and outcomes of patients with different types of NAFLD. Patients were separated into four histologic types: Simple fatty liver; steatohepatitis;

steatonecrosis; and steatonecrosis plus either Mallory hyaline or fibrosis. Cirrhosis and liver-related death were seen almost exclusively in patients with steatonecrosis with or without Mallory hyaline or fibrosis^[39]. The study also confirmed that the prognosis of simple steatosis is favorable.

A number of risk factors for more histologically advanced disease have been identified. These include central weight distribution and metabolic syndrome. Dixon *et al.*^[40] studied 105 severely obese individuals undergoing bariatric surgery, and showed that hyperinsulinemia and increased insulin resistance were associated with adverse histologic findings. The study found that C-peptide was the best predictor of advanced fibrosis (stage 3-4) and that patients with advanced fibrosis had significantly higher C-peptide levels. The insulin resistance index and systemic hypertension were independently associated with advanced NAFLD. Insulin resistance was found to be the best predictor of zone 3-centric steatosis, inflammation and fibrosis. Interestingly, this study found that moderate alcohol consumption reduced the risk of NAFLD by decreasing insulin resistance. Angulo *et al.*^[41] studied liver biopsies from 144 patients with NASH. In multivariate analysis, older age (>45 years), obesity, diabetes mellitus and an AST/ALT ratio >1 were significant predictors of severe fibrosis (bridging/cirrhosis). The investigators concluded that this subgroup would benefit most from liver biopsy and investigational therapies^[41]. Researchers in France investigated 93 obese patients, and found that age ≥ 50 years, BMI >28 kg/m², triglycerides >1.7 mmol/L and ALT >2 times normal value were independently associated with septal fibrosis^[42]. A univariate analysis showed that diabetes and impaired glucose tolerance were significantly associated with fibrosis. Another recent study evaluating steatosis in chronic hepatitis C found that an increased BMI had a role in pathogenesis of steatosis in chronic hepatitis C, and that this may contribute to fibrosis^[43]. Studies by both Marceau *et al.*^[23] and Willner *et al.*^[16] showed that patients with cirrhosis were more obese than those without cirrhosis. In addition, Marceau *et al.*^[23] found the presence of diabetes to be the strongest predictor of cirrhosis. Finally, a recent investigation of NAFLD and the metabolic syndrome showed that the presence of metabolic syndrome carried a high risk for NASH among NAFLD patients, and was also associated with a high risk of severe fibrosis^[19].

Thus, features of the metabolic syndrome like obesity, insulin resistance and hypertriglyceridemia are not only predisposing factors for NASH, but are also risk factors for more severe fibrosis and advanced disease.

TREATMENT OPTIONS

In light of the increasing incidence of NAFLD-associated comorbid conditions and NAFLD itself, as well as increased awareness of adverse outcomes associated with steatohepatitis, a number of treatment options are being explored. These combine specific therapies for NAFLD as well as the management of comorbid conditions. Therapies that have been evaluated include lifestyle changes such as

diet and exercise, antioxidants like vitamin E and betaine, cytoprotective agents such as ursodeoxycholic acid, lipid-lowering agents, anti-diabetics, weight-loss agents like orlistat and iron reduction therapy, i.e. phlebotomy. The management of associated conditions, such as diabetes, obesity and hyperlipidemia, is especially important, given their association with more advanced liver disease. This may be achieved by optimizing medical treatment of these conditions, as well as through weight loss strategies.

EFFECT OF WEIGHT LOSS ON NAFLD

Because obesity is the most commonly associated condition with NAFLD, weight loss has traditionally been the most commonly suggested intervention. Patients are encouraged to lose weight through exercise and dietary fat restriction. 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. A number of studies suggest that NAFLD may improve after weight loss. Improvement in liver biochemistry and ultrasonographic appearance is a consistent finding with moderate weight reduction. However, serum aminotransferases are unreliable markers for follow-up, and do not provide accurate data on prognosis. Worsening of fibrosis can occur even as the levels of transaminases decline^[44]. A few studies have evaluated and shown histologic improvement.

The effects of weight reduction on hepatic tests and physical findings were studied in a retrospective review of thirty-nine obese patients without primary liver disease. A weight loss of >10% corrected abnormal liver tests, decreased hepatosplenomegaly and resolved some stigmata of liver disease^[45]. Early case series showed that improved liver chemistry and histology was evident with even a modest reduction in weight, as considerable extra weight persisted in the subjects under evaluation^[46,47].

