

Nutritional Approaches to Achieve Weight Loss in Nonalcoholic Fatty Liver Disease^{1–3}

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) can range in spectrum from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), which is characterized by lipotoxicity, hepatocellular ballooning, and inflammation and can progress to cirrhosis. Weight loss is the cornerstone treatment for NAFLD and NASH. Various randomized controlled trials have shown that weight loss of ≥ 5 –10% leads to significant improvements in hepatic steatosis. Diets high in sodium and fructose have been implicated in the pathogenesis of NAFLD. Although some clinical studies suggest that an isocaloric high-fructose diet does not worsen NAFLD, these clinical studies are often short in duration. More recently, the Dietary Approaches to Stop Hypertension diet, a sodium-restricted diet, has been associated with less prevalence of NAFLD and has been shown to improve NAFLD. In addition, the Mediterranean diet has been promising in improving hepatic steatosis, and a larger randomized controlled trial is currently enrolling subjects. For those who are unable to pursue weight loss through dietary approaches, bariatric surgery has been shown to improve hepatic steatosis and steatohepatitis. This method has been variable in improving hepatic fibrosis. In conclusion, weight loss is crucial to the improvement of NAFLD and NASH, and patients should attempt various diets in an attempt to achieve weight loss. *Adv Nutr* 2017;8:253–65.

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Introduction

Nonalcoholic fatty liver disease (NAFLD)⁶ is defined as evidence of hepatic steatosis by imaging or histology and the absence of secondary causes of hepatic fat accumulation (1). NAFLD is further categorized based on histology, with nonalcoholic fatty liver characterized by hepatic steatosis without evidence of hepatocellular injury, and nonalcoholic steatohepatitis (NASH) defined as hepatic steatosis with associated hepatocyte injury (e.g., ballooning)

and inflammation, with or without fibrosis (1). NAFLD has more of a benign course, with <4% of cases progressing to cirrhosis, whereas NASH has more of an aggressive course, with 21–28% of cases progressing to cirrhosis (2).

NAFLD Incidence and Prevalence

Incidence data are limited and variable worldwide for NAFLD. In studies from Japan and England, the incidence of NAFLD ranged from 18.5 to 31 cases/1000 person-years (3, 4). Similarly, there are wide discrepancies between prevalence data, depending on the populations studied and definitions used. NAFLD has now become the most common cause of abnormal liver tests in industrialized countries (5, 6). In the United States, when using NHANES III from 1988 to 1994, the overall prevalence of NAFLD and NASH in the lean population was $\sim 19\%$ and $\sim 3\%$, respectively (7). Various studies that used ultrasound estimate prevalence rates in the general population to be from 13% to 46% (8–12). With the use of magnetic resonance spectroscopy in the Dallas Heart Study, an estimated NAFLD prevalence of 31% was noted in the general population, with a higher prevalence in Hispanics (45%) than in whites and blacks (33% and 24%, respectively) (6). A summary review of prevalence data by Vernon et al. (12) estimates a US

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⁶ Abbreviations used: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BPD, biliopancreatic diversion; DASH, Dietary Approaches to Stop Hypertension; FGF21, fibroblast growth factor 21; HF, high-fat; HFHC, high-fat, high-carbohydrate; HFHCH, high-fat, high-cholesterol; LAGB, laparoscopic adjustable gastric banding; LS, lifestyle intervention; LSG, laparoscopic sleeve gastrectomy; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; RYGB, Roux-en-Y gastric bypass; TLR, toll-like receptor; VBG, vertical banded gastroplasty.

NAFLD prevalence rate in the general population of 30%, with the rest of the world ranging from 6% to 35%, with a median of 20%. NASH rates are lower, on the order of 3–5% (12). The estimated worldwide prevalence is 20–30% in Western countries and 5–18% in Asia (13).

Risk Factors for NAFLD

Nonmodifiable risk factors for disease progression include age, race, genetic background, and baseline histology, whereas modifiable factors include weight gain, insulin resistance, and diabetes (14, 15). An increasing prevalence (66%) of bridging fibrosis is observed if the patient's age is >50 y and he or she is obese or diabetic (14, 15). Increasing age, male sex, and Hispanic ethnicity are associated with increased NAFLD prevalence (6, 11, 16–22). In a cohort of 400 subjects recruited from an army medical center, the overall prevalence of NAFLD was 46%, but was highest in Hispanics (58.3%), and lower in Caucasians (44.4%) and African Americans (35.1%) (22). In this study, NAFLD patients had a higher BMI, ate fast food more often, and exercised less often than those without NAFLD (22).

Obesity, metabolic syndrome, and diabetes mellitus play a central role in the development of and progression to NASH. In 432 patients with histologically proven NAFLD, NASH patients were more likely to be male, have a lower hip-to-waist ratio, have higher aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations, have higher serum triglycerides and have lower HDL (23). Patients with moderate to severe fibrosis were more likely to be male and Caucasian, have type 2 diabetes, and have higher ALT and AST concentrations (23). The prevalence of NAFLD and NASH was higher (74% and 22.2%, respectively) in diabetic patients (22). Similarly, Leite et al. (24) showed a 69% prevalence of NAFLD in patients with type 2 diabetes. Obesity and NAFLD are also strongly correlated (25–29).

Natural History

Adams et al. (30) demonstrated that NAFLD patients in Olmsted County, Minnesota, were at increased mortality compared with what is expected (HR: 1.34; 95% CI: 1.003, 1.76; $P = 0.03$), secondary to malignancy (28%), ischemic heart disease (25%), and liver disease (13%). Liver disease was the third-leading cause of death in NAFLD patients, but only the thirteenth-leading cause in the general Minnesota population (30). Risk factors associated with increased mortality included impaired fasting glucose, increased age, and cirrhosis (30). NASH patients specifically have increased mortality from liver-related issues (31–34). The prevalence of cirrhosis (10.8% compared with 0.7%, respectively) and liver-related mortality (7.3% compared with 0.9%, respectively) were significantly higher in a 15-y follow-up for NASH patients than they were for NAFLD patients (34). Another study further supported overall increased mortality in 229 NAFLD patients (HR: 1.29; 95% CI: 1.04, 1.59; $P = 0.02$) in a mean follow-up of 26.4 y (35). NAFLD patients were again shown to be at increased risk of

cardiovascular disease (HR: 1.55; 95% CI: 1.11, 2.15; $P = 0.01$), but also at increased risk of liver-specific mortality, including from hepatocellular carcinoma (HR: 6.55; 95% CI: 2.14, 20.03; $P = 0.001$), cirrhosis (HR: 3.2; 95% CI: 1.05, 9.81; $P = 0.041$), and infections (HR: 2.71; 95% CI: 1.02, 7.26; $P = 0.046$) (35). Advanced fibrosis and not the nonalcoholic fatty liver disease activity score (NAS; based on steatosis, hepatocyte ballooning, and lobular inflammation) predicted increased liver specific mortality (35). In a meta-analysis, NASH patients had accelerated fibrosis when compared with NAFLD patients (1 stage over 7.1 y compared with 1 stage over 14.3 y, respectively) (36).

