Today's Dietitian
The Magazine for Nutrition Professionals
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Nonalcoholic Fatty Liver Disease
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Suggested CDR Learning Codes: 5000, 5240, 5370; Level 3

Nonalcoholic fatty liver disease (NAFLD) is characterized by the accumulation of triglycerides in the hepatocytes of patients who don't abuse alcohol. It ranges in severity from simple steatosis (excessive fat accumulation) to steatohepatitis (liver cell injury and inflammation). Nonalcoholic steatohepatitis (NASH) is a subtype of NAFLD in which steatosis coexists with steatohepatitis. NASH can progress to cirrhosis and hepatocellular carcinoma.

NAFLD is associated with cardiometabolic risk factors and the metabolic syndrome, and it's the most common chronic liver disease among adults in developed countries; 34% of adults in the United States have NAFLD.[1] Individuals with the disease have a higher risk of all causes of mortality, largely because of the coexistence of the metabolic syndrome.[2] Despite considerable research in this area, NAFLD's pathogenesis isn't fully understood.

Most patients with a fatty liver have excess body weight; obesity is a common and well-documented risk factor for NAFLD and a predictor of advanced disease. Both BMI and visceral obesity are risk factors for NAFLD.

Given the close relationship between obesity, the metabolic syndrome, and the development of NAFLD, it isn't surprising that many NAFLD patients have multiple components of the metabolic syndrome, whether or not they're overweight or obese.

No specific medications are approved for treating NAFLD.[3,4] The current standard of care for treating patients with NAFLD focuses on lifestyle interventions, particularly diet and exercise. Sustained weight loss is the most effective treatment and should be the foundation of any treatment plan.

Sufficient weight reduction can be an effective treatment to improve the histology of NASH.[5] A 5% weight loss is believed to improve steatosis, whereas a 10% weight loss is necessary to improve steatohepatitis.[6]

RDs are the cornerstone of NAFLD treatment and should be up-to-date on the current recommendations for medical nutrition therapy. Nutrition professionals should work with patients' health care team members, including primary care physicians, hepatologists, exercise physiologists, and health psychologists, to provide the best care. They also should monitor patients' dietary intake and physical activity (both daily and structured), obtain food logs, and monitor patients' glucose levels. A nonpharmacological intervention based on personalized diet, physical activity, and behavior therapy should aim to encourage lifestyle change, the only therapy proven to effectively treat NAFLD.[7]

This continuing education course reviews the dietary factors associated with NAFLD as well as the lifestyle and nutrition options for treating the disease.

Lifestyle and Dietary Factors

Dietary factors may contribute to liver fat accumulation through multiple pathways, such as the following:

Obesity

Obesity, combined with host factors such as diet, sedentary lifestyle, and genetic predisposition, has been directly associated with increases in the prevalence of insulin resistance, type 2 diabetes, metabolic syndrome, and NAFLD among adults.[8] Estimates suggest that about 80% of adults who are class 1 or 2 obese and 90% who are class 3 obese have NAFLD, with 36% having the more aggressive form of fatty liver, NASH.[9]

Obesity itself is a chronic inflammatory condition resulting from the failure of normal homeostatic regulation of energy intake, storage, and utilization.[10] With obesity, particularly central obesity, there's an expansion of visceral adipose tissue. Weight loss can change the activity of adipose tissue and reverse many negative consequences of the condition, including NAFLD, as can dietary macronutrient content.

Energy balance is a major factor in liver fat accumulation. NAFLD can be a precursor to developing the metabolic syndrome or a "hepatic manifestation" of insulin resistance.[11] Although the liver isn't meant to store fat, caloric excess coupled with and unmatched caloric expenditure can result in fat accumulation in this organ.

NASH patients have been shown to have higher energy intake compared with healthy controls.[12] Overfeeding studies have clearly shown that an increased intake of fat,[13,14] glucose, or fructose can increase liver fat in young, healthy individuals.

In addition, several mechanisms may play a role in the pathogenesis of NAFLD, including insulin resistance, oxidative stress, and cytokine toxicity.[15] These factors likely are present in those with severe obesity and NAFLD and at a significantly increased prevalence than in their normal-weight counterparts.

