The Role of Diet and Nutrient Composition in Nonalcoholic Fatty Liver Disease

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the developed world. NAFLD is tightly linked to insulin resistance and considered to be the hepatic manifestation of the metabolic syndrome. The cornerstone of any treatment regimen for patients with NAFLD is lifestyle modification focused on weight loss, exercise, and improving insulin sensitivity. Here we review the literature and discuss the role of diet and nutrient composition in the management of NAFLD. Because there are currently no specific dietary guidelines for NAFLD, this review proposes a dietary framework for patients with NAFLD based on the available evidence and extrapolates from dietary guidelines aimed at reducing insulin resistance and cardiovascular risk. J Acad Nutr Diet. 2012;112:401-409.

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) IS THE most common cause of chronic liver disease in the developed world (1). NAFLD is a significant health problem and affects 70 million adults in the United States (~30% of the adult population). NAFLD encompasses a spectrum of liver diseases that ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), its progressive subtype. An estimated 20% of patients with NAFLD have NASH, which can progress to cirrhosis necessitating liver transplantation. NAFLD in both forms represents the hepatic manifestation of the metabolic syndrome that also includes dyslipidemia, central obesity, hypertension, and insulin resistance (IR) (2). Most patients with fatty liver have excess body weight. Although promising pharmacologic therapies are emerging, sustained weight loss is the most effective treatment for NAFLD and should be the foundation of any treatment plan.

A thorough discussion of the pathophysiology of NAFLD is beyond the scope of this review; however, how obesity and dietary composition affects hepatic fat accumulation and inflammation will be briefly discussed. Obesity itself represents a chronic, inflammatory condition resulting from the failure of the normal homeostatic regulation of energy intake, storage, and use (3,4). In the setting of obesity, particularly central obesity, there is an expansion of active visceral adipose tissue. This adipose tissue compartment becomes infiltrated by inflammatory cells that lead to a milieu in which proinflammatory cytokines such as tumor necrosis factor α and interleukin-6 increase while adiponectin, which counteracts the effects of tumor necrosis factor α, decreases (1). This leads to hepatic steatosis and a state of heightened IR and increased oxidative injury. Weight loss can change the activity of adipose tissue and reverse many of these consequences as can, potentially, dietary macronutrient content (see the Figure). In the setting of excessive nutrient intake, diets rich in fat or carbohydrate can decrease insulin sensitivity and increase serum free fatty acid levels, leading to hepatic steatosis. A critical review of diets for the metabolic syndrome and popular diets as they might relate to NAFLD is discussed elsewhere (5). This review discusses the existing data on the effects of diet-induced weight loss and dietary composition and proposes a rational dietary approach that promotes slow and controlled weight loss designed to improve insulin sensitivity and reduce cardiovascular risk in patients with NAFLD.

METHODS

Articles featured in this review were identified through an electronic database search using PubMed with dates ranging from 1990 through 2011. Randomized controlled trials, case control studies, and observational studies of adult patients were included. The search terms used for this review included: fatty liver disease, fatty liver nutrition, NASH nutrition, NASH diet, fructose NAFLD, saturated fat liver, carbohydrate metabolic syndrome, insulin resistance and diet, antioxidants, and bariatric surgery.

Effects of Weight Loss on NAFLD

Although the liver is not meant to store fat, excess energy and unmatched energy expenditure can result in the accumulation of fat in the liver. Weight management, dietary macronutrient composition, physical activity, and behavior therapy all play a critical role in successful weight loss.