Pathophysiology

NAFLD is a result of an imbalance between hepatic TG production and export. Studies that use radioactive labeling have shown that most of the hepatic FFAs arise from the lipolysis of visceral fat (60–80%) and de novo lipogenesis (26%), rather than from dietary FFAs (37–39). Hepatic FFA deposition further leads to lipotoxicity, hepatic inflammation, oxidative stress, activated apoptotic pathways, and hepatic fibrogenesis (2). Visceral fat, and to a lesser degree subcutaneous fat, can produce many of the adipocytokines that drive the chronic inflammatory response seen in obesity (40–42). The adipose tissue becomes a source of hormones (such as leptin and adiponectin) or cytokines (TNF- α and IL-6) that are important contributors in worsening the FFA load, insulin resistance, and tissue injury (40). Increased hepatic exposure of fat-derived TNF- α can inhibit adiponectin and promote steatosis, oxidative stress, and hepatic inflammation and apoptosis (43). Klein et al. (44) illustrated that visceral fat is a predominant producer of inflammatory adipocytokines by showing that liposuction, which removes exclusively subcutaneous fat, does not improve insulin resistance or affect concentrations of inflammatory mediators such as adiponectin, TNF- α , or IL-6 (44). Therefore, treatment should be targeted at the metabolic obesity that is central to the pathology of NASH.

Weight Loss in NASH

Lifestyle modifications should be the foundation of any treatment plan, with the goals of increased energy expenditure and decreased caloric intake. Dietary weight loss and exercise have been examined in various studies. Because most liver-related mortality is observed in NASH patients, clinical trials are often targeted at NASH patients rather than those with NAFLD. The NAS, a scoring system devised by the NASH Clinical Research Network, is used in clinical trials as an objective measure of histologic improvement. The NAS is based on steatosis, lobular inflammation, and hepatocyte ballooning, but it can vary significantly even between pathologists.

Two randomized controlled trials illustrated the benefits of weight loss on histologic markers. Fifty NASH patients were randomly assigned to a diet of 1400 kcal/d and vitamin E, with or without orlistat (which inhibits fat absorption),

and had paired liver biopsies 36 wk after random assignment (45). The orlistat did not enhance weight loss or improve histology, NASs, or liver enzymes (45). However, in the stratified analysis according to weight loss, patients who had a $\geq 5\%$ total body weight loss had improvements in insulin sensitivity, adiponectin concentrations, and hepatic steatosis and lower NASs compared with those who did not have weight loss (45). In another randomized controlled trial, 31 individuals who had biopsy-proven NASH were randomly assigned to 48 wk of intensive lifestyle intervention (LS) compared with structured education (control). A higher proportion of patients in the LS group had more significant weight loss (9.3% compared with 0.2%, respectively, $P = 0.003$) and improved NASs (46). A significantly larger proportion of the patients in the LS group (72%) had achieved their primary endpoint (reduction in NAS ≥ 3 or NAS ≤ 2) than did those in the control group (30%) ($P = 0.03$) (46).

Weight Loss in NAFLD

Dietary intervention has been shown to improve NAFLD in randomized controlled trials (45, 46). NAFLD patients with a larger percentage of weight loss were observed to have more NAFLD remission (Figure 1) (47). This was illustrated by a randomized controlled trial in Hong Kong, where 154 patients were randomly assigned to either dietitian-led LS or standard of care for 12 mo (47). The majority of the patients (97%) in the group who achieved a weight loss of $\geq 10\%$ had NAFLD remission, whereas only 13% of those who had a weight loss of $\leq 3\%$ achieved NAFLD remission (Figure 1) (47). In the cohort, 64% of the intervention group compared with 20% of the controls achieved NAFLD remission (95% CI: 30%, 58%; $P < 0.001$) (47). In the adjusted multivariate analysis, body weight reduction was the only independent predictor of NAFLD remission (47). The intervention group also had larger mean decreases in intrahepatic TG content as measured by proton magnetic resonance spectroscopy (47). This was further corroborated by another prospective study in which 293 patients underwent 52 wk of lifestyle changes and received paired liver biopsies (48). Ninety percent of patients who were able to achieve $\geq 10\%$ weight loss had resolution of their NASH, and 45% of patients who achieved that amount of weight loss had regression of their fibrosis (48). Patients who lost $\geq 5\%$ of their weight had higher rates of NASH resolution (58%) than did those who lost $< 5\%$ of their weight (10%; $P < 0.001$), and a ≥ 2 -point improvement in NASs without fibrosis worsening (82% compared with 32% in those who lost $< 5\%$ of their weight; $P < 0.001$). Hepatic fibrosis either stabilized or improved in patients who were able to achieve a significant amount of weight loss (the groups that had > 7 –10% and $\geq 10\%$ weight loss) (Figure 2) (48). Fibrosis was unchanged or improved in 85 of 88 (95%) patients who achieved $\geq 5\%$ weight loss, in contrast to 162 of 205 (79%) individuals without this extent of weight loss. However, most of the patients with worsening fibrosis [43 of 46 (93%)] were associated with little or no weight reduction