An increasing number of patients with NAFLD have been described as having a normal BMI, although these individuals tend to have central adiposity and insulin resistance.[16,17] Clinical and epidemiologic studies suggest a direct association between hepatic fat content and visceral adiposity.[18]

Total Fat

Aside from weight gain and obesity, dietary composition can influence the development of NAFLD. The amount and type of dietary fat may directly affect liver fat content, with high-fat diets being potentially harmful. Research participants with NAFLD who were fed a three-day isoenergetic diet containing 30% energy from fat had 15% of the triglycerides in their liver derived directly from dietary fat.[19]

A higher dietary fat intake with an increased ratio of omega-6 to omega-3 polyunsaturated fatty acids (PUFAs) and an increased intake of saturated and trans fatty acids is associated with liver inflammation and NAFLD.[20-22] In contrast, 74 severely obese patients undergoing bariatric surgery demonstrated that a higher total fat intake was associated with lower odds of hepatic inflammation.[23] It appears that the type of fat rather than the amount of fat makes the most difference in NAFLD patients.

Saturated Fatty Acids

Diets high in saturated fat have been shown to induce insulin resistance.[24-26] In epidemiologic studies, both total fat and saturated fat in the diet have been correlated with liver triglyceride content and the presence of NASH.[27,28] Patients with NAFLD ingested a higher percentage of their calories from fat (21% to 37%) compared with controls in two small-scale studies.[28,29]

While no human studies have linked NAFLD and diets high in saturated fat, evidence from experimental animal studies demonstrates that high dietary saturated fatty acid consumption worsens insulin resistance, NAFLD, and cardiovascular disease in rodents.[30,31]

In a double-blind randomized controlled trial of two reduced-fat diets, one containing 30% total fat with 9% saturated fat and one containing 25% total fat with 6% saturated fat, compared with a control diet (38% fat with 14% saturated fat), both reduced-fat diets decreased LDL cholesterol in healthy male test subjects.[32] HDL cholesterol also decreased, and triglyceride levels increased with the reduced-fat diets. This suggests that while reduced saturated fat intake (below 10%) may benefit patients with NAFLD, intake of less than 6% may have counterproductive effects on plasma lipids, specifically triglycerides.

Another study suggested that a low total fat and low saturated fat diet (23% fat and 7% saturated fat) predicted changes in lipid parameters (total, HDL, and LDL cholesterol) but not liver fat.[33]

Trans Fatty Acids

Trans fatty acids are implicated in the metabolic syndrome, as they're strongly associated with an increase in inflammatory processes, plasma triglycerides, and cholesterol as well as a reduction in HDL cholesterol.[34,35] While there are no human studies on trans fatty acids and NAFLD/NASH, animal studies have shown positive relationships between the increased consumption of trans fatty acids from oxidized oils and liver inflammation.[36,37] Little is known about how lipids and trans fatty acids affect hepatic functions and oxidative stress.

PUFAs

Individuals with NASH have a lower intake of PUFAs and, in particular, omega-3 PUFAs.[38,39] Omega-3 PUFA levels also are decreased in the hepatic tissue of patients with NAFLD.21,40 In addition, a higher omega-6 to omega-3 PUFA ratio within the liver of NAFLD patients may contribute to the development of a fatty liver because of a decreased capacity to regulate liver lipid metabolism.[40]

High Carbohydrate Intake

Extrapolating from the diabetes literature and available data about NAFLD, the amount and type of carbohydrate in the diet likely have an important impact on NAFLD.[41]

NASH patients have been found to consume more sweets and simple carbohydrates.[38] Diets rich in carbohydrate sources lead to increased circulating insulin concentrations, which contribute to elevated fasting triglyceride concentrations even under isocaloric conditions.[42,43] A low-fat, high-carbohydrate diet promotes the development of a fatty liver through increased de novo fatty acid synthesis (fatty acid and triglyceride synthesis).[44] A higher carbohydrate intake (more than 54% of calories) has been associated with significantly higher odds of liver inflammation.[23]

Excess High-Fructose Corn Syrup Intake

Growing evidence suggests that the epidemic of NAFLD is closely related to the Western dietary pattern and an increased intake of simple sugars, especially fructose.[45,46] Whether there's a link between fructose or high-fructose corn syrup and an increased risk of fatty infiltration of the liver or muscle is uncertain.

