Review

Nutrition as Therapy in Liver Disease

Neil D. Shah, MD; and Alfred Sidney Barritt IV, MD, MSCR

UNC Liver Center, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA

ABSTRACT

Purpose: The importance of nutrition is often underrecognized in the routine clinical care of patients with chronic liver disease. Nutrition therapy plays a significant role in the management of alcohol-related liver disease and nonalcoholic fatty liver disease. In patients with cirrhosis from any etiology, malnutrition and sarcopenia are directly related to mortality, and nutritional interventions play an important role in the management of these patients. This review explores the role of nutritional intervention as adjuvant therapy across all chronic liver disease.

Methods: A narrative, qualitative systematic review was performed via searches of PubMed for nutritional aspects in the care of chronic liver disease.

Findings: Nutritional therapy plays a critical role in the management of chronic liver disease. In nonalcoholic fatty liver disease, specific macronutrient management can lead to weight loss and improved outcomes in these patients. In patients with alcohol-related liver disease, chronic cholestatic liver disease, and decompensated cirrhosis, caloric and protein intake plays a vital role improving outcomes in these patients. Micronutrient deficencies are also common in these patients and require supplementation to prevent other complications of malnutrition. Assessment and management of nutrition should accompany the typical care plan of patients with chronic liver disease.

Implications: This review of nutritional therapy in chronic liver disease highlights the current evidence-based and societal recommendations of macronutrient and micronutrient management across the spectrum of all chronic liver disease. (*Clin Ther.* 2022;44:682–696.)

INTRODUCTION

The liver plays a central role in nutritional metabolism, including glucose homeostasis, protein synthesis, and drug/toxin metabolism. Nutritional metabolism may be reduced in patients with chronic liver disease and can worsen as liver disease progresses to cirrhosis. In patients with alcohol-related liver disease (ALD), macronutrient and micronutrient deficiencies are common. For patients with cirrhosis, malnutrition and sarcopenia are seen in 50% to 90%[1] of patients and are associated with a myriad of outcomes, including higher mortality, hepatic decompensation, and reduced quality of life.[2] On the other end of the spectrum, high-caloric diets high in excess carbohydrates and fats have led to the nonalcoholic fatty liver disease (NAFLD) epidemic.[3]

Unfortunately, these nutritional issues are often underrecognized in chronic liver disease, and interventions for nutritional therapy are often underused. Multiple recommendations are available for the use of nutrition as adjuvant therapy in the comprehensive management of these patients. These include changes in caloric intake, protein supplementation, sodium restriction, and micro/macronutrient supplementation. This review highlights the current nutritional interventions that are used to treat across the spectrum of chronic liver disease, from decompensated cirrhosis to those without advanced fibrosis.

MATERIALS AND METHODS

A narrative, qualitative systematic review was performed of English language articles through December

Accepted for publication April 27, 2022
https://doi.org/10.1016/j.clinthera.2022.04.012
0149-2918/$ - see front matter

2021 via searches of PubMed for nutritional aspects in the care of chronic liver disease. The search was then updated in April 2022. Pertinent manuscripts relating to nutrition, frailty, and sarcopenia in fatty liver disease (alcoholic and nonalcoholic), cholestatic liver disease, and cirrhosis were reviewed. The references for these papers were reviewed as well to find additional manuscripts for consideration in this narrative review.

Nonalcoholic Fatty Liver Disease

NAFLD as a cause of chronic liver disease is highly prevalent, both globally and in the United States. NAFLD encompasses nonalcoholic fatty liver, defined as at least 5% intrahepatic triglyceride content, as well as nonalcoholic steatohepatitis (NASH), which features hepatic inflammation and can progress to cirrhosis. Approximately one third of the population in the United States and 25% of the global population have NAFLD, and up to 5% to 8% have NASH.[4] Factors, including dietary fat, genetic predisposition, and the gut microbiome, lead to increased visceral adipose tissue and subsequent hepatic fat accumulation. Although some aspects are poorly understood, it is known that hepatic fat is responsible for hepatic inflammation, which leads to chronic hepatocyte injury and progression of disease leading to cirrhosis and hepatocellular carcinoma in some patients.

Lifestyle modification, with dieting and exercise and sustained weight loss, has been shown to improve the histopathologic features of NASH. A meta-analysis of 4 randomized controlled trials revealed that a weight loss of ≥7% improved histologic, radiologic, and biochemical features of NASH.[5] A more recent study has supported these data, showing the results of paired liver biopsies in 261 patients undergoing lifestyle modifications for 1 year.[6] A dose–response curve was seen in this study, with improvement in all histologic features of NASH for patients attaining ≥10% weight loss. However, it is worth noting that a ≥5% weight loss was able to stabilize inflammation and fibrosis in the majority of patients. However, only 50% of patients were able to achieve significant weight loss, illustrating one of the largest barriers faced in the management of NASH. A study from a real-world cohort was even less optimistic in which only 32% of patients were able to lose 5% body weight and, unfortunately, 21% of these patients ultimately regained the weight.[7] To help with lifestyle changes, several strategies have been studied that can allow providers to educate their patients on how to successfully achieve the weight loss needed to treat NASH.