Patients with NAFLD have been shown to have higher energy intake when compared with healthy controls (6). Long-term well-controlled dietary intervention studies are limited; however, the preponderance of the evidence suggests that it is effective in improving liver disease related to NAFLD because it improves insulin sensitivity, hypertension, and dyslipidemia. Several studies show that diet-induced weight loss reduces liver enzymes and hepatic steatosis, with less consistent effects on other components of liver histology (7-9). In patients with NASH, some studies have shown that a 1,400 kcal/day diet and weight loss of ~3.5 kg improve histology on liver biopsy and liver enzyme levels (10). In the larg-
est randomized controlled trial of lifestyle intervention in NASH, patients were randomized 2:1 to a combination of diet, exercise, and behavior modification (lifestyle intervention group) or a control group, with a goal of 7% to 10% weight reduction (11). The primary outcome measure was an improvement in the NAFLD activity score after 48 weeks of treatment. Subjects in the lifestyle intervention group (n=21) were assigned an energy goal based on their starting weight (1,000 to 1,200 kcal/day if baseline weight <200 lb or 1,200 to 1,500 kcal/day if baseline weight >200 lb) and were instructed to consume a 25% fat diet. Participants in the control group (n=10) attended group sessions providing basic education about NASH and principles of healthy eating and physical activity. The lifestyle intervention group had an average weight loss of 9.3% of their weight compared with only 0.2% in the control arm (P<0.005). Furthermore, after treatment, NAFLD activity score was lower in the lifestyle intervention group compared with the control group (P<0.05). Those who lost ≥7% of their body weight had significant improvements in steatosis (P<0.001), lobular inflammation (P=0.03), and NAFLD activity score (P<0.001).

Although weight loss is the most effective treatment for NAFLD, excessive energy restrictions and sudden weight loss may worsen liver injury (12). In fact, rapid weight loss (>2.5 lb/week) as seen in antiquated bariatric procedures such as the jejunooileal bypass often worsened steatohepatitis or resulted in cirrhosis and liver failure (13,14). In patients with NAFLD, particularly those with advanced liver disease, slow and controlled weight loss over time is the goal. Short-term and pilot studies have shown that a 25 kcal/kg/day diet or a reduction of ~200 kcal/day produces significant decreases in aspartate aminotransferase, alanine aminotransferase (ALT), fasting glucose, body mass index, and the degree of hepatic steatosis (9,15). Modest weight loss, <2 lb (1 kg) per week, is associated with a decrease in the incidence of the metabolic syndrome and improvement in the histologic features of NASH in >80% of cases (16). As little as 5% weight loss can have beneficial effects on NAFLD, although an initial 10% weight loss is typically recommended and supported by the National Heart, Lung, and Blood Institute–National Institute of Diabetes and Digestive and Kidney Diseases clinical guidelines (17). To avoid rapid weight fluctuations, the recommended rate of weight loss is 1 to 2 lb/week (17).

### Influence of Dietary Macronutrients

Aside from the possibility of achieving weight loss through caloric restriction as a treatment of NAFLD, dietary composition can directly influence the development of NAFLD. Various types of diets (either low in carbohydrates or low in fats) are equally effective for long-term weight reduction (18). However, there is evidence that manipulation of either micronutrient or macronutrient content can affect hypertension, levels of inflammation, serum lipids, and IR independent of weight loss (19-21). This is illustrated by the differences in recommended macronutrient content by various societies (Table 1). Animal data and observational studies suggest that a diet high in carbohydrates worsens liver injury related to NAFLD. Although no prospective study has compared the effects of popular fad diets on patients with NAFLD, this is thoroughly reviewed elsewhere (5).

### Carbohydrate

Extrapolating from the diabetes literature and available data on NAFLD, the percentage of carbohydrate in the diet and the Glycemic Index (GI) value of the carbohydrates is likely to have an important influence on NAFLD (22). Diets enriched in carbohydrate lead to increased circulating insulin concentrations, which contribute to elevated fasting triglyceride concentrations even under isocaloric conditions (23,24). A low-fat, high-carbohydrate diet promotes the development of fatty liver via increased de novo fatty acid synthesis (25). In patients with the metabolic syndrome and NAFLD, a diet containing more carbohydrate and less fat has been associated with greater histologic severity (26). In one study, patients consuming >54% of energy from carbohydrates compared with those consuming <35% had a 6.5-fold increased risk of hepatic inflammation (27). Ryan and colleagues (28) randomized patients to hypocaloric diets containing either 60% carbohydrate/25% fat or 40% carbohydrate/45% fat (15% protein in both) of equal energy deficit (750 kcal/day) for 16 weeks. Patients receiving the lower carbohydrate diet had lower ALT concentrations compared with those given a high-carbohydrate/low-fat diet, despite equal weight loss. This suggests that a hypocaloric, lower carbohydrate diet may be beneficial to patients with NAFLD, independent of weight loss (28). In another study (29), patients with NAFLD following an energy-restricted (1,200...
stress pathways such as the unfolded protein response directly (37).