Drenick *et al*^[48] studied liver biopsies of 41 obese patients undergoing massive weight reduction (>100 lb). Biopsies were obtained at various stages before, during and after weight loss. Based on the method of weight loss, patients were divided into three groups, including prolonged fasting, low-calorie dieting and intestinal bypass surgery. In the non-surgical groups, a transient increase in hepatocellular degeneration and focal necrosis was noted along with progressive diminution of fatty infiltration during weight loss. However, late biopsies revealed normal histology. In patients who underwent intestinal bypass, biopsies variously revealed massive fatty changes, cholestasis, polynuclear inflammatory infiltrates, diffuse fibrosis, bile-duct proliferation and fatal hepatic necrosis^[48]. These findings relating to jejunoileal bypass have been demonstrated in several studies^[49-51]. This surgical procedure has been abandoned in favor of safer weight-loss surgery.

In a study of twenty-five obese Japanese subjects^[52], fifteen underwent a program of restricted diet and exercise for a period of three months, while ten did not. Patients in the intervention group showed a significant decrease in BMI, aminotransferases, total protein, cholinesterase, total

cholesterol and fasting plasma glucose levels. In addition, steatosis was significantly improved on liver biopsy in these patients. The ten patients in the control group did not show any change in biochemical parameters or liver histology.

Regular body weight and biological measurements were obtained from 505 severely obese patients before and after undergoing gastroplasty^[53]. There was a high prevalence of biologic abnormalities associated with the metabolic syndrome at baseline. After a mean follow-up of 21 ± 14 mo post-surgery, significant reductions in biological markers of metabolic syndrome, such as blood glucose, insulin, and triglycerides, were noted. Also, total cholesterol, uric acid and fibrinogen and ALT levels were reduced, along with an increase in HDL cholesterol levels. Data on children with NASH, who underwent weight reduction, also showed improvement in biochemical and ultrasonographic findings^[54,55].

The effect of weight loss on NAFLD was studied in 36 obese patients. Paired liver biopsies were obtained, the first at the time of laparoscopic adjustable gastric band placement and the second after weight reduction. Initial biopsies showed steatosis alone in 12 patients and NASH in 23 patients. Initial fibrosis score of 2 or more was noted in 18 patients. Follow-up biopsies were obtained at 25.6 ± 10 mo after surgery. Weight loss resulted in a significant improvement in liver histology, with repeat biopsies showing NASH in only 4 patients and a fibrosis score of 2 or more in only 3 patients. Greater improvement was seen in patients who had been diagnosed with metabolic syndrome prior to surgery^[56].

Knobler *et al*^[57] suggested that NAFLD is not only associated with biochemical abnormalities of the metabolic syndrome, but it responds to their amelioration. Forty-eight patients with chronically elevated liver enzymes with clinical, ultrasound, and histologic findings consistent with fatty liver were evaluated. Most of the patients were overweight or obese (64%), 44% had diabetes mellitus, 29% had impaired glucose tolerance, and 17% were hyperinsulinemic. Dietary intervention was the primary mode of weight loss. This was supplemented by oral hypoglycemic or lipid-lowering drugs as needed. The results showed moderate weight loss (3.7 kg), improvement in fasting plasma glucose and lipid levels. An improvement in liver enzymes was noted in 96% patients with normalization in 50% patients.

In a recent pilot study, ten obese patients with NASH were treated with orlistat in addition to diet for weight reduction over a period of 6 mo^[58]. BMI, liver enzymes, hemoglobin A1c, fasting lipids, glucose and liver histology were assessed at baseline and at completion of the study. Mean weight loss was 22.7 lb. There was a significant decrease in the BMI, and levels of hemoglobin A1c, ALT, AST. Steatosis improved in six patients and fibrosis in three patients. Hickman *et al*^[59] found that modest weight loss through exercise and dietary intervention resulted in sustained improvements not only of ALT and fasting insulin levels, but also of health-related quality of life.