Role of Calories and Macronutrients in NAFLD

Hypocaloric diets are an important part of the treatment of NAFLD. These diets vary in macronutrient composition of carbohydrates and fats but often call for significant reduction of intake of these macronutrients. However, it remains inconclusive if significant reduction of a single macronutrient alone can lead to sustained weight loss.[8] Rather, caloric restriction alone can help drive weight loss as well as the reduction of liver fat.[9,10] Very-low-calorie diets (<800 kcal/d) can induce rapid weight loss in the first 6 months, but similar amounts of weight loss are seen in longer term analysis compared with more moderate calorie reduction.[11] Very rapid weight loss can actually exacerbate steatohepatitis or even lead to acute liver injury as reported after bariatric surgery.[12] Hence, multiple societies recommend more 500 to 1000 kcal/d moderate calorie reduction by 500 to 1000 kcal/d to help achieve weight loss.[13–15] This recommendation can also help patients with NASH and normal weight, colloquially referred to as "lean" NASH. A few studies have suggested that when paired with exercise, the calorie restriction leading to 3% to 5% of weight loss can enable NAFLD resolution in up to 70% of patients.[16,17]

Within diets and calorie restriction, food choices are equally important, as the relationship between NAFLD and particular foods is well described across cohort studies of varying age groups and ethnicities. Specific dietary intake patterns related to the risk of fatty liver disease include red meats, processed meats, hydrogenated/saturated fats, and sugar-sweetened beverages, which are often components of the Western diet.[18–21] A Western dietary pattern has also been shown to lead to NAFLD in adolescents in just 3 years, consistent with the increasing prevalence of NASH/NAFLD in younger populations.[22] Improving diet quality alone can actually improve fatty liver disease, and it is now becoming increasingly recognized that specific macronutrient combinations (rather than complete fat or carbohydrate elimination) may benefit NAFLD independent of weight loss. A recent meta-analysis of randomized controlled trials examined the effects of altering total dietary carbohydrate and fat content on intrahepatic triglyceride content (as assessed

by magnetic resonance spectroscopy).[23] As expected, a hypoenergetic (>500 calorie deficit per day) diet leads to reductions in hepatic fat content in both "low-fat, high-carb" diets as well as ketogenic diets that are "high-fat, low-carb," in which "low-carb" is defined as <60 g of carbohydrate intake per day. In the studies of isoenergetic diets, ketogenic diets higher in fats (43%–56% of energy intake) led to increased fat deposition as opposed to "low-fat, high-carb" diets. For hyperenergetic diets, the increase in hepatic triglycerides was almost 2 to 3 times more than that in "low-fat, high-carb" diets. Fat quality also made a difference, with studies consistently showing that saturated fats increased intrahepatic triglyceride content more than polyunsaturated fats by 40% to 50%.[23] These data are limited because of the short duration of the trials and lack of clinical outcomes data. Despite these limitations, the results are consistent and favor monounsaturated and polyunsaturated fatty acids over saturated fats in diets treating those patients with NAFLD.

Dietary sugars also have a role in the development of NAFLD. In particular, fructose has been associated with rapid fatty liver accumulation as well as increasing fat mass, de novo lipogenesis, and insulin resistance. Table sugar or sucrose (fructose + glucose), as well as high-fructose corn syrup, are the 2 major dietary sources of fructose and currently estimated to comprise ~10% of the caloric food intake for persons in the United States.[24] Arguably the largest source of this in the Western diet is through sugar-sweetened beverages. One study showed that intake of ≥7 sugar-sweetened beverages per week was associated with higher fibrosis, inflammation, and hepatocyte ballooning.[24] More recent data also support the relationship between these beverages and the risk of developing NAFLD.[25,26] Furthermore, fructose-sweetened beverages are a source of additional calories, which leads to the progression of NAFLD. Reducing intake of fructose, especially high-fructose corn syrup, can be a useful tool to help in the management of patients with NAFLD.

Role of Specific Diets in NAFLD

The Mediterranean diet is an isocaloric, high-fat and low-carbohydrate diet that has been suggested as a "model" diet for patients with NAFLD given its favorable macronutrient allocation. Fat composition is increased with ~30% to 40% of caloric intake but contains a higher ratio of monounsaturated and polyunsaturated fats compared with saturated fats. Carbohydrate intake is reduced to ~40% of caloric intake while protein comprises the remainder of the diet. Multiple studies have evaluated the effect of the Mediterranean diet on patients with NAFLD. A meta-analysis of 6 randomized controlled trials assessed the effect of the Mediterranean diet versus a control diet by evaluating differences in the fatty liver index, a surrogate for hepatic steatosis, as well as the homeostasis model assessment of insulin resistance. The Mediterranean diet significantly reduced the fatty liver index (standardized mean difference, –1.06; CI, –1.95 to –0.17; $P = 0.02$), as well as the homeostasis model assessment of insulin resistance (standardized mean difference, –0.34; CI, –0.65 to –0.03; $P = 0.03$).[27]

Another recent study compared the Mediterranean diet versus a "green-rich" Mediterranean diet to see the effect on hepatic fat.[28] The "green" group consumed green tea, Mankai, and a "green" shake on top of the typical isocaloric Mediterranean diet. Both groups had moderate weight loss, but the "green" group achieved almost double intrahepatic fat loss (–38.9% vs –19.6%; $P = 0.035$) as determined by using proton magnetic resonance spectroscopy. Greater intrahepatic fat loss was associated with intake of less red meat, less processed meats, more walnuts, more green tea, and more polyphenols. Again, these studies are limited because they do not evaluate histologic or clinical data. However, the benefits of the Mediterranean diet are promising and currently recommended as the diet of choice by the European associations for the study of diabetes, obesity, and the liver (European Association for the Study of Diabetes, European Association for the Study of Obesity, and European Association for the Study of the Liver, respectively),[13] as well as the American Gastroenterological Association.[29]