Increased fat intake has been linked to insulin resistance and impaired postprandial lipid metabolism. Western diets contain more saturated fat, vegetable oil rich in n-6 polyunsaturated fatty acid (PUFA), and less n-3 PUFA. Patients with NASH ingest a higher percentage of their energy from fat (37%) and this may be an independent nutritional risk factor for the development or progression of NAFLD (odds ratio [OR] = 2.51) (42,43). In a study by Yamamoto and colleagues (15) the reduction of fat consumption from 27% to 19% for 6 months decreased aspartate aminotransferase and ALT from 68 IU/L to 42 IU/L, respectively. Although few studies on fat intake exist on which to base recommendations for NAFLD, evidence supports the benefits of a Mediterranean diet for patients with NAFLD (44-46).

**Table 1. Diets for a healthy lifestyle,* as recommended by authoritative groups in the United States**

<table>
<thead>
<tr>
<th>Component</th>
<th>American Heart Association</th>
<th>Academy of Nutrition and Dietetics</th>
<th>US Department of Agriculture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruits</td>
<td>4 servings</td>
<td>2-4 servings</td>
<td>1.5-2 c</td>
</tr>
<tr>
<td>Vegetables</td>
<td>3-4 servings</td>
<td>3-5 servings</td>
<td>2-3 c</td>
</tr>
<tr>
<td>Whole grains</td>
<td>6 servings</td>
<td>6 servings</td>
<td>6 oz grains</td>
</tr>
<tr>
<td>Lean meat</td>
<td>3-6 oz (cooked)</td>
<td>2-3 servings</td>
<td>5.5-6.5 oz</td>
</tr>
<tr>
<td>Low-fat dairy</td>
<td>2-3 servings</td>
<td>2-3 servings</td>
<td>3 c</td>
</tr>
<tr>
<td>Fat/oils</td>
<td>2 servings</td>
<td>Avoid trans &amp; saturated</td>
<td>5-6 tsp</td>
</tr>
<tr>
<td>Nuts, seeds</td>
<td>3-4 servings/wk</td>
<td>Include</td>
<td></td>
</tr>
<tr>
<td>Sweets</td>
<td>0 servings</td>
<td>Cut back on snacks</td>
<td>150-200 kcal/d</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>↓ 500 kcal/d</td>
<td>No fad diets</td>
<td>Energy balance</td>
</tr>
<tr>
<td></td>
<td>1 lb/wk</td>
<td>Count kilocalories</td>
<td>Nutrient-dense foods</td>
</tr>
<tr>
<td>Physical activity</td>
<td>2 h 30 min/wk moderate-intensity cardio</td>
<td>Exercise regularly</td>
<td>≥2 d/wk resistance training</td>
</tr>
</tbody>
</table>

*All dietary recommendations represent servings per day based on a 1,600 kcal/d diet.