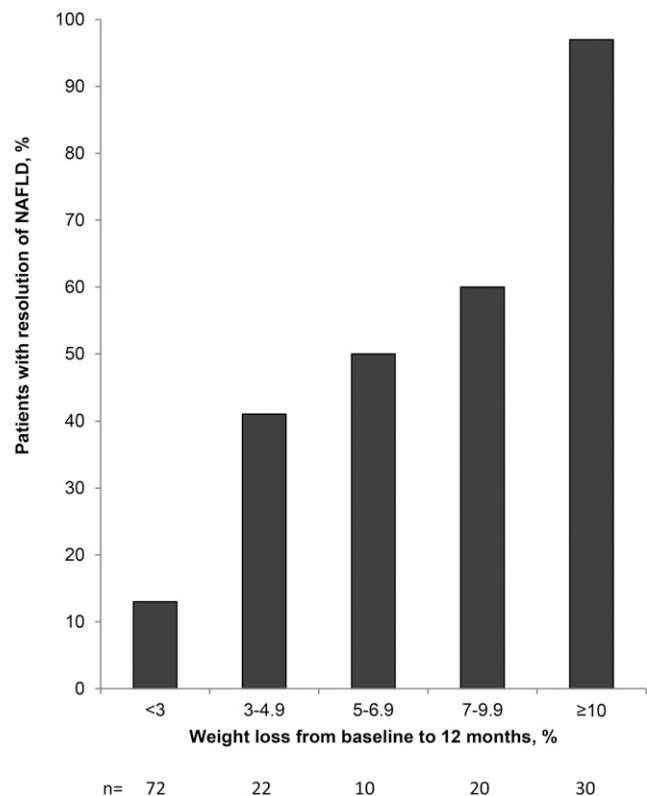


FIGURE 1 NAFLD patients ($n = 154$) randomly assigned to a dietitian-led lifestyle modification compared with standard of care for 12 mo. The figure represents the percentage of patients who had NAFLD resolution according to the percentage of weight loss when compared with their baseline. P -trend < 0.001 . NAFLD, nonalcoholic fatty liver disease. Adapted from reference 47 with permission.

($< 5\%$) (48). In the small number of patients who had worsening fibrosis in the setting of weight loss, this could be reflective of a liver biopsy sampling error. Regardless, overall, the data suggests that a higher amount of weight loss is associated with higher rates of NASH resolution and fibrosis improvement.

Different Diets in NAFLD

Dietary salt in NAFLD. Animal studies have shown that a high-sodium diet is associated with obesity and visceral adipose hypertrophy, as well as increased leptin concentrations (49). The adipocytes taken from rats on a high-sodium diet were observed to have the increased ability to convert glucose into lipids (49). Rats fed a high-sodium diet (91 mg sodium \cdot kg $^{-1}$ body weight \cdot d $^{-1}$) had increased hepatic steatosis, serum FFAs, insulin concentrations, and TGs (50). Further associations between a high-sodium diet and NAFLD were observed in clinical studies. In a Korean study of 100,177 patients, men and women who consumed a higher-sodium diet had an increased prevalence of NAFLD (51). In this study, patients were given questionnaires that quantified their sodium intake and were divided into quintile groups, and NAFLD

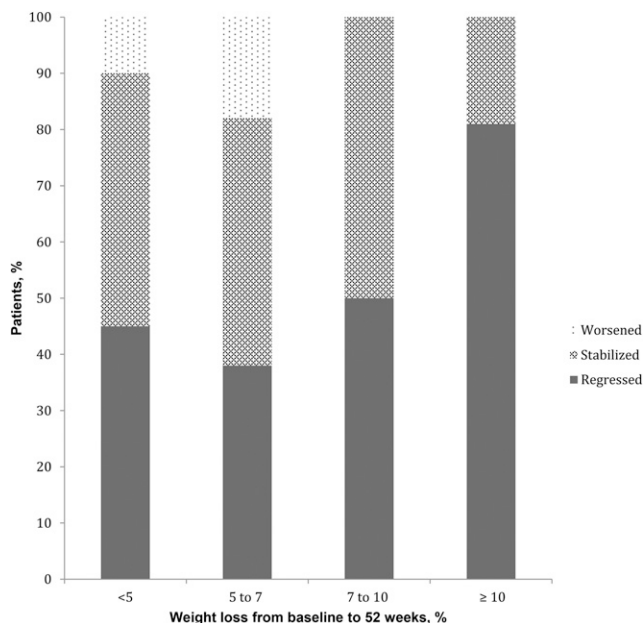


FIGURE 2 NASH patients ($n = 293$) who underwent 52 wk of lifestyle changes. This figure represents hepatic fibrosis stabilization, regression, or worsening according to the percentage of weight loss from baseline to 52 wk. $P = 0.04$. NASH, nonalcoholic steatohepatitis. Adapted from reference 48 with permission.

was diagnosed by ultrasound and exclusion of chronic alcohol use (≥ 20 g/d in women and ≥ 30 g/d in men). Men and women who were in the top quintile group for consuming sodium (mean sodium intake of 3485 mg/d in men and 3310 mg/d in women) had an increased prevalence of NAFLD, by 25% and 32%, respectively [prevalence ratio (PR) = 1.25; 95% CI: 1.18, 1.32; $P < 0.001$ and PR = 1.32; 95% CI: 1.18, 1.47; $P < 0.001$, respectively] compared with sodium users in the lower quintile group. In another Chinese study, patients in the high-salt quartile group had an increased prevalence of NAFLD compared with patients in the lowest quartile group (37.5% compared with 28%, $P < 0.05$) (52). However, in a multivariable analysis that adjusted for BMI, there was no association of NAFLD with a high-salt diet, which suggests that the association between salt and NAFLD may still be secondary to obesity (52). Only subjects in the highest quartile of regular animal food pattern consumers were associated with NAFLD (HR: 1.35; 95% CI: 1.063, 1.724; $P < 0.05$) compared with subjects in the lowest quartile. However, the limitations of the study include the lack of objective definition of a high-salt diet, with patients being categorized into the high-salt diet group if they were noted to have consumed large amounts of rice, pickled vegetables, processed meat, bacon, salted duck eggs and fish, and tea.

Furthermore, studies have suggested that the Dietary Approaches to Stop Hypertension (DASH) diet is associated with a lower prevalence of and improvement in NAFLD. In a randomized controlled trial, 60 NAFLD subjects

(diagnosed by ultrasound and elevated liver enzymes) were randomly assigned to either the DASH diet or control diet for 8 wk (53). DASH is a sodium-restricted (<2400 mg/d) diet rich in vegetables, fruits, whole grains, and low-fat dairy, and low in saturated fats, cholesterol, refined grains, and sweets. Both groups were calorie-restricted to 350–700 kcal less than the computed energy requirement and had a diet composed of 52–55% carbohydrates, 16–18% proteins, and 30% total fats, but the DASH diet had a higher content of fruits, vegetables, and whole grains (53). Initial and follow-up ultrasounds showed that more patients in the DASH diet group (80% compared with 43.3%, $P = 0.003$) had a decreased NAFLD grade by ultrasound (53). Patients in the DASH diet group also had more significant decreases in their BMI, insulin and ALT concentrations, serum TGs, and total-to-HDL cholesterol ratio (53). This suggests that caloric restriction alone may be inadequate and that diet type may be more important in improving liver enzymes and hepatic steatosis. In a separate smaller case-control study, patients who adhered to the DASH diet in the top quartile group were 30% less likely to have NAFLD (HR: 0.70; 95% CI: 0.61, 0.80) (54). However, the results of this study may be of less significance given the small numbers (102 patients), and the association was not significant after adjusting for confounders such as dyslipidemia and BMI. Because the DASH diet has been shown to have benefits that include lowering cardiovascular disease risk and hypertension, we advise that patients with NAFLD or NASH attempt to adhere to a low-sodium diet (55).