There are other popular diets that have early data regarding the management of patients with NAFLD. Intermittent fasting (IF) refers to low caloric food consumption for a predetermined amount of time, followed by a normal feeding period. Several forms of IF have been described. Alternate day feeding is a form of IF in which an individual fasts for 24 hours, followed by an ad libitum feeding day. The 5:2 fasting is severely reducing caloric intake for 2 days (~500 calories per day) followed by 5 days of normal consumption. Periodic fasting is intermittent fasting for 2 or more days with minimal caloric intake

(<500 calories) without repeated fasts. Finally, time-restricted fasting is eating only during certain hours of the day.[30] The hypothesized mechanism behind IF and its effect on the liver is a shift to ketones as the primary energy source during extended fasts, leading to increased catabolism of hepatic triglycerides. Recently, there have been data looking at the impact of IF on patients with NAFLD. One study randomized (3:1) 43 patients with elevated liver enzyme levels and risk factors for NAFLD to modified alternate day feeding or usual habitual diet over 8 weeks.[31] The study group had significant reductions in weight, body mass index (BMI), and alanine aminotransferase levels but no differences in glucose control or lipid levels. Liver steatosis and fibrosis were estimated by using shear-wave elastography, and there was a statistically significant reduction in the study group versus control for liver steatosis (ultrasound steatosis grade,mean difference, 0.38; 95% CI, −0.02 to 0.79; $P = 0.01$) and fibrosis (kPa, mean difference, 0.74; 95% CI, 0.19 to 1.29). Another similar randomized study looked at a 5:2 diet compared with a standard diet for 12 weeks.[32] The 5:2 group (n = 25) had significantly higher reduction of hepatic fat by magnetic resonance spectroscopy (–2.6%; 95% CI, –5.0 to −0.2), as well as a reduction in liver stiffness (–1.2 kPa; 95% CI, –2.3 to –0.1). These studies are limited due to their small size, lack of histologic impact, and variability in the type of IF used. However, they do show that IF can induce safe and effective weight loss in patients with NAFLD and lead to improvements in markers of hepatic steatosis and even inflammation.

Ketogenic diets have also been popular as a means to lose weight. By definition, these are diets that restrict carbohydrate substantially with variability in daily caloric allowance or fat allowance. Some examples of a "keto" diet include a low-carbohydrate diet (<130 g carbohydrates/d), very low caloric diet (20–50 g carbohydrates/d, <800 calories/d), very low calorie ketogenic diet (<20–50 carbohydrates/d, <800 calories/d), and a high-fat ketogenic diet (HFKD; <20–50 carbohydrates/d, unrestricted fat intake).[33] The traditional ketogenic diet is the HFKD, for which several concerns have been raised regarding its safety due to its unrestricted and often high-fat intake that could lead to progression of NAFLD. However, multiple studies have shown that the ketosis effect from these diets may actually be beneficial. Kirk et al[9] evaluated 22 obese patients with hepatic steatosis and randomized them (1:1) to an HFKD or hypocaloric/low-fat/high-carbohydrate diet. Both groups were able to manage ∼7% weight loss at 11 weeks, and magnetic resonance spectroscopy revealed that intrahepatic triglyceride content was similar in both groups (44.5% vs 38%; P = not significant). Another study randomized 18 patients with NAFLD to an HFKD or hypocaloric (1200-1500 kcal/d) diet for 2 weeks. Magnetic resonance spectroscopy showed that liver triglyceride levels decreased significantly more in the HFKD group (–55% [14%] vs –28% [23%]; $P = 0.008$), with both groups achieving about equal amounts of weight loss (4.3%).[34] These studies have the same limitations as those that evaluate the Mediterranean diet and IF and still require longer term studies with histologic outcome data.

The studies of these diets in patients with NAFLD are heterogeneous and make it difficult to draw definitive conclusions on their effectiveness in NAFLD. The common theme emerges that weight loss is associated with amelioration of NAFLD. However, this weight loss can be achieved through various distributions of macronutrients in a diet, balancing amounts of calories, carbohydrates, and fats. At very low caloric intake, the distribution may not be as crucial, and weight loss alone leads to improvements in hepatic fat content. However, as seen in the Mediterranean and ketogenic diets, isocaloric and hypercaloric diets can still lead to improvements in NAFLD if the appropriate ratios of macronutrients are used.

There still remains a lack of data comparing these diets to each other in the management of NAFLD, but the basic concepts of the Mediterranean diet seem to be the most beneficial for patients as nutritional therapy for fatty liver disease.

Role of Micronutrients and Other Nutritional Therapy in NAFLD

Multiple studies have looked at the role of micronutrients in the management of patients with NAFLD. Vitamin A, vitamin B_3, folic acid, vitamin C, and vitamin D have all been studied in the context of NAFLD, but these studies fail to provide any conclusive evidence on the routine administration of such micronutrients for the management of NAFLD.[35] However, among the micronutrients, vitamin E is the most validated to treat patients with NAFLD. The PIVENS (Pioglitazone, Vitamin E or Placebo for the

Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis) trial showed that 800 IU of vitamin E daily was associated with improvement in transaminases and histologic steatosis and inflammation. However, it had no benefit in fibrosis and also carries the risk of prostate cancer and all-cause mortality, limiting its use.[36] Current guidelines do acknowledge that vitamin E can be used in the treatment of patients with biopsy-proven NASH but not in those with comorbid diabetes or underlying cirrhosis.[14]

Alcohol use in patients with underlying NAFLD has conflicting data with respect to a potential benefit of moderate alcohol use. Cross-sectional studies have shown that drinking <20 g of alcohol per day may have a protective effect, with improvement in steatosis and even ballooning/fibrosis.[37,38] However, a recent, large prospective study of >8000 patients with NAFLD found that even low alcohol use doubled the risk for advanced liver disease compared with lifetime abstainers.[39] Therefore, multiple guidelines have recommended that adults with NAFLD should restrict alcohol intake significantly or avoid it altogether.[13,29]