GI

Low-GI foods, also called slow release carbohydrates, exert a second meal effect whereby the glycemic response to the subsequent meal is enhanced. Furthermore, such foods (eg, oats) have been shown to decrease total cholesterol levels (38,39). Although there are no studies in human beings examining the effects of GI specifically in patients with NAFLD, the effects of the GI on other comorbidities associated with NAFLD suggest that GI may be an important factor to consider when giving dietary recommendations to patients with NAFLD (22). A low-GI diet alone does not improve hepatic insulin sensitivity but in conjunction with exercise it does reduce post-prandial hyperinsulinemia (40). A randomized controlled trial by Fraser and colleagues (41) found that ALT levels decreased by 35% in patients following a low-carbohydrate/low-GI diet when compared with those following a high-carbohydrate/high-GI diet (P=0.05). Given the available evidence it is reasonable to favor the incorporation of lower GI foods into a diet for patients with NAFLD. However, the GI is a gross measurement whose direct influence on NAFLD remains unknown.

**Fat**

Increased fat intake has been linked to insulin resistance and impaired postprandial lipid metabolism. Western diets contain more saturated fat, vegetable oil rich in n-6 polyunsaturated fatty acid (PUFA), and less n-3 PUFA. Patients with NASH ingest a higher percentage of their energy from fat (37%) and this may be an independent nutritional risk factor for the development or progression of NAFLD (odds ratio [OR] = 2.51) (42,43). In a study by Yamamoto and colleagues (15) the reduction of fat consumption from 27% to 19% for 6 months decreased aspartate aminotransferase and ALT from 68 IU/L and 104 IU/L to 33 IU/L and 42 IU/L, respectively. Although few studies on fat intake exist on which to base recommendations for NAFLD, evidence supports the benefits of a Mediterranean diet for patients with NAFLD (44-46).

**Saturated/Trans-Fatty Acids.** Saturated fatty acids (SFA) have adverse effects on lipid and glucose homeostasis, which in turn worsen the progression of metabolic syndrome and possibly NAFLD (47).
Two studies in patients with fatty liver further support this association, and have shown that NAFLD patients consume more SFA while consuming less PUFA, fiber, and antioxidants (33,48). However, whereas diets containing <10% SFA are likely to be beneficial, extreme reductions in SFA may have deleterious effects on plasma lipid levels. In a double blind randomized controlled trials of two reduced-fat diets (30% SFA with 9% SFA or 25% fat with 6% SFA) compared with a control diet (38% fat with 14% SFA) in healthy adults, the reduced-fat diets reduced low-density lipoprotein cholesterol levels. Interestingly, high-density lipoprotein cholesterol levels also decreased and triglyceride levels increased after the 6-week intervention. This effect was most pronounced in insulin resistant or overweight subjects in whom low-density lipoprotein cholesterol level benefits were less pronounced and unfavorable changes in high-density lipoprotein cholesterol and triglyceride were more prominent (49). This suggests that although reduced SFA intake (<10%) might be beneficial to patients with NAFLD, intake of <6% may have counterproductive effects on plasma lipid levels. Although no studies in human beings have made a direct link between NAFLD and cardiovascular disease in rats (50-52).

**Monounsaturated Fat.** Compared with high-carbohydrate diets, diets high in monounsaturated fat (MUFA) may be preferable if they are not coupled with increased energy intake or contain higher quantities of cholesterol. An increase in MUFA intake, especially as a replacement for SFA, may offset the proinflammatory effects of SFA and decrease IR and hepatic steatosis. Epidemiologic studies have shown anti-inflammatory and cardiovascular benefits of a Mediterranean-style diet rich in MUFA (46,53). There appears to be a direct beneficial role of olive oil (73% MUFA) in improving plasma lipid levels in the treatment of the metabolic syndrome (54). An olive oil-rich diet decreases the accumulation of triglycerides in the liver as well as improves postprandial triglyceride level and glucose response in subjects with IR (55). Incorporating MUFA into Western dietary patterns, particularly at the expense of SFA, may reduce the risk of metabolic syndrome and NAFLD/NASH.