Carbohydrates and fat in NAFLD. High-carbohydrate (specifically fructose or sucrose) and high-fat (HF) diets have been implicated in the development of NAFLD in animal studies (56–58). In a study of Wistar rats that were fed either an HF diet (45% fat and 34.1% carbohydrate), a control diet (57.9% carbohydrates and 13.4% fat), or a high-sucrose diet (20% sucrose in drinking water, 57.9% carbohydrates, and 13.4% fat) for 12 wk, rats consuming the HF diet had developed grade 2–3 steatosis in 34–66% of their hepatocytes, whereas rats consuming the high-sucrose diet had developed grade 1–3 steatosis in 5–33% of their hepatocytes (56). None of the controls developed steatosis (56). Fructose alone has been implicated in the development of NAFLD and severe hepatic fibrosis in NAFLD in animal studies (57–59). Rats fed an HF diet (58% fat) and a high-fat, high-carbohydrate (HFHC) diet (58% fat, 42 g carbohydrates/L drinking water with a 55% fructose and 45% sucrose solution) gained more weight, consumed more calories, and had increased fasting glucose and insulin concentrations (57). In addition, rats fed HF and HFHC diets had increased hepatic steatosis, liver weights, hepatic TGs, and ALT concentrations compared with controls (57). However, only rats consuming the HFHC diet developed perisinusoidal and periportal fibrosis (57). The high-fructose diet caused NAFLD and fibrosis by increasing reactive oxygen species, inflammatory macrophages, and hepatic stellate cell activation (when mRNA levels of α -smooth muscle actin were measured), and increased concentrations

of plasma coenzyme Q9 (57). Plasma coenzyme Q is important in the mitochondrial respiratory chain and in mitochondrial ATP production, which is needed for fructose metabolism (57). In the first step of fructose metabolism, fructose is first phosphorylated to fructose-1-phosphate by means of fructokinase with the use of a substrate ATP (60). NASH has been associated with mitochondrial damage and ATP depletion (61).

However, the proposed mechanism by which fructose causes NAFLD in animal studies remains to be further elucidated and may be multifactorial. Both animal studies and clinical studies show that high fructose intake can cause NAFLD by increasing intestinal permeability and endotoxemia, and decreasing *Lactobacillus* and *Bifidobacterium* in the gut flora (62–64). There is increasing evidence that increased intestinal permeability and bacterial overgrowth is important in the pathogenesis of NAFLD (65, 66). Gut microflora-derived bacterial products (such as LPS) activate hepatic toll-like receptors (TLRs), which then activate an inflammatory cascade that contributes to the pathogenesis of NAFLD in animal models (67, 68). Mice deficient in TLR-4 and myeloid differentiation factor 2 (downstream inflammatory cascade of TLR-4) that were fed a methionine choline-deficient diet (a dietary model of NASH) had less evidence of NASH, hepatic fibrosis, and hepatic TGs (68). In addition, TLR-4 deficient mice fed a fructose-containing diet (30% fructose water for 8 wk) had decreased hepatic TG accumulation by almost 40% compared with fructose-fed wild-type mice (63). The TLR-4-deficient mice that were fed fructose also had less hepatic lipid peroxidation and less activation of inflammatory pathways, or less myeloid differentiation primary response gene 88 (*Myd88*) and TNF- α expression, compared with the wild-type mice that were fed fructose (63). This suggests the importance of TLR-4 in the role of pathogenesis of NAFLD.

NAFLD is associated with increased intestinal permeability and bacterial endotoxins in both animal and clinical studies. In fructose-fed mice (30% fructose water for 8 wk), plasma obtained from the portal vein demonstrated increased bacterial endotoxin concentrations by almost 40% compared with control, and antibiotics attenuated this effect (62). In this study, fructose-fed mice had increased hepatic lipids and TGs by almost 8-fold and 4-fold, respectively, compared with controls. A high-fructose diet was also associated with increased TNF- α expression and increase lipid peroxidation (increased 4-hydroxynoneal adducts and I κ B expression) (62). In mice fed a high-fructose diet and antibiotics, hepatic lipid and TG accumulation significantly decreased by 55% and 48%, respectively, and portal vein endotoxin concentration decreased by 40%, which is similar to concentrations in the control mice (62). This was further observed in clinical studies; high fructose intake was also associated with increased portal vein endotoxins in NAFLD patients. In a pediatric cohort study, obese Hispanic adolescents with hepatic steatosis (magnetic resonance spectroscopy >5%), were noted to have increased plasma bacterial endotoxin concentrations compared with those without NAFLD. NAFLD adolescents who

were also provided high-fructose beverages at 3 meals/d for 4 wk had higher plasma endotoxin concentrations at weeks 2 and 4 compared with adolescents who received high-glucose beverages (64). Although these were short-term studies, it is quite notable that the consumption of fructose was associated with transient increases in plasma endotoxin, and further studies are needed to delineate the gut microflora of patients consuming a diet that includes high-fructose corn syrup. In animal studies, probiotics such as *Lactobacillus* have attenuated the NAFLD induced by a fructose diet. Mice fed *Lactobacillus* and a fructose diet had a portal ALT that was almost normalized, and this was associated with less hepatic steatosis and TNF- α expression (69–71).

High fructose consumption has been associated with increased severity of hepatic fibrosis in NAFLD patients. In the NASH Clinical Research Network, 427 NAFLD subjects were enrolled in a study that required a food questionnaire data and a follow-up liver biopsy after 3 mo (72). After researchers controlled for age, sex, BMI, and total caloric intake, daily fructose consumption was associated with a lower steatosis grade, but a higher fibrosis grade. In older patients (≥ 48 y of age), fructose consumption was associated with increased hepatic inflammation and hepatocyte ballooning (72). Surprisingly, minimal-to-moderate consumers of fructose had lower fasting serum glucose and TGs and a better insulin sensitivity profile than those not consuming fructose (72). However, the authors concluded that these appreciable differences in insulin sensitivity were related to lifestyle changes patients pursued after enrolling in the trial. They also concluded that fructose consumption is a modifiable risk factor in preventing the progression of NAFLD and the increased risk of hepatic fibrosis. In addition, 47 patients with NAFLD (without cirrhosis) with paired liver biopsies and dietary questionnaires were compared with 24 controls, and there was a 2- to 3-fold higher consumption of high-fructose corn syrup-related food products (carbonated beverages, artificially sweetened drinks, baked goods, candies, canned fruits, jams, and dairy products) in patients with NAFLD (60). Patients with NAFLD had a higher daily consumption of high-fructose corn syrup beverages than did control patients (365 compared with 170 kcal/d, $P < 0.05$) and higher mRNA levels of fructokinase, suggestive of higher fructose metabolism (60). However, in a meta-analysis of 7 isocaloric trials in which fructose was exchanged for carbohydrates and 6 hypercaloric trials in which fructose was supplemented, only the fructose-supplemented hypercaloric diets were associated with increases in intrahepatocellular lipids and increased ALT concentrations (73). The isocaloric exchange of fructose for other carbohydrates did not cause NAFLD; only excess caloric intake supplemented with fructose was associated with NAFLD (73). However, the limitation of the meta-analysis was that it included trials that were short in duration (≤ 4 wk) and of poor quality (73). In addition, this meta-analysis did not include trials that evaluated for NAFLD improvement. A randomized controlled