Coffee intake has also been shown to be beneficial in patients with NAFLD. It is composed of hundreds of chemical compounds, some that are believed to have beneficial effects, including caffeine, chlorogenic acid, kahweol, and cafestol.[40] Earlier cross-sectional and case-control studies showed that coffee was associated with a lower risk of NAFLD and also decreased the risk of fibrosis among patients with NASH.[41] More recent systematic reviews of these studies show no association between coffee consumption and NAFLD incidence or prevalence but did have a 35% decreased odds of significant liver fibrosis (relative risk, 0.65; 95% CI, 0.54–0.78; $P < 0.00001$).[42] A large population-based study in the United Kingdom also showed that coffee intake is protective against chronic liver disease, death from chronic liver disease, and also hepatocellular carcinoma.[40] These studies do not offer insight into a dose recommendation for coffee, but it is generally accepted that at least 1 cup of coffee per day can be beneficial to patients with NAFLD. Additional data will be required to determine coffee's effect on clinical outcomes related to progression of NASH.

Overall, the amount of data available to patients and providers can be overwhelming and often conflicting. Keeping dietary interventions simple and, most importantly, sustainable over the long term is key to any lifestyle intervention for NALFD (Figure 1).

OTHER NONCIRRHOTIC CHRONIC LIVER DISEASE

Alcohol-Related Liver Disease

ALD refers to a wide spectrum of pathologies ranging from steatosis (fatty liver) to steatohepatitis, acute alcohol-associated hepatitis (AAH), and liver cirrhosis. Malnutrition in cirrhosis is extremely common, reported in 20% to 60% of outpatients with alcohol-related cirrhosis and approaching 100% for hospitalized patients with acute alcohol–associated hepatitis.[42,43] The presence of malnutrition in alcohol-related cirrhosis worsens outcomes as well, including survival, quality of life, risk of variceal bleeding, ascites formation, hepatic encephalopathy, infection, hospital length of stay, and hepatorenal syndrome.[43]

The malnutrition in patients with ALD is multifactorial and mostly related to primary effects of alcohol on absorption and utilization of nutrients (Figure 2). Decreased oral intake of nutrients begins as alcohol makes up ~50% of daily caloric intake.[44] This is further exacerbated by alcohol-induced anorexia, nausea/vomiting, and gastritis. In patients with cirrhosis, dysgeusia and ascites can further decrease oral intake. Alcohol also directly affects nutrient absorption as it can result in mucosal damage along the stomach and small intestine, leading to impaired absorption of protein as well as micronutrients such as folate and vitamin B_{12}.[45] More severe forms of this include protein-losing enteropathy and steatorrhea. Chronic alcohol ingestion is also associated with bacterial overgrowth, which can increase intestinal permeability and alters motility, which also contributes to malnutrition.[46] Studies have also shown that chronic alcohol ingestion leads to an increase in resting energy expenditure.[47] Over time, this increased expenditure can result in significant muscle wasting and sarcopenia that are often encountered in patients with ALD. Chronic alcohol use also leads to consumption of hepatic glycogen stores and to hypoglycemia. In an attempt to maintain euglycemia, increased gluconeogenesis of peripheral adipose and muscle tissue occurs because of the lack of glycogen stores, which further contributes to sarcopenia.[43]

Micronutrient and vitamin deficiencies are also very common in ALD. Table 1 outlines some of the most common deficiencies seen in those with chronic alcohol abuse. Thiamine (vitamin B_1) deficiency is the most common deficiency found in patients with ALD and is due to decreased absorption of thiamine from the gastrointestinal tract. Wernicke encephalopathy can