**PUFA.** PUFAs of the n-3 and n-6 series are essential fatty acids that must be provided by the diet. Fish oils, rich in eicosapentaenoic and docosahexaenoic acids, are the most biologically active n-3 PUFAs and exhibit protective effects. They promote oxidation of fatty acids via peroxisome proliferator-activated receptor-α activation and downregulate fatty acid synthesis (56,57). In insulin resistant animal models, the consumption of a diet high in n-3 PUFA has favorable effects on the regulation of plasma lipid levels, cardiovascular disease, immune function, and insulin (58). Three recent clinical trials in human beings support these findings by showing that n-3 PUFA administration (1.0 to 2.7 g/day for 6 to 12 months) to patients with NAFLD improved hepatic steatosis, inflammation, and fibrosis (59-61). Capani (59) and Spadaro (60) both demonstrated that triglyceride level decreased an average of 25 to 37 mg/dL (0.28 to 0.39 mmol/L) when supplemented with 1 g PUFA/day for 6 and 12 months, respectively. Furthermore, other studies have shown that increased n-3 PUFA consumption improves dyslipidemia related to the metabolic syndrome and cardiovascular disease (62,63). Supplementation with n-3 PUFA decreases plasma triglyceride levels by 25% and by 50% in individuals with normolipemia and hypertriglyceridemia, respectively (2,3). Specifically, because the dyslipidemia of NAFLD is characterized by high triglyceride level and low high-density lipoprotein cholesterol level, n-3 PUFA supplementation is likely to be beneficial. Although eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are associated with higher levels of specific liver enzymes, all of which can worsen hepatic steatosis (65). The available data suggest that decreased intake of n-3 fatty acids could have an adverse effect on NAFLD and its associated comorbidities. Therefore, higher consumption of fish rich in n-3 PUFAs or walnuts may reduce the risk for NAFLD or improve the dyslipidemia that characteristically accompanies it (33).

**Protein.** Very few clinical studies have examined the effect of protein consumption in subjects with metabolic syndrome or NAFLD. Protein intake, expressed as the percentage of energy from protein, has generally not been reported to be altered in NAFLD, although Zelber-Sagi and colleagues (33) found significantly higher meat protein consumption in NAFLD after adjustment for age, sex, body mass index, fat intake, and alcohol consumption. Protein supplementation may reduce hepatic lipogenesis and improve insulin sensitivity (48,66). In human beings, there is only one study suggesting that the short-term consumption of soy protein as part of a low-energy diet may provide an additional benefit for weight reduction in subjects with obesity (67). Currently, conclusive evidence is lacking to make a definitive statement regarding the effect of dietary protein on NAFLD. Protein is well represented in the American diet, thus deficiency is unlikely. Excess protein intake can have untoward effects on renal function in susceptible individuals (58,69).

**Promoting Sustained Weight Loss.** Maintenance of weight loss is one of the biggest challenges of dietary interventions. Although the data are incomplete, most evidence suggests that the vast majority of people who lose weight regain it during the subsequent months or years (70,71). Several variables have been related to weight loss maintenance such as increased moderate-intensity physical activity 60 min/day, eating breakfast daily, increases in emotional support, and less sugar-sweetened soft drink consumption (70,72). Also, improved weight loss maintenance is associated with creating long-term goals, taking personal responsibility for weight management, and self-monitoring (73). Obesity surgery provides the most effective therapy for sustained weight loss (74). The effects of bariatric surgery on NAFLD are encouraging and are reviewed extensively elsewhere (74,75). For weight maintenance, meal replacements in combination with regular physical activity can be used to get patients back on track if they start to regain weight (75,76). To date, it remains largely unknown how effective weight loss maintenance interventions are in clinical or community practice settings.

**Understanding Barriers to Maintaining Weight Loss.** Maintenance of weight loss can be difficult to achieve due to physical, economic, or other barriers in patients’ lives. In patients with advanced liver disease, it is particularly important to achieve slow and sustained weight loss because large fluctuations in weight can exacerbate liver injury and result in liver dysfunction. Patients with NAFLD often have other medical conditions such as diabetes, heart disease, or immobility. Furthermore, economic limitations, work schedules, or limited access to good quality food can make maintaining healthy eating habits difficult. It is important to keep these limitations in mind when designing a weight loss plan for patients. Sustainable changes in lifestyle that naturally result in weight loss over time should be the goal, rather than weight loss itself through any specific dietary intervention.