double-blinded study of 24 overweight Hispanic American adolescents with NAFLD showed that there was no difference in fructose-only compared with glucose-only beverages (74). After 4 wk of calorie-matched glucose- or fructose-only beverages, there was no significant difference in change in hepatic fat or body weight (74). The glucose-only beverage group did have better adipose insulin sensitivity, decreased circulating concentrations of oxidized LDL, and decreased plasma FFA (74). Glucose-only beverages were associated with a better cardiovascular profile than fructose-only beverages. However, similarly, the limitation of this study was the short duration, and it would be difficult to ascertain the long-term effects of the chronic consumption of fructose beverages. However, because of the short duration of fructose consumption in the meta-analysis and randomized controlled trial, it is difficult to make conclusions that the long-term consumption of fructose would not worsen NAFLD. Thus, based on animal studies and some of the preliminary clinical studies, we would advise patients to avoid beverages and diets that are high in fructose.

Studies do show low-carbohydrate diets to be comparable with low-fat diets, but many of the studies include lifestyle changes (e.g., an increase in physical exercise) and hypocaloric diets. One study randomly assigned 54 women with NAFLD diagnosed by ultrasound and ALT >29 U/mL to either a low-carbohydrate diet (27% protein, 28% fat, and 45% carbohydrate) or a low-fat diet (25% protein, 21% fat, <10% saturated fat, and 54% carbohydrate) for 6 mo (75). However, these patients also participated in lifestyle changes that included 1 h of physical exercise 5 d/wk. The 2 groups lost a similar amount of weight (5.7% and 5.5% of their initial weight, respectively) and received a mean of 1593 ± 82 kcal/d. The decrease in ALT was higher (41%) in the low-carbohydrate diet group than it was in the low-fat diet group (33.3%), but whether changes from baseline were significant was not reported (75). The limitation of the study was that only AST and ALT were measured as primary endpoints, and no follow-up ultrasound was obtained. Another study randomly assigned 170 overweight and obese subjects to hypocaloric diets (with a 30% energy reduction) that were low fat (fat $\leq 20\%$ total energy, 0.8 g/kg protein, and remaining energy from carbohydrates) or low carbohydrate (≤ 90 g carbohydrates, minimum of 30% fat intake, and 0.8 g/kg protein) for 6 mo (76). These patients did not necessarily have NAFLD, and only approximately one-half of the patients had an intrahepatic lipid content (as measured by MRI spectroscopy, $>5.6\%$) (76). Similar reductions in weight (change in body weight of 7.5 ± 0.6 compared with 6.5 ± 0.7 kg, $P = 0.25$), intrahepatic fat (measured by MRI spectroscopy), abdominal visceral fat, TGs, FFAs, and HDL were observed with both the low-fat and low-carbohydrate diets (76). Intrahepatic fat decreased by a significant 47% in the reduced-carbohydrate group and by 42% in the reduced-fat group (76). Abdominal visceral fat mass decreased significantly by 22% in the former and by a similar 21% in the latter group (76). Another study

also randomly assigned 52 obese patients (not patients with NAFLD) to hypocaloric (reduction of 750 kcal/d) low-fat (60% carbohydrate and 25% fat) or low-carbohydrate (40% carbohydrate and 45% fat) diets for 4 mo, and showed the low carbohydrate diet to be associated with greater reductions in ALT (-9.5 ± 9.4 U/L) when compared with the low-fat diet (-4.2 ± 8.3 U/L; $P < 0.01$), and this remained significant even when adjusted for weight loss, baseline ALT concentration, age, and sex (77). However, the 2 groups lost similar amounts of weight [7.0 ± 3.8 and 5.7 ± 4.1 kg, respectively, relative to baseline ($P < 0.001$)] (77). These studies either restrict subjects to hypocaloric diets or require them to engage in lifestyle changes (physical exercise) in addition to the low-carbohydrate or low-fat diet. It is difficult to ascertain whether the metabolic improvements are secondary to weight loss or secondary to the specific macronutrients. In one small pilot study, 4 of 5 NASH patients who underwent a 6 mo low-carbohydrate ketogenic diet that was not restricted in caloric intake and not accompanied by an exercise program had improvements in hepatic steatosis, necroinflammatory grade, and fibrosis at their follow-up biopsy (78). The diet limited carbohydrate intake to <20 g/d, without meat or egg intake or caloric restrictions. One patient in this study had worsening steatohepatitis, but this was attributed to nonadherence to the dietary recommendations and lack of weight loss. Regardless, if consuming a low-fat or low-carbohydrate diet can lead to substantial reductions in weight loss, and weight loss is shown to be beneficial in NAFLD, patients should be advised to try such diets.