Researchers have hypothesized that fructose can be linked to NAFLD through both indirect and direct mechanisms.[47,48] Indirectly, fructose can lead to adverse metabolic effects that can increase the risk of developing NAFLD. Directly, fructose may cause hepatotoxic damage such as that seen with hereditary fructose intolerance.

Fructose may indirectly predispose someone to fatty liver infiltration by creating an adverse metabolic profile. Studies have indicated that increased fructose consumption boosts fat mass, de novo lipogenesis, and inflammation. It also induces insulin resistance and fasting and postprandial triglycerides, which can, in turn, result in liver steatosis.[49-52]

In case-controlled studies, sugar-sweetened beverage consumption was associated with hepatic steatosis independent of the degree of obesity.[53,54] In other studies, total fructose consumption was associated with NAFLD, and NASH in particular.[55,56]

In a cross-sectional analysis of 427 older adults (aged 48 and older), daily fructose consumption (at least seven times per week) was associated with a lower steatosis grade but a higher fibrosis stage as well as increased hepatic inflammation and cellular injury.[57]

Inactivity

Patients with NAFLD generally engage in less than one-half the amount of exercise performed by age- and sex-matched controls, and in one study, less than 20% met current recommendations for physical activity (at least 150 minutes of moderate-intensity physical activity per week).[58,59]

In a large-scale study of 349 individuals, the NAFLD group engaged in less reported leisure time physical activity, including total, aerobic, and resistance, although only the association with resistance physical activity remained significant when adjusted for BMI.[58]

In a small study of 37 NAFLD patients, there was a lower level of cardiorespiratory fitness among patients with higher NAFLD activity scores and NASH.[59]

Decreased physical activity correlates with intrahepatic fat, decreased insulin sensitivity, and increased abdominal fat.[60,61] Sedentary time alone is associated with metabolic status. The amount of time patients were sedentary predicted higher levels of fasting insulin, independent of the amount of time spent engaging in moderate- or vigorous-intensity activity.[62] This highlights the importance of reducing sedentary time to improve metabolic health, possibly in addition to the benefits associated with a physically active lifestyle.

Treatments

At this time, there's no evidence-based, approved drug therapy for NAFLD/NASH. Lifestyle change is a critical part of any attempt to reverse the course of NAFLD/NASH. NASH should be treated aggressively to prevent progression to cirrhosis, as these patients are seldom candidates for liver transplantation because of morbid obesity, cardiovascular disease, or other complications of their underlying conditions.

Dietary macronutrient composition, physical activity, and behavioral therapy all play critical roles in successful weight loss.

Weight Reduction

The minimal amount of weight loss for improving NASH hasn't been determined. Long-term dietary intervention studies are limited; however, evidence suggests that weight loss is effective for improving liver disease related to NAFLD, as it positively influences insulin sensitivity, hypertension, and dyslipidemia.

Data from a small study have shown that a 9% weight loss significantly improves steatosis and marginally improves inflammation but doesn't affect fibrosis.[63] In the same study, subjects with NASH who lost 5% of their body weight experienced improvements related to insulin sensitivity and hepatic steatosis compared with those who lost less than 5% of their body weight. However, only in subjects who achieved at least a 9% weight reduction were there significant improvements in inflammation, ballooning (a form of liver cell death), and steatosis.[63]

One study demonstrated that a decrease of about 200 kcal/day and a weight loss of about 3.5 kg (roughly 8 lbs) improved liver histology and enzymes in NASH patients.[64] In older adults who were obese, a 10% weight loss over six months resulted in a 45% reduction in liver fat.[65]