**Behavior Modification.** Dietary modification is most successful when accompanied by behavioral modification. Only a behavioral approach may give patients the practical instruments to achieve their dietary and exercise goals, incorporate them into their lifestyle, and maintain the results for a prolonged period. Cognitive-behavior treatment should be provided to patients at risk of advanced liver disease (77). Increased effectiveness is associated with increased contact frequency and using self-regulatory behavior change techniques (eg, goal setting and self-monitoring). Moscaletto and colleagues (78) examined NAFLD subjects and compared a cognitive-behavior treatment program to a prescriptive diet group. The cognitive-behavior treatment program consisted of 13 weekly sessions, 120 minutes each supported by the LEARN program for weight loss and exercise treatment program. The LEARN program is a cognitive-behavior program that includes education, environmental modification, reinforcement, modeling, and nutrition. This program is designed to help patients make long-term changes in their lifestyles and behaviors, and it is designed to be applied in the patient’s everyday life. The program is based on the principles of cognitive-behavior therapy, which aims to change patients’ thoughts and behaviors in order to achieve and maintain healthy weight loss. The program focuses on helping patients identify and change negative thoughts and behaviors that contribute to weight gain, and replace them with more positive and healthy thoughts and behaviors. The program also provides patients with strategies to help them maintain their weight loss over time, such as setting realistic goals, tracking progress, and using self-monitoring techniques. The program is tailored to the individual patient’s needs and goals, with the goal of helping patients achieve and maintain healthy weight loss for the long term.
control. At 2 years, cognitive-behavior treatment was associated with increased weight loss (OR = 2.56), normalization of liver enzymes (OR = 3.57), and a higher probability of maintaining weight loss. Evidence for long-term effectiveness for weight loss and dietary interventions emphasizes the role of cognitive-behavior treatment in the treatment of NAFLD (79).

Physical Activity. Exercise, in the absence of weight loss, improves skeletal muscle insulin sensitivity, which may improve IR in patients with NAFLD (80,81). On average, subjects who increased moderate-vigorous physical activity to a level of 150 minutes/week or more have the greatest improvements in liver enzymes independent of weight loss (82,83). There are clear benefits of exercise on NAFLD (84,85); however, a thorough discussion is beyond the scope of this review. Incorporating physical activity has many benefits and should be part of any healthy lifestyle.

Nutrient and Antioxidant Treatments
Oxidative injury is a well-accepted cause of liver injury in NASH. Vitamin E is the best-studied antioxidant for the treatment of

### Table 2. The effects of nutrient supplements on nonalcoholic fatty liver disease

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Study</th>
<th>Type</th>
<th>Duration</th>
<th>Dose</th>
<th>Liver histology result</th>
<th>Liver enzymes result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamins</td>
<td>Sanyal and colleagues, 2010 (87)</td>
<td>RCT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>96 wk</td>
<td>800 IU vitamin E daily vs placebo</td>
<td>↓*</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Foster and colleagues, 2011 (91)</td>
<td>RCT</td>
<td>3.6 y</td>
<td>1,000 IU vitamin E, 1,000 mg vitamin C, Atorvastatin</td>
<td>↓*</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Sanyal and colleagues, 2004 (89)</td>
<td>Pilot study; RCT</td>
<td>6 mo</td>
<td>Vitamin E 400 IU daily NHLBI&lt;sup&gt;c&lt;/sup&gt; guidelines for diet</td>
<td>↓**</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Kugelmas and colleagues, 2003 (90)</td>
<td>Pilot study</td>
<td>6 wk</td>
<td>800 IU vitamin E daily Step 1 AHA&lt;sup&gt;d&lt;/sup&gt; diet + exercise</td>
<td>↓**</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Harrison and colleagues, 2003 (92)</td>
<td>RCT</td>
<td>6 mo</td>
<td>Vitamin E 1,000 IU + vitamin C 1,000 mg or placebo daily Low-fat diet (30 g/d)</td>
<td>↓ fibrosis</td>
<td>↓</td>
</tr>
<tr>
<td>Betaine</td>
<td>Abdelmalek and colleagues, 2009 (97)</td>
<td>RCT</td>
<td>12 mo</td>
<td>20 g daily or placebo</td>
<td>↓**</td>
<td>NA&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Modi and colleagues, 2010 (107)</td>
<td>Observational</td>
<td>6 mo</td>
<td>NA</td>
<td>NA</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Ruhl and Everhart, 2005 (109)</td>
<td>Observational</td>
<td>6 y</td>
<td>NA</td>
<td>NA</td>
<td>↓</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Loguericio and colleagues, 2005 (100)</td>
<td>Control trial</td>
<td>4 mo</td>
<td>Probiotic VSL #3&lt;sup&gt;g&lt;/sup&gt;</td>
<td>NA</td>
<td>↓</td>
</tr>
</tbody>
</table>