Mediterranean diet and NAFLD. The Mediterranean diet has been associated with overall decreased mortality and decreased cancer incidence and cardiovascular events (79). A pilot study compared the Mediterranean diet with a low-fat, high-carbohydrate diet in 12 patients with NAFLD who underwent a 6-wk crossover intervention study (80). The Mediterranean diet is mostly composed of vegetables, whole grains, and fruit, with increased intake of legumes, raw unsalted nuts, and oily fish (81). In the pilot study, patients then underwent a 3-h hyperinsulinemic-euglycemic clamp study to determine insulin resistance, and hepatic steatosis was measured by magnetic resonance spectroscopy (80). A significant relative reduction in hepatic steatosis and improvement in insulin sensitivity was observed in the patients who followed the Mediterranean diet compared with those on a low-fat, high-carbohydrate diet ($39\% \pm 4\%$ compared with $7\% \pm 3\%$, respectively, $P = 0.012$) (80). Based on this pilot study, a larger randomized controlled trial called the Mediterranean Dietary Intervention for Adults with Non Alcoholic Fatty Liver Disease is now underway and currently enrolling patients until 2017 (81). This was further corroborated by another study in which NASH patients were noted to have lower adherence to the Mediterranean diet than were NAFLD patients (82). Seventy-three NAFLD patients (diagnosed by elevated ALT and hepatic steatosis on an ultrasound) participated

in an FFQ over 12 mo and then crossmatched to healthy controls (82). Adherence to the Mediterranean Diet was measured by the MedDietScore (range 0–55) (82). Liver biopsies were available in 34 of the 73 NAFLD patients, with 68% of the patients classified as having NASH and 32% classified as having NAFLD (82). The MedDietScore negatively correlated with serum ALT ($P = 0.03$), insulin concentrations ($P = 0.001$), and steatosis severity ($P = 0.006$), and positively correlated with serum adiponectin concentrations ($P = 0.04$) (82). Patients with NASH were noted to have a lower adherence to the Mediterranean diet than were NAFLD patients (29.3 ± 3.2 compared with 34.1 ± 4.4 , $P = 0.004$), and were associated with higher abdominal fat and a higher BMI (82). In a logistic regression analysis, a 1-unit increase in the MedDietScore was associated with a 36% lower likelihood of having NASH (OR: 0.64; 95% CI: 0.45, 0.92; $P = 0.02$) even after adjusting for sex and abdominal fat (82). These are promising preliminary studies that the Mediterranean diet could improve NAFLD and prevent NASH and hepatic fibrosis.

The Mediterranean diet is rich in olive oil, or MUFAs, and improvements in NAFLD may be due to MUFAs or PUFAs content. Animal studies have shown that oils high in MUFAs or PUFAs have attenuated the effects of dietary-induced NAFLD. Mice that were fed an HF diet (49% energy from fat) for 12 wk and fed phenol-rich extra virgin olive oil (41.7% energy from olive oil) had an improved lipid profile, decreased visceral adipocyte inflammatory cytokine expression, and improved NASs compared with mice fed an HF diet without extra virgin olive oil (83). The mean NAS of mice fed the HF diet was >4 , whereas mice fed the extra virgin olive oil and phenol-rich extra virgin olive oil had NASs of 3 and 2, respectively (83). In addition, menhaden oil, which is rich in PUFAs such as EPA (20:5n–3) and DHA (22:6n–3), has been shown to improve the hepatic damage induced by a high-fat, high-cholesterol (HFHCH) diet in both wild-type mice and genetic animal models of hyperlipidemia (84). In wild-type and LDL-receptor knockout ($Ldlr^{-/-}$) mice (the genetic model of hyperlipidemia) fed an HFHCH diet supplemented with olive oil or menhaden oil for 12 wk, the addition of menhaden oil decreased liver enzymes and hepatic TGs to concentrations similar to controls, and reduced markers of hepatic inflammation and fibrosis when compared with olive oil (84). Mice consuming an HFHCH diet supplemented with olive oil still had hepatic steatosis, increased liver enzymes, increased body weight, and increased expression of markers of inflammation and fibrosis (84). The discrepancy can be explained by the percentage of energy from olive oil. In the first mouse study, 41.7% of the energy was from olive oil, whereas in the second study, PUFA content was 2% of the total energy. However, a subsequent mouse study from the same group that used $Ldlr^{-/-}$ mice fed a Western-type diet showed that olive oil, DHA alone, EPA alone, or EPA and DHA supplementation for 16 wk significantly attenuated the Western diet–induced NASH phenotype and decreased markers of inflammation, fibrosis, and

oxidative stress (85). Further clinical studies will be needed to extrapolate this data to humans, but given the initial promising results from the Mediterranean diet, it seems consistent that MUFAs and PUFAs may have some beneficial effects on NAFLD.

High-protein diet and NAFLD. A mouse study showed that a high-protein diet (35% protein and 42% fat) prevented mice from gaining total body weight and the epididymal fat pad associated with an HF diet (86). Although the high-protein diet did not decrease liver weights overall, it did decrease hepatic FFAs, total cholesterol, and phospholipid content, and the hepatic lipid content for mice on the high protein diet was only 35–40% than that of lipid content for mice on the low protein diet in mice on the high-protein diet (86). Mice on the high-protein diet had elevated mRNA expression of $Pgc1\alpha$ (PPAR gamma co-activator 1- α) which is a coactivator of the $Pparg$ (PPAR gamma) receptor involved in hepatic mitochondrial FA oxidation, oxidative phosphorylation, and gluconeogenesis (86). The high-protein diet was associated with increased import and oxidation of FAs into the hepatic mitochondria (86). Interestingly, mice on the high-protein diet did not have increased plasma amino acids, but had elevated plasma BCAAs, which was thought to be important in protein catabolism. A rat study showed that a high-protein diet (52.4% protein) reduced the adiposity that was gained from a high-sucrose (39.8% carbohydrate and 9.4% fat) and HF, high-sucrose diet (33.1% fat and 14.4% carbohydrate) by 20% (87). In addition, the high-protein diet was associated with decreased markers of lipogenesis [mRNA expression of FA synthase, acetyl-CoA carboxylase a ($Acaa$), acetyl-CoA carboxylase b ($Acab$), and sterol regulatory element binding transcription factor 1c ($Srebf-1c$)] and increased ketogenesis (elevated β -hydroxybutyrate concentrations) (87). More recently, in a prospective study of 37 NAFLD patients with type 2 diabetes placed on an isocaloric diet (30% protein, 40% carbohydrates, and 30% fat) with high animal or plant protein for 6 wk, the high-protein diet was associated with significant 36–48% reductions in hepatic steatosis by measurement with MRI spectroscopy (animal protein diet, $P = 0.0002$; plant protein diet, $P = 0.001$) (88). Both groups had decreased BMI, visceral adipose tissue, liver enzymes, plasma FFAs, and insulin and glucose concentrations (88). Again, with both high-protein diets, free amino acid concentrations were unchanged after the diet, but the animal-protein diet was associated with higher postprandial concentrations of BCAAs and methionine, suggestive of increased amino acid catabolism in skeletal muscle and liver (88). Both high-protein diets also significantly decreased serum concentrations of fibroblast growth factor 21 (FGF21) and decreased FGF21 receptor cofactor $klotho \beta$ expression in adipose tissue (88). Elevated FGF21 is associated with NAFLD and is positively correlated with intrahepatic TG content (89, 90). FGF21 is predominantly synthesized in

the liver, and the influx of FFAs from adipose tissue induces FGF21 receptor expression (90). The FGF21 receptor then decreases serum FFAs by inhibiting visceral adipose from undergoing further lipolysis, inhibiting further hepatic TG synthesis, and promoting FFA oxidation and ketogenesis (90). Another smaller prospective study of 60 patients showed that a hypocaloric (1000 kcal/d) high-protein diet (41% protein, 29% carbohydrate, 24% fat, and 6% fiber) decreased liver stiffness, alkaline phosphatase, γ -glutamyl transferase, lipid concentrations, and controlled attenuation parameters, or measurements of hepatic steatosis through transient elastography, by 14.0% ($P < 0.001$) (91). Thus, these studies are promising, but participants were only given a high-protein diet for short duration of time. Thus, more studies would be needed to assess the long-term effects of a high-protein diet, because a high-protein diet can worsen chronic kidney disease (92).