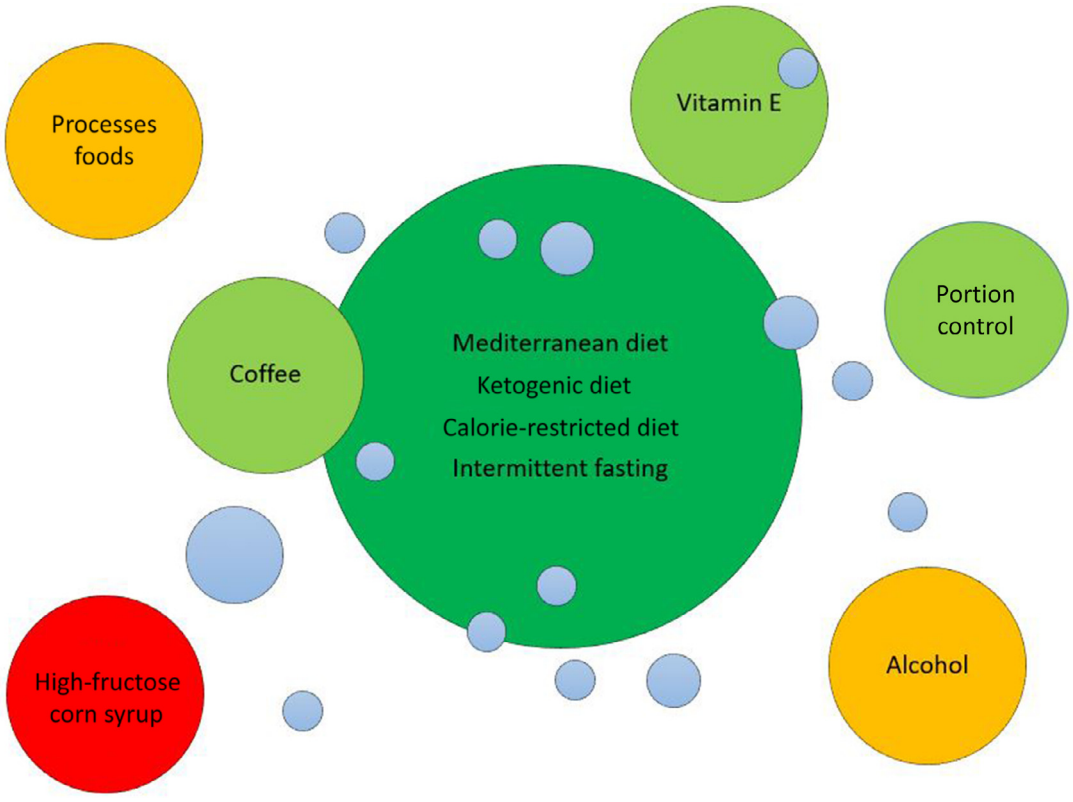

Figure 1. There is abundant information about diet and fatty liver; unfortunately some of it is ambiguous or conflicting. Following data-supported interventions (green), limiting some choices (yellow), and avoiding pitfalls (red) are often the first steps in a nutritional intervention.

Table 1. Common vitamin and micronutrient deficiencies in alcohol-related liver disease.

Nutrient Deficiency	Clinical Signs/Symptoms	Recommended Supplementation
Thiamine (vitamin B_1)	Wernicke-Korsakoff encephalopathy, beriberi cardiomyopathy	100 mg/d
Pyridoxine (vitamin B_6)	Neuropathy, sideroblastic anemia	2 mg/d
Vitamin B_{12}	Macrocytic anemia, neuropathy, spinal cord degeneration	50 µg/d (may require more)
Folate	Macrocytic anemia	1 mg/d
Vitamin A	Night blindness	10,000 U/d
Vitamin C	Scurvy, poor wound healing	60 mg/d
Zinc	Dysgeusia, dermatitis	220 mg BID
Magnesium	Cardiomyopathy, neuromuscular abnormalities	400 mg daily

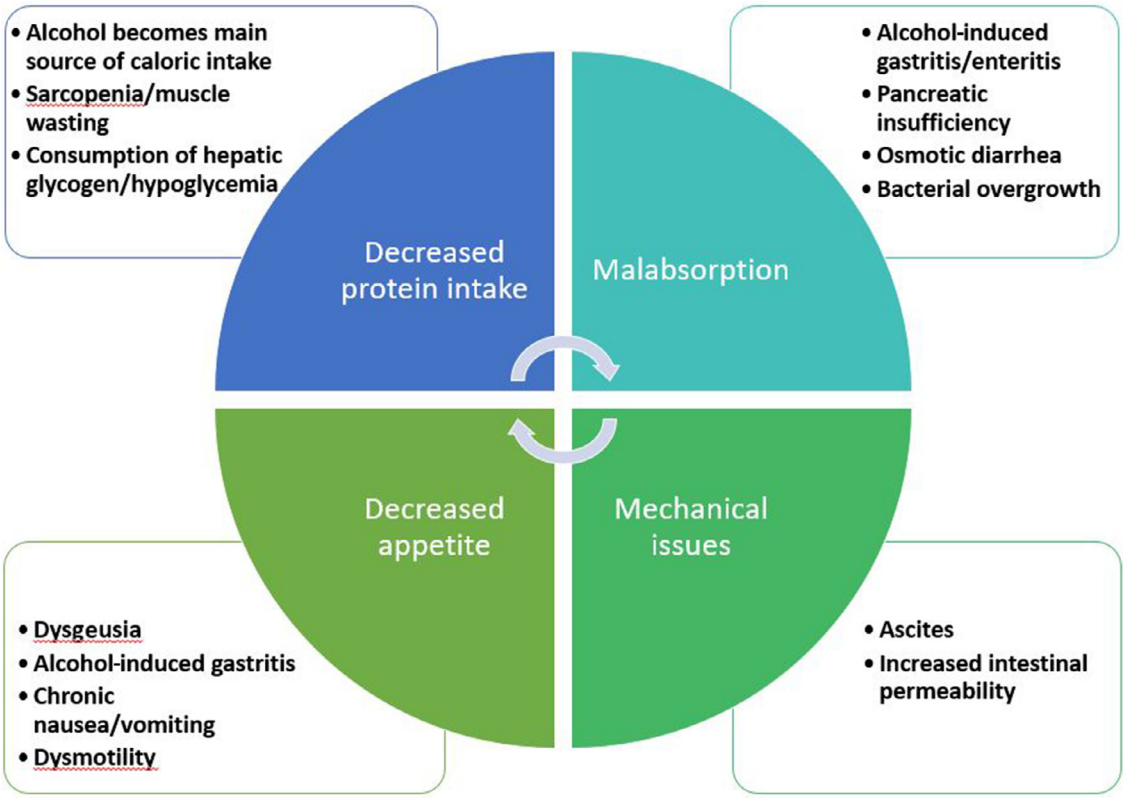

Figure 2. Mechanisms of malnutrition in alcohol-induced liver disease.

develop in patients who have exhausted thiamine stores; it clinically presents as confusion, oculomotor dysfunction, and ataxia. Untreated patients can go on to develop Korsakoff syndrome, which is permanent and leads to marked memory deficits. Vitamin B_{12} and folate deficiencies are also very common and lead to macrocytic anemia. Vitamin A metabolism relies on the same pathways as alcohol metabolism, and retinol homeostasis is therefore disrupted in chronic alcohol use. This disruption leads to depletion of retinoid-binding proteins and increased bile excretion of retinoids, eventually causing vitamin A deficiency.[44] Zinc deficiency is directly caused by poor intestinal absorption and manifests as loss of taste/smell that can further worsen nutritional intake, and therefore should be supplemented if found.