<sup>a</sup> Decreased/improved.
<sup>b</sup>RCT = randomized controlled trial.
<sup>c</sup>NHLBI = National Heart, Lung, and Blood Institute.
<sup>d</sup>AHA = American Heart Association.
<sup>e</sup>NA = not applicable.
<sup>f</sup>NHANES III = Third National Health and Nutrition Examination Survey.
<sup>g</sup>VSL Pharmaceuticals, Inc. ©2011 Sigma-Tau Pharmaceuticals, Inc.
<sup>**</sup>P < 0.001.
<sup>*</sup>P < 0.05.
NAFLD. Many small studies have addressed the efficacy of various nutrient and antioxidant therapies, many of which are discussed below. Table 2 summarizes the largest studies of antioxidants in patients with NAFLD. The available evidence for other antioxidants requires further study before any conclusions can be drawn.

Vitamin E. Patients with NASH have been shown to have lower intakes of the antioxidant vitamin E (48). Vitamin E supplementation suppresses lipid peroxidation and oxidative stress, which improves inflammation and fibrosis in patients with NASH (86). Several studies have shown significant improvements in hepatic steatosis with 800 and 1,000 IU/day (87-90). In the largest randomized controlled trial to date, Sanyal and colleagues (87) evaluated the effectiveness of vitamin E in 247 patients with NASH. After 96 weeks of treatment, vitamin E (800 IU/day) improved liver histology compared to placebo (87). Despite not improving insulin resistance, vitamin E met the primary endpoint of improving the NAFLD activity score. Others have looked at the combination of vitamins C and E (91). Harrison and colleagues (92) randomized 45 patients with NASH to 1,000 mg vitamin C and 1,000 IU vitamin E or placebo daily for 6 months. Fibrosis improved to a significant degree in those treated with vitamins C and E. There were no improvements in inflammation/necrosis scores or ALT levels with vitamin E and C supplementation. Although the risk is believed to be low, certain high-dosage (≥400 IU/day) trials have shown an increase in all-cause mortality and clinicians should be mindful of this when considering supplementation with vitamin E (93).

Table 3. Proposed lifestyle modification guidelines for persons with nonalcoholic fatty liver disease/nonalcoholic steatohepatitis