Various individual food sources and NAFLD. Studies show that broccoli protects against the development of NAFLD and liver adenomas in mice fed an HF diet and treated with diethylnitrosamine (an agent that induces hepatocellular carcinoma in mice). Mice fed an HF diet (19% fat and 31% sucrose) and 10% broccoli had decreased liver weight, hepatic TGs, plasma ALT concentrations, and number of liver nodules and adenomas compared with mice fed an HF diet without broccoli (93). In this study, mice were started on a Western diet and 10% broccoli at 5 wk before induction with diethylnitrosamine at 6 wk (93). A subsequent study from the same group again showed that broccoli attenuated the NAFLD effects of the Western diet (94). However, in the second mouse study, the broccoli did not slow down hepatocarcinogenesis, but mice were induced with diethylnitrosamine at a younger age (2 wk) and before the administration of broccoli and the Western diet (4 wk to 7 mo) (94). Based on these studies, broccoli can attenuate the effects of NAFLD in mouse models, minimizing the risk that they develop liver adenomas, but not necessarily alter the course of hepatocarcinogenesis. However, more clinical studies would be needed to extrapolate this preliminary data to humans.

Various other supplements, such as ginger, flaxseed, and green tea extracts, have been explored to improve NAFLD. In a smaller clinical study of 50 patients, flaxseed supplementation (30 g/d for 12 wk), in addition to lifestyle modifications, decreased AST and ALT and hepatic fibrosis and steatosis scores (as measured by transient elastography with controlled attenuation parameter measurements) (95). In a separate study of 44 patients, patients were randomly assigned to 12 wk of 2 g ginger supplementation/d or placebo, and ginger supplementation improved liver enzymes and hepatic steatosis, but not fibrosis scores (measured by transient elastography) (96). Finally, 80 participants were randomly assigned to green tea extract (500 mg/d) for 90 d or placebo, and green tea extracts were noted to improve liver enzymes (97). In this study, there was no

follow-up ultrasound to determine whether there was improvement in hepatic steatosis; thus, it is unclear whether the green tea extract had improved hepatic inflammation alone or had improved the hepatic steatosis. The limitations of these clinical studies are their small size and short duration of supplementation. This data would have to be further corroborated by larger studies with long-term follow-up.

Surgical Weight Loss in NASH and NAFLD

The prevalence of NAFLD and NASH is particularly high in morbidly obese patients. In a review of 12 observational cohorts of morbidly obese patients [BMI (kg/m^2) >40 or >35 with a serious comorbid condition], the prevalence of NAFLD, NASH, and cirrhosis was 91%, 37%, and 1.7%, respectively (29). According to the NIH Consensus Development Conference on Gastrointestinal Surgery for Severe Obesity (1991), indications for gastrointestinal surgery include a BMI >40 or BMI >35 with serious cardiopulmonary complications such as type 2 diabetes, obstructive sleep apnea, hypertension, and cardiomyopathy (98). These patients should also be aged 18–60 y, be an acceptable surgical risk, and also have a history of multiple failed weight loss attempts (98).

Bariatric surgeries include restrictive procedures such as vertical banded gastroplasty (VBG), laparoscopic adjustable gastric banding (LAGB), and laparoscopic sleeve gastrectomy (LSG), whereas restrictive and malabsorptive procedures include Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD), and BPD with duodenal switch (42, 99). Bariatric surgery has been shown to decrease overall mortality by decreasing the incidence of cardiovascular disease, malignancy, and diabetes (100, 101). Obese Swedish subjects who underwent bariatric surgery had decreased overall mortality (HR: 0.71, $P = 0.01$) secondary to decreases in cancer- and cardiac-related deaths (100). Mean weight loss was highest for gastric bypass ($25\% \pm 11\%$ from baseline), followed by VBG and banding ($16\% \pm 11\%$ and $14\% \pm 14\%$, respectively) after 10 y (100). Another large retrospective US study showed a 40% reduction (HR: 0.60; 95% CI: 0.45, 0.67; $P < 0.001$) in overall mortality in those who underwent RYGB (102). A subanalysis of nondiabetic obese Swedish subjects showed that bariatric surgery decreased the overall incidence of diabetes (HR: 0.17; 95% CI: 0.13, 0.21; $P < 0.001$) (101). A more recent randomized trial compared RYGB, LAGB, and LS in a 3-y follow-up of obese (BMI 30–40) subjects with type 2 diabetes, and showed that gastric surgery, in addition to LS, had higher rates of achieving complete or partial remission of diabetes (40% for RYGB and 29% for LAGB) than did LSs alone (0% for LSs) (103).

Most studies have shown that bariatric surgery, predominantly RYGB, improves hepatic steatosis and steatohepatitis, but they have reported variability in the improvement of hepatic fibrosis (104–107). In 109 morbidly obese patients who underwent bariatric surgery, NASH disappeared in 85% of the patients ($n = 70$, 95% CI: 75.8, 92.2), along