A randomized controlled trial involving patients with biopsy-proven NASH involved a combination of diet, exercise, and behavior modification.[66] Participants who achieved the study weight loss goal of 7% or more experienced significant improvements in steatosis, inflammation, and ballooning injury.[66] Weight loss also has been shown to prevent the progression of fibrosis in NASH.[67]

Several recent studies[27,68-70] using a variety of interventions, either diet alone or in combination with different exercise prescriptions,[71-74] have consistently reported reduction in liver fat ranging from 20% to 81% (average of 40%). The degree of hepatic fat reduction was

proportional to the intensity of the lifestyle intervention and generally required a weight loss of 5% to 10%. Aiming for a weight loss of 7%, as proposed by the international societies on the basis of an extensive body of literature, appears to be a reasonable recommendation in overweight and class 1 obese patients.[4]

Bariatric Surgery

Bariatric surgery is the most effective strategy to help people who are obese achieve and maintain weight loss.[75] However, no randomized controlled trials have examined bariatric surgery as a treatment option for NAFLD or NASH. But results from several uncontrolled studies[76-78] and two small controlled studies[79,80] indicate that weight loss (average 30% reduction in BMI and/or 60% excess weight loss) achieved through bariatric surgery reduces transaminases (alanine transaminase and aspartate transaminase) and NAFLD.

In the Swedish Obese Subjects study, researchers compared the long-term effects of bariatric surgery in 1,775 subjects who underwent gastric banding, vertical banded gastroplasty, or gastric bypass with 1,795 controls and found that bariatric surgery was associated with lower serum alanine transferase and aspartate aminotransferase levels at two and 10 years follow-up.[81]

In a Medline review, many studies showed that patients who underwent gastric bypass experienced a histological improvement in steatosis, inflammation, and fibrosis, with resolution or improvement in a significant portion of participants (50% to 80%).[82]

One meta-analysis found that steatosis, steatohepatitis, and fibrosis improved or resolved after bariatric surgery in the majority of patients.[83] However, a Cochrane review concluded that the lack of randomized controlled trials and high-quality clinical studies prevents the determination of benefits and risks of bariatric surgery as a treatment option for patients with NASH.[84]

Cirrhosis has been associated with adverse outcomes following bariatric surgery, including progression to liver transplantation.[85] Hepatic decompensation can occur after gastric bypass, so a careful assessment for liver disease is indicated in gastric bypass candidates based on the high prevalence of NAFLD, including cirrhosis, in this population.

In 2012, the American Gastroenterological Association and the American College of Gastroenterology concluded that bariatric surgery isn't contraindicated in otherwise eligible obese individuals with NAFLD or NASH.[86]

Nutrition Therapy

Aside from the possibility of achieving weight loss through caloric restriction as a treatment for NAFLD, dietary composition can directly influence NAFLD development. There's evidence that manipulating either macronutrient or micronutrient content can affect levels of inflammation, serum lipids, and insulin resistance independent of weight loss. A summary of nutrition therapy for NAFLD is provided in the table below.

Proposed Nutritional Guidelines for NAFLD/NASH

Weight loss	10% of initial body weight over six months Maintenance of weight loss Bariatric surgery when individuals qualify
Calorie intake	1,200 to 1,500 daily **Energy deficit of 500 kcal/day based on Mifflin-St Jeor formula*
Total fat	≤ 35% of total calories
Monounsaturated fatty acids	15% to 25% of total calories
Polyunsaturated fatty acids	5% to 10% of total calories Omega-3 fatty acids
Saturated fatty acids	7% to 10% of total calories
Carbohydrate	50% of total calories > 50% carbohydrate sources from whole grains Avoid high-fructose corn syrup Added sugars < 10% of total calories
Protein	15% of total calories Lean and vegetable protein
Antioxidants	None
Physical activity	≥ 150 minutes/week at moderate intensity or ≥ 75 minutes/week at vigorous intensity Cardiovascular exercise five times weekly Resistance training two or more times weekly Decrease time spent sedentary

— Sources: References 58, 63, 65, 81, 83, 89, 156-161

Healthful Fats

Randomized trials have shown an inverse association between the Mediterranean diet and cardiovascular risk.[87] Cross-over design studies have determined that, in obese women and overweight men, a low-fat diet decreased liver fat compared with a high-fat diet.[68,88]