<table>
<thead>
<tr>
<th>Modification</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Initial goal: 5-10% body weight lost over 1 y</td>
</tr>
<tr>
<td></td>
<td>Long-term goal: ideal body weight</td>
</tr>
<tr>
<td></td>
<td>Maintenance of weight loss</td>
</tr>
<tr>
<td>Energy intake</td>
<td>1,200-1,500 kcal/d</td>
</tr>
<tr>
<td>Total fat intake</td>
<td>&lt;35% of total energy</td>
</tr>
<tr>
<td>Monounsaturated fatty acid intake</td>
<td>Up to 25%</td>
</tr>
<tr>
<td>Polyunsaturated fatty acid intake</td>
<td>Increase n-3 fatty acids</td>
</tr>
<tr>
<td>Saturated fatty acid intake</td>
<td>&lt;7% of total energy</td>
</tr>
<tr>
<td>Carbohydrate intake</td>
<td>≥50% whole grain; avoid high-fructose corn syrup</td>
</tr>
<tr>
<td>Protein intake</td>
<td>Lean animal- or vegetable-based protein</td>
</tr>
<tr>
<td>Antioxidant intake</td>
<td>Vitamin E 800 IU/d</td>
</tr>
<tr>
<td></td>
<td>Fish oil 1 g/d (eicosapentaenoic + docosahexaenoic acids)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>≥150 min/wk at moderate-vigorous intensity</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular 5 times/wk</td>
</tr>
<tr>
<td></td>
<td>Resistance training ≥2 times/wk</td>
</tr>
</tbody>
</table>

**Betaine.** Betaine (trimethylglycine) is a precursor of S-adenosyl methionine, a hepatoprotective factor. Therapeutic effects of betaine on NAFLD have been reported in both clinical and experimental studies (94,95). Betaine may improve in adipose tissue function, which could have beneficial effects on the development of NAFLD (96). However, clinical data have not shown dramatic effects. In the only randomized placebo-controlled study of betaine (20 g daily) in 55 patients with NASH, betaine had no effect on liver enzymes or histology when compared with placebo (97). Therefore, although mechanistically one could foresee a benefit in NASH, larger clinical studies may be needed to show a benefit.

**Probiotics.** Probiotics are live microbial food supplements or components of bacteria and may have beneficial effects on human health. Emerging data suggest that modifications of the gut microbiota may play a role in the development of NAFLD and progression to NASH (98). No randomized clinical trials have been done on probiotics and NAFLD. Preliminary data from two pilot nonrandomized studies suggested that probiotics may improve liver chemistry tests and may decrease markers of lipid peroxidation (99,100).

**Other Nutrients that May have Hepatoprotective Effects.** Ginger (Zingiber officinale) has medicinal properties that could be beneficial to patients with NAFLD. Small, mostly animal, studies suggest it has antioxidant properties and can improve insulin sensitivity and reduce hepatic fat content (101). Genistein, a soy isoflavone, has been shown to improve insulin sensitivity in insulin resistant animal models and improved oxidative stress in animals with NASH (102-104). Studies in human beings have not been published and, thus, nutritional supplementation with genistein cannot be recommended. Animal data and several observational studies in human beings suggest that caffeine may have a hepatoprotective role (105-109). The mechanisms by which caffeine—specifically coffee, as suggested by some—protect the liver are not well understood.

**CONCLUSIONS**

NAFLD leads to substantial morbidity and mortality in the United States and other developed countries. Although pharmacologic therapies are lacking, sustained and gradual weight loss is the most effective treatment for NAFLD. Early identification and treatment could prevent the development of cirrhosis, cardiovascular disease, and diabetes mellitus in this population. Lifestyle modification through diet and exercise must be the cornerstone of any treatment plan for patients with NAFLD (see Table 3). Long-term, moderate weight loss through the reduction of energy intake and regular physical exercise is recommended for patients with NAFLD. The influence of the macronutrient composition of the diet is important and can help reduce hepatic fat and inflammation.

The role of weight loss in the treatment of fatty liver is well established. Based on data from cardiovascular or diabetes trials and limited studies in patients with NAFLD, a diet that is lower in carbohydrates and saturated fat and higher in lean protein, fiber, and n-3 PUFA is likely to be beneficial. Vitamin E supplementation reduces liver enzymes and improves liver histology in patients with NASH but without diabetes; however, sufficient evidence for other antioxidants or nutritional supplements is lacking. Therefore, well-designed dietary intervention trials are needed to create definitive evidence-based dietary guidelines for patients with NAFLD.

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