with there being significant improvements in BMI, liver enzymes, insulin resistance profile, and fasting blood glucose (108). In this cohort, 64.2% (70) had gastric bypass, 29.4% (32) had gastric banding, 5.6% (6) had sleeve gastrectomies, and 1 had a biliointestinal bypass. Patients underwent a nutrition program prior to surgery, but it was not mentioned that they continued intensive lifestyle intervention after surgery. However, notably, patients with persistent NASH after 1 y had less significant weight loss and a worse insulin resistance profile than did those with NASH resolution (mean \pm SD BMI decrease of 9.1 ± 1.5 compared with 12.3 ± 0.6 , respectively; $P = 0.005$) (109). In addition, patients with gastric banding tended to have less weight loss and worse NASHs. This suggests that NASH improvement is correlated with sustained weight loss, and it stresses the importance of nutritional approaches in conjunction with gastric surgery. In this study, hepatic fibrosis was reduced in only 33.8% of the subjects (95% CI: 23.6, 45.2), and most patients (85%) had a METAVIR F0 to F2 fibrosis score (108). This is similar to other studies, in which less than one-half of the patients had fibrosis improvement after gastric surgery; however, the follow-up time was only 1 y, and fibrosis resolution could take longer. Thus, it is difficult to ascertain the effects of bariatric surgery on fibrosis resolution. In another study of 70 patients who underwent bariatric surgery (43 with RYGB, 23 with LSG, and 6 with LAGB) with paired liver biopsies, subjects had improvement in steatosis, inflammation, and fibrosis after surgery (105). However, only 20% of the patients had fibrosis resolution and 2 cirrhosis patients did not have improvements in their hepatic fibrosis. Similar to the previous study, the majority of the patients (84.3%) had METAVIR F0 to F2 fibrosis scores. Again, the mean follow-up was only 15 ± 9 mo between paired liver biopsies. Thus, with longer-term follow-up, there may be a higher percentage of patients with fibrosis resolution. In this study, RYGB subjects had more weight loss and hepatic histologic improvements than did those who underwent restrictive procedures (93% of RYGB patients compared with 66% patients of restrictive procedures had improvement in hepatic histological grade; $P = 0.004$). Weight loss again correlated to the degree of hepatic histologic improvement, suggestive of the importance of maintained weight loss even after gastric surgery and potentially the importance of lifestyle intervention. More recently, LSG was compared with intragastric balloon placement and LS alone in obese adolescents during a 1-y follow up, and there was more significant weight loss in patients who underwent LSG than in those who used any of the other measures (LSG subjects lost 21.5% of baseline body weight; those who used intragastric balloons lost 3.4%, and those who underwent LSs lost 1.7%). NASH was resolved in 100% of LSG patients ($n = 20$) and in only 24% of intragastric balloon patients ($n = 20$), whereas fibrosis was resolved in 90% of LSG patients (all with a METAVIR F2 fibrosis score) and 37% of the intragastric balloon patients. None of the patients who had LS alone had significant improvements in fibrosis or NASH. Again, the reduction in NASHs correlated with the degree of weight loss and improvements in insulin resistance.

Although the numbers are small but similar to other studies, this study suggests the importance of degree of weight loss correlating to improvement in NASH and fibrosis.

In another study with morbidly obese patients (mean \pm SD BMI: 52.8 ± 1), 51 patients underwent VBG. Although 84–86% had improvement in their steatosis and steatohepatitis scores, only 47% had improvement in their hepatic fibrosis scores. In fact, 11.7% also had worsening hepatic fibrosis, whereas 41.1% remained unchanged. Grade 3 steatosis and steatohepatitis were present in 98% of the subjects, and 84.3% had METAVIR F0 to F2 fibrosis scores. Patients in this study were placed on a special liquid diet of 655 calories (61.4 g protein, 91.2 g carbohydrates, and 4.9 g fat), which was distributed in 5 meals for the first 3 mo after VBG, and placed on regular diet afterwards. Thus, long-term nutritional approaches were not used in conjunction with gastric surgery. A meta-analysis showed bariatric surgery to have a beneficial effect overall on hepatic histology, with the observed pooled proportion of patients with improvement or resolution of steatohepatitis at 81.3% (95% CI: 61.9%, 94.9%). For fibrosis, this was 65.5% (95% CI: 38.2%, 88.1%) (109). However, only 5 of 15 studies had paired liver biopsies in which fibrosis could be evaluated; thus, assessment of fibrosis was more limited. The variability of fibrosis improvement suggests a more permanent liver damage that may take longer periods of time to reverse than described in these studies. In addition, there may also be certain time points at which fibrosis is not reversible. Therefore, more biomarkers are needed to determine which type of patients would or would not have fibrosis reversal with gastric surgery.

Although there are certain benefits to gastric surgery, obese patients are at increased risk of nutritional or vitamin deficiencies preoperatively and postoperatively (110, 111). Preoperatively, most obese subjects are already at risk of vitamin D deficiency secondary to a sedentary lifestyle, lack of sun exposure, and vitamin D sequestration in adipose tissue (111). Moreover, hyperinsulinemia is associated with increased urinary excretion of zinc, and obesity-related chronic inflammation induces hepcidin production, which blocks iron absorption in duodenum (111). In an observational cohort of 318 RYGB patients, 12 mo after surgery, the incidence of postoperative vitamin A deficiency was 11%, that of vitamin C was 34.6%, and that of 25-hydroxyvitamin D was 7%. Those of vitamin B-1, vitamin B-2, and vitamin B-12 were 18.3%, 13.6%, and 3.6%, respectively (112). In addition, various studies have compared RYGB to BPD with duodenal switch (113, 114). Although patients who underwent BPD had more weight loss and more significant reductions in total cholesterol and LDL compared with those undergoing RYGB, they were also at increased risk of 25-hydroxyvitamin D and vitamin A deficiency, and had an increased number of follow-up operations related to the initial gastric surgery (113, 114). Both groups had similar remission rates of diabetes, metabolic syndrome, and changes in blood pressure (113). Thus, the benefits of gastric surgery in improving NASH and NAFLD would have to be outweighed against the potential

long-term nutritional deficiencies and side effects. We would advise patients to pursue LAGB, LSG, or RYGB, over BPD. However, the long-term benefits of improving hepatic fibrosis would need to be furthermore clarified in future studies.

Conclusion

Obesity is a rising epidemic and is central to the pathogenesis of NAFLD and NASH. Insulin resistance is the first step in NAFLD, leading to an imbalance of hepatic lipid metabolism, which then leads to oxidative stress, lipotoxicity, hepatic inflammation, apoptosis, and hepatic fibrogenesis. Cardiovascular disease is often the most common cause of mortality in NAFLD patients, but NASH patients have increased liver-specific mortality. Weight loss and dietary intervention has been shown in randomized controlled trials to improve NAFLD and NASH, with the larger benefit seen with larger amounts of weight loss (>5%). High-salt and high-fructose diets have been implicated in the development of NAFLD and associated with the increased prevalence of NAFLD in clinical studies. The DASH and Mediterranean diets have proven to be promising in the improvement of hepatic steatosis. Thus, NAFLD patients should pursue any of the dietary approaches and adhere to a low-sodium and low-fructose diet. Bariatric surgery is often effective in patients with morbid obesity in improving hepatic steatosis and steatohepatitis, but its effects have been variable in improving hepatic fibrosis. More studies are needed to compare various diets and their impacts on NASH and obesity-related disease complications in long-term follow-ups.

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