Assessment of the nutritional status of patients with ALD should be made on initial evaluation given the high prevalence of malnutrition in this population. History and physical examination should focus on energy intake, amount of weight loss, decrease in muscle mass, loss of subcutaneous fat, and presence of edema. In general, due to the increased resting energy expenditure of these patients, they require increased caloric intake. Current guidelines recommend ~30 to 40 kcal/kg per day with an emphasis on the need for small, frequent meals as these patients may not be able tolerate large meals 3 times per day.[48] In patients with severe AAH, the presence of malnutrition is associated with higher mortality and complications, especially if they cannot maintain such adequate caloric intake. Therefore, supplementation in the form of enteral nutrition should be considered in these patients. A systematic review of 18 randomized controlled trials has shown some of the benefits of supplemental nutrition, including reduced incidence of infections, quicker resolution of hepatic encephalopathy, and decreased hospital length of stay.[49] However, overall survival benefit remains controversial, and these same trials reported risks associated with nasogastric tubes, including aspiration pneumonia, uncontrolled hyperglycemia, and other intolerance of support

devices.[50,51] Parental nutrition does not significantly improve mortality or hepatic encephalopathy, and is associated with risk of line infections.[50] Given the known complications of hepatic complications associated with parental nutrition, including worsening coagulopathy and hepatic function, this modality should be avoided until further evidence is available.

In general, nutritional therapy needs to be offered to all patients with ALD but especially those patients with severe AAH who cannot maintain caloric intake requirements. It is preferred to do this through per oral intake, but if patients are encephalopathic or intubated, enteral nutrition should be considered while monitoring for complications associated with the use of this therapy.[15] Micronutrient and vitamin deficiencies should also be evaluated for each patient with ALD and supplemented, as supplementation can help improve various complications associated with chronic alcohol abuse.

Cholestatic Liver Disease

Chronic cholestasis seen in primary liver diseases such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis are characterized by reduction or stoppage of bile flow into the small intestine. Bile is required for fat absorption, and its relative lack can lead to fat malabsorption, micronutrient deficiencies, and a subsequent malnourished state. Patients may present with steatorrhea, reporting greasy, foul-smelling, pale or floating stools. Fecal fat can be measured qualitatively or quantitatively through 24-hour stool collection. The formal definition of steatorrhea is >7 g of fecal fat in 24 hours.[52] To help improve symptoms, fat intake should be restricted to <20 g/d. Medium-chain triglycerides (MCTs) can also be recommended to counteract any undesired weight loss that may be encountered with fat restriction. These are water soluble and therefore can be absorbed passively without the need for bile salts. Examples include coconut and palm kernel oils, which can contain up to 50% of MCTs. It is also known that these patients have an increase in serum lipid levels. In a review of patients with PBC, up to 75% of patients will have elevated serum lipid levels.[53] The mechanism is related to decreased LDL receptors on injured hepatocytes combined with an inability to excrete cholesterol through bile salts. This leads to an increase in lipoprotein-X, which is rich in free cholesterol and phospholipids. As such, patients may present with xanthomas, particularly around the eyelids (xanthelasma), neck, trunk, shoulders, and axillae. Despite an elevated cholesterol level, these patients are not believed to be at increased risk for cardiovascular disease unless they have other contributing, traditional risk factors for this disease.[54] Supplementation with MCTs can therefore still be used if needed for these patients.

Fat malabsorption in chronic cholestasis also leads to deficiencies of fat-soluble vitamins (A, D, E, and K). In one study of patients with PBC, vitamin A deficiency was the most prevalent (33.5%), followed by vitamin D (13.2%), vitamin K (7.8%), and vitamin E (1.9%).[55] Current guidelines recommend that these should be checked in patients with chronic cholestatic liver disease and supplemented if low levels are found.[56] It is important that supplementation be given via water-soluble formulas given the lack of fat absorption in these patients. Vitamin A repletion should be given intramuscularly with 100,000 IU daily × 3 days, followed by 50,000 IU daily × 2 weeks. Then oral supplementation at 15,000 IU daily should be given for 2 months. Levels should be frequently checked to avoid hyperalimentation, which can lead to liver injury.[57] For vitamin D repletion, 50,000 IU of cholecalciferol (vitamin D_3) should be given weekly × 8 weeks, with maintenance of 400 to 2000 IU of vitamin D_3 daily. Vitamin K can be measured directly but also indirectly through prothrombin time and internationalized normalized ratio. Repletion can be done through 5 to 10 mg of vitamin K daily × 3 days. Maintenance doses should be given with caution as patients could theoretically be at risk for thrombosis. Vitamin E repletion dosages range from 200 to 1200 IU daily with a maintenance dose of 15 mg daily.[56] These fat-soluble vitamins should be monitored annually in patients with jaundice, typically defined as a bilirubin level >2 mg/dL.