Dietary recommendations for heart health include a decrease in saturated fats (to less than 7%) and trans fats (to less than 1%) as well as keeping total fats to 25% to 35% of total calories.[89]

Monounsaturated Fats

Replacing carbohydrate with monounsaturated fatty acids (MUFAs) increases triglyceride-rich lipoprotein catabolism. One study of weight-stable patients showed that liver fat decreased

significantly in those following a diet that was high in monounsaturated fat (32 g/day) and low in fat and saturated fat (23% fat and 7% saturated fat).[33]

Epidemiologic studies have shown anti-inflammatory and cardiovascular benefits from the Mediterranean diet, which is rich in MUFAs.[90] Olive oil (73% MUFAs) appears to provide a direct benefit in improving plasma lipids in the treatment of the metabolic syndrome.[91]

In two small randomized trials, patients following the Mediterranean diet, compared with those following an individualized isocaloric low-fat/high-carbohydrate diet, experienced a 29% to 38% reduction in hepatic fat and improved insulin sensitivity.[92,93] The Mediterranean diet was high in MUFAs from olive oil and also contained omega-3 PUFAs from both plant and marine sources. The macronutrient composition of the diet was 40% of energy from fat (50% MUFAs and 18% omega-3 PUFAs), 40% from carbohydrate, and 20% from protein. These findings were independent of weight loss.

Given the close relationship among the metabolic syndrome, obesity, and NAFLD, patients with NAFLD can benefit from including healthful fats in their diet.

Omega-3 PUFAs

Evidence from epidemiologic and randomized controlled trials indicate that supplementation with omega-3 PUFAs lowers triglyceride levels and reduces the risk of coronary heart disease and mortality.[94,95] High consumption of omega-3 PUFAs derived from fish diminishes hepatic triglyceride lipoprotein secretion and inhibits de novo lipogenesis.[96,97]

Using the Therapeutic Lifestyle Change diet criteria with a diet high in fish-derived omega-3 fatty acid (1.23 g/day EPA + DHA) vs. a low fish diet (0.27 g/day EPA + DHA) for 24 weeks, the higher fish diet decreased plasma triglycerides by 24%.[98]

Three human clinical trials support these findings by showing that giving patients with NAFLD omega-3 PUFAs (1 to 2.7 g/day for six to 12 months) improved hepatic steatosis, inflammation, and fibrosis.[21,22,99] Capanni and Spadaro both demonstrated that triglyceride levels decreased 25 to 37 mg/dL when patients' diets were supplemented with 1 to 2 g of omega-3 PUFAs per day for six and 12 months, respectively.

Omega-6 PUFAs

Dietary changes over the past few decades in the intake of omega-6 and omega-3 PUFAs show striking increases in the omega-6 to omega-3 ratio (15:1), which coincide with increases in chronic inflammatory diseases such as NAFLD, cardiovascular disease, and obesity.[100]

In contrast, a randomized 10-week study found that a diet high in omega-6 PUFAs (15% of energy as linoleic acid) reduced liver fat compared with a diet high in saturated fatty acids in abdominally obese patients.[101] However, this study was not standardized or controlled.

No conclusions can be made regarding whether increased omega-6 PUFA consumption, above the currently recommended levels (5% to 10% of energy), may be suggested in NAFLD patients, as reduced simple carbohydrate intake may confer similar benefits.[102,103]

Low Sugar Intake

Diets with less carbohydrate and more fat have relatively greater benefits for insulin levels, triglycerides, and HDL cholesterol concentrations than do hypocaloric, low-fat diets.[104,105] Ryan and collegues found that a hypocaloric diet moderately lower in carbohydrate (40% carbohydrate and 45% fat) decreased serum alanine transaminase concentrations to a greater degree than did a higher-carbohydrate, low-fat diet (60% carbohydrate and 25% fat).[106] For individuals with NAFLD who were glucose intolerant, the low-carbohydrate caloric restriction significantly improved hepatic insulin sensitivity compared with the low-fat diet.