The above data demonstrates that NAFLD and NASH improve significantly with weight reduction. However, this must be done in a controlled manner over a period

of time, as rapid weight loss may lead to exacerbation of liver disease. This has been shown following drastic weight reduction through diet as well as through bariatric surgery. Forty-one patients who had weight loss on a very-low-calorie diet showed improvement in fatty change on liver biopsy. However, 24% developed portal inflammation or fibrosis. These were patients who underwent a very rapid weight reduction (>1.6 kg per week)^[60]. Liver biopsies obtained from patients undergoing gastroplasty for morbid obesity were compared before surgery and after weight loss (mean 32 ± 19 kg). There was a significant decrease in the prevalence of steatosis (38% of patients after weight loss *vs* 83% before). However, an increase in the prevalence of hepatitis was observed after significant weight reduction (26% of biopsies after weight loss *versus* 14% before)^[61]. The pathogenesis appears to be massive mobilization of fatty acids from visceral stores, which reach the liver via the portal vein and may be toxic to the liver. Therefore, initial target weight reduction should be 10% of baseline weight and should not exceed 1.6 kg/wk.

POPULAR DIETS

The effects of many popular diets on fatty liver are not known. However, metabolic improvements related to dietary weight reduction may favorably influence NASH. If dietary intervention can positively affect insulin resistance and other features of the metabolic syndrome, it would be important to know which particular diet is most beneficial. Conventional diets usually fall into two main categories. Those that alter the macronutrient composition of the diet and those that limit overall energy intake.

Alterations in macronutrient composition

Diets that promote weight loss by emphasizing their macronutrient make-up, as opposed to caloric intake, include low-fat and low-carbohydrate diets. Low-fat diets are traditionally the most recommended by medical professionals. Over time, these have been shown to be safe, cardio-protective and effective in weight loss. Adherence, however, has been a problem. Energy density of food is an important consideration. This refers to the energy (calories) in a given weight of food. Weight loss from a low-fat diet may be due to the low energy density of the diet. Both carbohydrates and proteins have an energy density of 4 kcal/kg, compared to 9 kcal/kg for fats. Researchers for the National Weight Control Registry found that members who maintained successful weight loss, consumed less energy and a lower percentage of energy from fat when compared to the general population^[62]. The low-fat (30%) diet is advocated by the National Cholesterol Education Program and by the American Heart Association.

Low carbohydrate diets have been popular periodically over the last several decades, and are currently undergoing a resurgence. An NPD survey on diet trends in the United States showed that in early 2004 about 9% of the population was on a low carbohydrate diet. These diets limit the composition and/or amount (<100 g/d) of carbohydrates, with an increase in dietary protein and

fat. They are marketed as low carbohydrate, high protein diets, although they could also be called low carbohydrate, high fat diets. A diet high in carbohydrates results in an increase in blood glucose, insulin and triglycerides, all of which are risk factors for the development of NAFLD. Carbohydrate restriction leads to ketosis resulting not only in weight loss, but also a decrease in blood glucose, insulin and triglyceride levels. Studies have shown these diets to be effective in short-term weight loss^[63,64]. Early weight loss is a result of diuresis associated with ketone and urea nitrogen excretion^[65]. However, over time, weight loss is a result of loss of body fat. Proponents believe that these diets have a high satiety level, which make them easier to adhere to. This is very important, as dietary adherence is one of the main challenges faced by dieters. Questions with regard to their nutritional adequacy and long-term effects have been raised. In the short-term, these diets have been found to be safe.

Popular low carbohydrate diets include the Atkins, South Beach and the Zone diets. Originally published by Dr. Robert Atkins in 1972 (Dr. Atkins diet revolution), the Atkins diet is the most popular low carbohydrate diet in the United States. Weight reduction is achieved in four phases. The first phase is an induction diet which limits carbohydrates to 20 g/d, but allows unlimited amounts of fat. In phase two, there is ongoing weight loss with easing of the carbohydrate restriction. Through phases three and four, pre-maintenance and maintenance, individuals determine the amount of carbohydrate they can consume while maintaining their weight loss^[66]. The South Beach diet consists of 3 phases, gradually increasing in proportion of carbohydrates and emphasizes good carbohydrates and fats. The Zone diet recommends a low carbohydrate, high protein diet, with macronutrient intake in the 40:30:30 ratio, i.e. 40% calories from carbohydrates, 30% from protein and 30% from fat.