Another nutritionally relevant complication of chronic cholestasis is metabolic bone disease. Patients with PBC and primary sclerosing cholangitis have a significantly greater risk of osteopenia and osteoporosis compared with age- and sex-matched control subjects.[58,59] It is hypothesized that hyperbilirubinemia leads to a reduction in osteoblast activity as well as osteoclast activation, resulting in increased bone resorption and decreased bone formation. To assess this risk, all patients should be screened for bone disease

with dual-energy X-ray absorptiometry and undergo screening every 2 years for osteoporosis. All patients should be provided 1000 to 1500 mg of calcium and 1000 IU of vitamin D_3, with close monitoring of these levels.[56] In those with osteoporosis, bisphosphonate therapy is recommended.

Nutrition in Cirrhosis

The prevalence of malnutrition in cirrhosis is very common but highly variable in reports, ranging from 5% to 92%, suggesting a knowledge gap or difficulties in diagnosing this disorder.[60] However, a high prevalence is seen in those who have decompensated disease as defined by ascites, hepatic encephalopathy, jaundice, or variceal bleeding. Clinically, malnutrition can present as sarcopenia or frailty. Sarcopenia is defined as a progressive loss of skeletal muscle mass with an increased likelihood of adverse outcomes.[2] Frailty is defined as a clinical state of decreased physiologic reserve, often a phenotypic representation of sarcopenia. Multiple studies have reported poor outcomes in patients with either sarcopenia or frailty. These have been associated with overall mortality as well as waitlist mortality. It is also associated with unplanned hospitalization, increased health care costs, re-admissions, and worsened health-related quality of life.

Mechanisms and Evaluation of Malnutrition in Cirrhosis

Multiple mechanisms are responsible for malnutrition in cirrhosis. There is reduced oral intake due to early satiety, anorexia, dysgeusia, impaired level of consciousness, and unpalatable prescribed diets. Malabsorption also occurs due to decreased fat malabsorption, altered intestinal flora, and chronic lactulose therapy. Similar to patients with ALD, patients with cirrhosis have increased macronutrient metabolism leading to an increase in resting energy expenditure. Finally, altered protein metabolism leads to reduced levels of branched-chain amino acids, resulting in accelerated muscle breakdown. This sarcopenia is exacerbated in patients with excess ammonia, which is directly myotoxic.[60]

Estimation of malnutrition in cirrhosis is difficult; fortunately, there are several diverse tools available for use (Table 2). Screening tools, including weight or BMI, have limited clinical value in cirrhosis due to fluctuations in body weight. Ideally, comprehensive nutritional assessment should be performed by a registered dietitian and nutrition expert, but this option is not practically available for all patients. The Royal Free Hospital-Nutritional Prioritizing Tool was developed in patients with cirrhosis and is able to discriminate patients into low-, medium-, and high-risk categories for malnutrition. In validation studies, this tool was identified as an independent predictor of clinical deterioration and transplant-free survival, and it also takes ~3 minutes to complete.[61] The gold standard for assessment of muscle mass is computed tomography (CT) imaging. The cost and exposure to radiation make routine use of CT imaging for sarcopenia impractical. However, if abdominal CT imaging is performed for clinical reasons such as hepatocellular carcinoma surveillance or surgical planning, muscle mass measurement via the skeletal muscle index can be calculated.[62]

Functional assessment of frailty can be performed through global assessment but also individual, physical components. Activities of daily living and the Karnofsky Performance Status can provide a global assessment of functional frailty and have been evaluated in patients with cirrhosis.[63,64] Specific physical tests for frailty have included hand grip strength, short gait speed, and the 6-minute walk test. These can estimate specific physical frailty but are not necessarily accurate in predicting outcomes in patients with cirrhosis. More recently, the Liver Frailty Index was created as a cirrhosis-specific tool consisting of grip strength, chair stands, and balance testing.[65] This index has been longitudinally studied and associated with various outcomes, including overall mortality and waitlist mortality.[66] There is not one recommended method for evaluation of malnutrition, frailty, or sarcopenia in patients with cirrhosis, but it is important to screen for these factors in patients with cirrhosis to initiate an appropriate nutrition treatment plan.

General Nutritional Interventions

Dietary intervention on patients with malnutrition in cirrhosis has clearly shown positive outcomes, including mortality and complications.[60] As a state of accelerated starvation, patients with cirrhosis have an increased resting energy expenditure, but this has been difficult to show by traditional calorimetry given variability in decompensated states of liver cirrhosis and physical activity. However, multiple societies, including the European Society for Clinical Nutrition

Table 2. Metrics to assess nutrition, frailty, and sarcopenia in patients with cirrhosis.

Assessment	Advantages/Disadvantages
Body mass index	Limited value due to edema, ascites, and fluctuations in daily weight
Comprehensive assessment by nutritionist/registered dietician	Ideal assessment but limited availability outside of academic institutions
Royal Free Hospital-Nutritional Prioritizing Tool	Discriminates patients into low-, medium-, and high-risk categories. Independent predictor of clinical deterioration and transplant-free survival Takes ~3 minutes to complete
Computed tomography imaging	Gold standard for assessment of muscle mass High cost, radiation exposure
Activities of daily living/ Karnofsky Performance Status	Global assessment of functional frailty
Physical tests for frailty Hand grip strength Short gait speed 6-minute walk test	Can estimate specific physical frailty but not necessarily accurate in predicting outcomes in patients with cirrhosis
Liver Frailty Index	Cirrhosis-specific tool consisting of grip strength, chair stands, and balance testing

and Metabolism, recommend a daily intake of 35 to 40 kcal/kg per day in nonobese patients.[15] The use of dry weight is recommended given the typical presence of ascites or lower extremity edema in these patients. Currently, there are no recommendations on specific fatty acid or carbohydrate intake. The sodium restriction commonly enforced upon patients with ascites may indirectly affect their overall caloric intake. Patients are asked to take in <2000 mg of sodium per day. However, the benefit of this may be offset by reduced intake of energy due to poor palatability of such a diet, preventing patients in achieving their caloric goals.[67] One study showed that appropriate caloric supplementation on top of a low-sodium diet led to decreased mortality.[68] Great care should be taken to ensure adequate nutrition in patients who are sodium restricted, even if it requires some liberalization of these sodium restrictions.[2]