In contrast, changes in visceral fat mass and insulin sensitivity were similar between a low-calorie, reduced-carbohydrate diet (fewer than 90 g of carbohydrate) and a reduced-fat diet (less than 20% fat).[107] No prospective controlled dietary intervention studies have evaluated whether a low-fructose diet improves NAFLD.

The World Health Organization recommends that the daily intake of added sugars makes up no more than 10% of total energy. The American Heart Association recommends limiting the amount of added sugars to no more than one-half of daily discretionary calories, which for women is approximately 100 kcal/day (6 tsp of sugar) and for men is 150 kcal/day (9 tsp of sugar).

Physical Activity Therapy

lt's well established that exercise enhances insulin sensitivity, reduces the progression to type 2 diabetes, and favorably modifies lipids independent of weight loss.[108,109] Physical activity can help maintain weight loss and improve insulin resistance, and recent data suggest that patients who demonstrate histological liver improvement tend to be more active.[110]

Improvement in insulin sensitivity has been shown to correlate with a reduction in total body fat, especially in visceral adiposity, which in turn contributes to the fatty acid delivery to the liver.[111] As a result, a physical activity intervention leads to improvement in insulin resistance and may decrease hepatic steatosis, inflammation, and disease progression in NAFLD.

Recent data from animal studies support the beneficial effects of exercise not only on the liver but also on adipose tissue and skeletal muscle.[112,113] Four studies have investigated the effects of exercise without dietary modification on hepatic steatosis. Participants engaged in 30 to 60 minutes of exercise two to three times per week over a period of six to 12 weeks. In all but one study, liver fat content diminished without a significant weight change.[114-117]

Intensity and Duration

Several investigators have studied the exercise intensity needed to improve metabolic profiles. According to the American Gastroenterological Association, both intermittent and daily exercise can help achieve weight loss and improve insulin sensitivity.[89]

O'Donovan and colleagues evaluated the effects of 24 weeks of moderate-intensity exercise (cycling three times per week at 60% VO_2 max) to burn 400 kcal vs. high-intensity exercise (cycling three times per week at 80% VO_2 max). Training at 60% VO_2 max was comparable

with 80% VO_2 max as far as the effects on insulin sensitivity, triglycerides, and glucose concentration.[118] It's possible that the overall energy expenditure achieved per workout session is more important than the intensity of the exercise.

Kistler and colleagues concluded that neither moderate-intensity exercise nor total exercise duration was associated with biopsy-proven NASH or fibrosis stage, although they did find that vigorous activity and doubling the duration of vigorous exercise was associated with decreased odds of developing NASH.[119]

St George and colleagues found that patients who increased their physical activity by 60 minutes or more per week significantly reduced their weight and all liver enzymes. The improvements in liver enzymes were independent of weight change.[120] Regular aerobic exercise for 30 minutes or more per day at 60% to 70% max heart rate at least five days per week normalized alanine transaminase levels in 45% of subjects.[121]

Aerobic vs. Resistance Exercise

The effects of aerobic training vs. resistance training also have been debated. Several studies have shown that regular increased aerobic exercise improves the metabolic parameters associated with NAFLD.[65,110,122] Combined exercise (aerobic plus resistance training) has been shown to be more effective than aerobic exercise alone for improving inflammation and cardiovascular risk factors in obese adolescents who had metabolic syndrome.[123] A one-year intervention of 30 minutes of aerobic training plus 20 minutes of resistance training three times per week was more effective for reducing NAFLD biomarkers in adolescents who were obese than were aerobic workouts alone.[124]

An exercise program of two resistance training sessions one hour per week for three months didn't change hepatic fat, but hepatic insulin sensitivity increased and glucose production rate decreased without weight loss.[116]

Researchers have demonstrated that resistance exercise for at least eight weeks reduces liver fat independent of weight loss.[125,126]

Cardiac Fitness

Higher cardiorespiratory fitness at baseline may contribute to a successful hepatic outcome during lifestyle modification. Among the parameters predicting change in liver fat, fitness at baseline emerged as the strongest factor, independent of exercise intensity during two interventions.[74,127]

Three cross-sectional studies investigated the association between maximal aerobic capacity (VO_2 max), an estimate of cardiorespiratory fitness, and liver fat. While a small study[128] found no significant difference in VO_2 max between subjects with high vs. low liver fat, two larger studies[129,130] showed a close relationship of fitness with both liver fat and NAFLD prevalence.