Reduction in energy intake

Studies have found that weight loss on a calorie-restricted diet is due to decreased energy intake and not nutrient composition. Golay *et al*^[67] evaluated the effect of diets that were equally low in energy, but widely different in amounts of fat and carbohydrate over a 6-wk period. No significant difference in amount of weight loss was noted^[67]. Alford *et al*^[68] studied the effects of three different diets with a fixed caloric intake of 1 200 kcal/d. They found no significant difference in weight loss among diets with 25%, 45%, 75% carbohydrate. The authors concluded that weight loss is the result of reduction in caloric intake in proportion to caloric requirements. Schlundt *et al*^[69] found greater weight loss with a low-fat, calorie-restricted diet when compared to a low-fat, *ad libitum* carbohydrate intake diet. A systematic review of low carbohydrate diets by Freedman *et al*^[70] found weight loss to be associated with energy restriction and not carbohydrate restriction. It is likely that individuals on diets that alter macronutrient composition (low fat or low carbohydrate) actually lose weight because of a concurrent reduction in energy intake.

LOW-CARBOHYDRATE *VERSUS* LOW-FAT DIETS: EFFECTS ON BIOCHEMICAL MARKERS OF METABOLIC SYNDROME AND NAFLD

As mentioned previously, dietary weight reduction has been shown to have a positive effect on biochemical markers of the metabolic syndrome. This may translate into a positive effect on NAFLD. Encouraging histologic findings have been noted in these patients. Therefore, it is important to compare the various diets and determine which, if any, is most beneficial in NAFLD.

Low-carbohydrate diets have long been considered fad diets by the medical profession. Several questions have been raised regarding their weight loss potential and possible adverse effects. Public interest continues unabated, and books detailing low carbohydrate lifestyles are regulars on best seller lists. A number of studies have been published in recent years evaluating the effects of low-carbohydrate diets on weight loss as well as on metabolic markers, comparing these diets to traditional low-fat diets. However, none has compared their effects on liver histology and NAFLD. Effects on obesity and biomarkers of the metabolic syndrome will be reviewed, given their important etiologic association with NAFLD.

In an uncontrolled study, Westman *et al*^[71] showed that in mildly obese, motivated persons, a very low-carbohydrate diet led to sustained weight loss during a 6-mo period. Positive effects were also noted on the serum lipid profile, with a decrease in triglycerides, total and low-density lipoprotein cholesterol and an increase in high-density lipoprotein cholesterol levels. More recently, several randomized controlled trials comparing various diets have been published. Brehm *et al*^[72] studied the effects of a very low-carbohydrate diet on body composition and cardiovascular risk factors. Fifty three healthy, obese women were randomized to 6 mo of an *ad libitum* very low-carbohydrate diet *versus* a calorie-restricted low-fat diet. The very low carbohydrate group had more weight loss (8.5 ± 1.0 *vs* 3.9 ± 1.0 kg, $P < 0.001$) without any deleterious effect on cardiovascular risk factors. Foster *et al* randomized 63 non-diabetic obese subjects to a low carbohydrate (Atkins) *versus* a conventional diet (low fat, high carbohydrate, calorie-restricted diet). The Atkins group had more weight loss at 3 mo (-6.8 ± 5.0 % *vs* -2.7 ± 3.7 %) and 6 mo (-7.0 ± 6.5 % *vs* -3.2 ± 5.6 %), but at 12 mo the difference between the 2 groups was not significant (-4.4 ± 6.7 % *vs* -2.5 ± 6.3 %). The low carbohydrate group was associated with a greater decrease in triglycerides and a greater increase in high-density lipoprotein cholesterol levels. No difference in the total of low-density lipoprotein cholesterol levels was seen between the both groups. Insulin sensitivity increased in both groups without any significant difference between groups^[64]. In a study by Samaha *et al*^[63], 132 severely obese subjects with a mean body mass index (BMI) of 43 (diabetes mellitus in 39% and metabolic syndrome in 43%) were randomized to a low-carbohydrate or a low-fat, calorie-restricted diet. At 6 mo, the low carbohydrate group had more weight loss (-5.8 ± 8.6 kg *vs* -1.9 ± 4.2 kg