Kantartzis and colleagues conducted a lifestyle intervention with 50 adults with NAFLD consisting of 10 sessions with a dietitian and more than three hours of moderate sports participation per week. The researchers determined that cardiorespiratory fitness as well as

exercise intensity at baseline were the greatest predictors of liver fat, independent of total and visceral adipose tissue.[74] Most studies reported negative relationships between liver fat and cardiorespiratory fitness or habitual physical activity,[60,128,130-132] which were independent of BMI but not visceral obesity. Abdominal obesity is a major risk factor for NAFLD and more important than BMI, and at any given weight, individuals who exercise more have less visceral fat than do those who are sedentary.[133]

Vitamin and Antioxidant Supplementation

Oxidative injury is a well-accepted cause of liver injury in NASH. Therefore, antioxidant treatments such as vitamin and mineral supplementation have been theorized to decrease oxidative stress and improve NAFLD.

Vitamin E

Oxidative stress is a key mechanism of hepatocellular injury and disease progression in subjects with NASH. The antioxidant vitamin E has been studied most in relation to NAFLD treatment. Comparing these trials is difficult because of different doses, varying criteria, and the use of other antioxidants to assess outcomes.

Many small studies have demonstrated conflicting results with vitamin E doses between 300 and 800 IU/day.[134,135] Two randomized controlled trials showed significant improvements in hepatic steatosis with 800 to 1,000 IU/day.[136,137]

Treatment with high-dose vitamin E should be carefully considered because of its association with an increased risk of hemorrhagic stroke and all-cause mortality.[138,139]

Vitamin D

Increasing evidence suggests that vitamin D may play an important role in modifying the risk of cardiometabolic outcomes such as type 2 diabetes and cardiovascular disease.[140,141]

In one study, decreased serum 25-hydroxy vitamin D concentrations were associated with NAFLD and specifically the severity of hepatic steatosis, nectroinflammation, and fibrosis.[142]

The association between vitamin D status and NAFLD warrants further research.

EPA + DHA

Only preliminary uncontrolled trials are available regarding omega-3 PUFAs and NAFLD. Despite strong beneficial animal evidence supporting the use of omega-3 PUFAs for treating NAFLD, published studies on humans have consisted of small sample sizes and had a number of methodological flaws.[143,144]

Probiotics

Accumulating evidence has linked the alteration of gut microbiota to the development of NAFLD in humans as well as animal models. Gut microbiota are thought to contribute to the development of obesity-related NAFLD through the small bowel and liver (gut-liver axis).[145]

Preliminary data from two nonrandomized pilot studies have suggested that probiotics may improve liver enzymes and decrease markers of lipid peroxidation.[146,147]

Prebiotics and probiotics have been used in an attempt to modify the microbiota as preventive or therapeutic strategies for this pathological condition.[148] Their beneficial effects on NAFLD have been demonstrated in animal models[149,150] and limited human studies.[151]

A randomized controlled pilot trial discovered that taking one tablet containing 500 million *Lactobacillus bulgaricus* and *Streptococcus thermophilus* for three months improved levels of liver aminotransferases in patients with NAFLD.[151]

A Cochrane review determined that randomized controlled trials are needed to determine whether prebiotics and probiotics that modify intestinal microbiota are modalities to treat NAFLD.[152]

Other Nutrients

Other hepatoprotective agents, such as betaine[153] and ursodeoxycholic acid,[154] weren't effective in randomized trials. Ginger (*Zingiber officinale*) has been studied in small, animal studies that suggest it can improve insulin sensitivity and reduce hepatic fat content.[155]

In Practice

NAFLD and NASH are increasingly relevant public health issues that are closely associated with the worldwide epidemics of diabetes and obesity. While pharmacologic therapies are lacking, sustained 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 first-line therapy of any treatment plan for patients with NAFLD. Available studies suggest that weight loss of 5% or more improves steatosis, and weight loss of 7% or more improves histological disease activity in NASH. Long-term, moderate weight loss, including bariatric surgery, through the reduction of energy intake and regular physical exercise is recommended for patients with NAFLD.

Five times weekly aerobic exercise of moderate to vigorous intensity lasting at least 30 minutes along with twice weekly resistance training should be a part of the lifestyle intervention, as this enhances whole-body lipid oxidation and improves steatosis and cardiometabolic risk regardless of weight loss. Reducing sedentary time should be highlighted and recommended to improve metabolic status.

The influence of the dietary macronutrient composition is important and can help reduce hepatic fat and inflammation. Based on data from cardiovascular or diabetes trials and from limited studies in patients with NAFLD, a diet that is lower in carbohydrate and saturated fat and is higher in monounsaturated fats as well as dietary sources of omega-3 PUFAs likely will be beneficial. Dietary advice to limit consumption of all added caloric sweeteners, including high-fructose corn syrup, is warranted.

There's insufficient data to either support or refute the use of antioxidant and probiotic supplements for patients with NAFLD.

In summary, weight loss, physical exercise, and dietary changes should be implemented on a long-term basis in all patients with NAFLD/NASH regardless of disease severity.

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Examination

1. Obesity has been directly associated with increases in the prevalence of which of the following?
A. Glucose resistance
B. Hypothyroid
C. Metabolic syndrome
D. Bone density

2. Weight gain in normal-weight or obese individuals may be associated with higher levels of which of the following?
A. Oxidative stress and insulin resistance
B. Cirrhosis
C. HDL cholesterol
D. VO_2 max

3. Which of these fatty acids has been linked to an increased risk of developing nonalcoholic fatty liver disease (NAFLD) in animal studies?
A. Cholesterol
B. Monounsaturated
C. Polyunsaturated
D. Saturated

4. Marge was diagnosed with nonalcoholic steatohepatitis (NASH) two months ago and learned from a website that fruit juicing with agave nectar and prunes is the best way to "shrink her liver." What nutrient could Marge consume in excess quantity if she followed that advice?
A. Glucose
B. Trans fatty acids
C. Protein
D. Fructose

5. What type of diet is best suited for treating NAFLD?
A. Probiotic
B. Mediterranean
C. Low-fat Ornish
D. Zone

6. An RD who works in an outpatient nutrition clinic has a patient who's obese and has been diagnosed with NAFLD. The patient is taking 1,000 mg of omega-3 PUFAs (300 mg of EPA + 200 mg DHA) to improve his liver enzymes. What steps should the RD take to inform the patient of proper supplementation?
A. Tell the patient to avoid all supplements.
B. Inform the patient that there's no conclusive data on how omega-3 fatty acid supplements may improve NAFLD, but discuss how to increase dietary omega-3 intake.
C. Tell the patient to discuss omega-3 fatty acid supplementation with his hepatologist or primary care physician.
D. Recommend the patient take 3 g of omega-3 PUFAs per day

7. Diets that are lower in _____ and higher in ____ have relatively greater benefits on insulin, triglycerides, and HDL cholesterol concentrations than hypocaloric, low-fat diets.
A. Carbohydrate; monounsaturated or polyunsaturated fats
B. Carbohydrate; total fat
C. Total fat; carbohydrate
D. Protein; carbohydrate

8. For how long and at what level of intensity should adults exercise on most or all days of the week?
A. Moderate intensity for 60 minutes or longer
B. Vigorous intensity for 60 minutes or longer
C. Moderate intensity for 30 minutes or longer
D. Vigorous intensity for 15 to 30 minutes

9. Resistance exercise reduces liver fat independent of weight loss in people with NAFLD.
A. True
B. False

10. Prebiotics and probiotics may improve liver enzymes by modifying which of the following?
A. Microbiota
B. Lipid peroxidation
C. Insulin resistance
D. Lean body mass