and a greater decrease in triglyceride levels (-20 ± 43 % *vs* -4 ± 31 %). In non-diabetics, the insulin sensitivity improved more, and in diabetics, fasting glucose levels decreased more in the low carbohydrate group^[63]. No adverse effects on the serum lipid levels were observed. The 12-mo data from this study was published in 2004. Weight loss between the two groups at this point was no longer significant. The favorable metabolic response to the low-carbohydrate diet, however, persisted^[73]. A recently published study of 120 overweight, hyperlipidemic subjects showed similar findings. At 24 wk, the low carbohydrate (Atkins) group had greater weight loss (mean -12.9 % *vs* -6.7 %, $P < 0.001$). Effects on triglyceride and high-density lipoprotein cholesterol levels were also more favorable with the low-carbohydrate diet^[74]. Comparison of the National Cholesterol Education Program (NCEP) diet with a modified low-carbohydrate diet (low in total carbohydrates but higher in complex carbohydrates, protein and monounsaturated fat) showed a significantly greater weight loss in the modified low-carbohydrate diet over a period of 12 wk. This study did not show any significant difference between groups in blood lipid levels^[75]. A low-carbohydrate diet over 12 wk was also found to be more effective than a low-fat diet for weight loss in overweight adolescents without adversely affecting their lipid profile^[76]. In comparing 4 popular diets (Atkins, Zone, Weight Watcher's and Ornish) over one year, all were found to reduce weight modestly, and to have a significant reduction in low-density lipoprotein/high-density lipoprotein cholesterol ratio. No significant difference was noted between diets, and no diet-related adverse effects were noted^[77]. Evaluation of 3 different diets in overweight, insulin-resistant women showed greater weight reduction from the Atkins and Zone diets when compared to a conventional low-fat diet. A greater reduction in triglycerides and waist circumference was also noted with these diets. A significant increase in low-density lipoprotein levels was noted in 25% of subjects on the Atkins diet, whereas this was seen in only 13% of subjects on the low-fat diet and 3% of those on the Zone diet^[78]. Improvement in characteristics of the metabolic syndrome as demonstrated by a decrease in triglycerides, triglyceride/high-density lipoprotein ratio, postprandial lipemia and increase in low-density lipoprotein particle size was shown in overweight men on a very low-carbohydrate diet^[79]. Similarly, improved insulin sensitivity and prevention of HDL cholesterol decline were noted in overweight men^[80].

Results from these studies suggest that a low-carbohydrate diet results in weight loss and may even be more effective than a conventional, low-fat diet in the short-term period. Greater weight loss may be the result of the monotony and simplicity of the diet inhibiting appetite and food intake^[81]. Enhanced satiety, palatability and novelty of the diet may also play a role^[63,73]. There has been great concern regarding negative effects on renal function, bone health and cancer risk. Some studies showed that low-carbohydrate diets had a higher incidence of minor side-effects, such as constipation, headache, halitosis, muscle cramps, diarrhea, rash and general weakness^[74]. The major concern of an adverse effect on serum lipids, renal and cardiovascular health was not realized in these

studies. Again, these studies have relatively short follow-up periods, and the effect on low-density lipoprotein cholesterol levels remains uncertain, and requires further study. Caution must be exercised in subjects with baseline abnormal low-density lipoprotein cholesterol levels. Effects on biochemical markers associated with the metabolic syndrome appear to be more favorable with low-carbohydrate diets. In general, these diets show greater improvements in insulin sensitivity, triglyceride and high-density cholesterol levels. It is possible that for patients with the metabolic syndrome, a low-carbohydrate diet may be more advantageous. This, in turn, may positively affect NAFLD.

CONCLUSION

As the prevalence of obesity increases, so will that of the metabolic syndrome and NAFLD. It is now recognized that the consequences of NAFLD are not always benign. While pure steatosis alone is generally an indolent disease, steatohepatitis can be a progressive disease leading to cirrhosis and even liver failure. The etiologic association between NAFLD and the metabolic syndrome is so well established that NAFLD is considered a hepatic manifestation of the disease. Obesity and insulin resistance are associated with more histologically advanced disease. Given this scenario, it is important to develop new strategies to treat and prevent NASH. While it is known that dietary weight loss improves markers of the metabolic syndrome and data also suggest that judicious weight loss affects the liver favorably in NAFLD, the best dietary approach is yet unknown. Traditionally, a low-fat diet has been recommended, but recent studies, show greater short-term weight loss and greater improvement in markers of the metabolic syndrome without significant adverse effects with low-carbohydrate diets. This raises the question of whether low-carbohydrate diets should be recommended as part of a weight loss strategy for our patients. At this point, questions regarding the nutritional adequacy and long-term safety remain. While studies have evaluated the effect of these diets on weight loss, cardiovascular and metabolic marker studies are needed to evaluate the effect of these diets specifically on NAFLD.

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