The protein needs in cirrhosis are based on the protein intake required to maintain nitrogen balance. Studies have shown that this is typically achieved with ~0.8 g/kg per day but that increasing amounts of protein intake are associated with improvement in multiple factors, including sarcopenia and mortality.[69] It is therefore recommended that patients consume ~1.2 to 1.5 g/kg per day of protein, with sarcopenic or decompensated patients aiming for 1.5 g/kg per day and even up to 1.8 g/kg per day.[15] Previously, controversy existed that protein supplementation led to worsening hepatic encephalopathy. However, multiple studies have shown that protein does not precipitate encephalopathy and could even improve mental status in the long term, whereas restriction may worsen sarcopenia.[70,71] Several older studies have also suggested that the type of protein consumed (animal vs plant based) could affect patients with hepatic encephalopathy, with animal-based proteins leading to more encephalopathy.[72,73] Given the risk of worsening sarcopenia by limiting animal-based proteins, however, it is generally encouraged that patients consume protein from a diverse range of sources, including vegetable and dairy products.

The timing of nutritional intake is also important as prolonged periods of fasting should be avoided in cirrhosis due to rapid exhaustion of glycogen stores. It is estimated that a six to ten hour fast in a patient with cirrhosis equates to two to three of starvation in a healthy person. European Society for Clinical Nutrition and Metabolism guidelines recommend at least 3 to 5 meals per day to avoid these periods of

fasting, and other societies recommend frequent meals or snacks every 3 to 4 hours while awake to avoid prolonged fasts.[2,15] To address overnight fasts, late-evening supplementation has been studied. The most prominent study randomized 103 patients to daytime or nighttime supplementation of 710 kcal over 12 months.[74] A nighttime "snack" led to accrual of 2 kg of lean protein mass versus no change for those patients undergoing daytime supplementation. Other studies have validated these findings, and it is recommended that patients consume a late-evening snack to help improve overall protein mass and quality of life.[75]

Sarcopenic Obesity

Sarcopenic obesity refers to a state of decreased muscle mass in the setting of increased fat mass. Clinically, it remains a challenge to both detect and treat in patients with cirrhosis, specifically in those with NASH given that fat mass can mask muscle wasting. A consensus definition of sarcopenic obesity has not yet been established, but studies often reference skeletal muscle index for sarcopenia and a BMI corrected for ascites for obesity. The prevalence of sarcopenic obesity in patients with cirrhosis ranges between 20% and 35%.[76–78] NAFLD has been shown to be an independent risk factor for sarcopenic obesity.[79,80] In patients undergoing liver transplant evaluation, the risk of sarcopenic obesity was 6 times higher in those with NASH cirrhosis.[80] Obesity itself is a strong predictor of hepatic decompensation and associated with worsening of the hepatic venous pressure gradient.[81] Sarcopenic obesity also has an association with increased mortality. Montano-Loza et al[76] showed that patients with sarcopenic obesity had worse median survival compared with those without muscular abnormalities (22 [3] months vs 95 [22] months; $P < 0.001$). These patients also had longer hospital and ICU stays after transplant. With the rising incidence of NASH cirrhosis in the United States, the prevalence of sarcopenic obesity will increase and likely play a large role in the outcomes of this population.

To date, there are no cirrhosis-specific intervention trials in patients with sarcopenic obesity. Lifestyle changes resulting in weight loss have shown improvements in parameters of portal hypertension in obese patients with cirrhosis. One study evaluated patients by using an intensive 16-week program consisting of a caloric reduction of 500 to 1000 kcal/d combined with 1 weekly 60-minute session of moderate exercise.[82] Lifestyle interventions were able to reduce weight by ≥5% in 52% of patients and by ≥10% in 16% of patients, with a greater decrease in hepatic venous pressure gradient in those patients able to achieve ≥10% weight loss. No adverse effects or episodes of clinical decompensation were observed. As such, societal recommendations do not recommend increased caloric intake in obese patients with cirrhosis.[15] Instead, energy intake can be modified according to BMI: 25 to 35 kcal/kg per day for individuals with BMI 30 to 40 kg/m^2 and 20 to 25 kcal/kg per day for individuals with BMI ≥40 kg/m^2.[2] Specific diets such as the Mediterranean diet or intermittent fasting have not been studied in patients with sarcopenic obesity. Aggressive calorie-restricting diets, including intermittent fasting, are likely harmful given the accelerated starvation state in cirrhosis and should be avoided. Future data are pending on the effect of the Mediterranean diet in those patients with sarcopenic obesity (but not cirrhosis).[83] Attention should still be given to adequate protein intake, still aiming for the recommended 1.2 to 1.5 g/kg per day, and avoiding long periods of fasting with incorporation of small, frequent meals and nighttime snack.

CONCLUSIONS

Nutrition has a large impact on the liver, playing a role along the spectrum of all chronic liver disease. Adjustment of macronutrient intake leading to weight loss remains the best therapeutic intervention for those patients with NAFLD, while pharmacologic therapies are still under evaluation for the treatment of this common disease. Malnutrition and sarcopenia are severe complications of ALD and cirrhosis, with a direct impact on prognosis and mortality. The use of "food as medicine," especially in this latter group, plays a crucial role in the management of these patients and can improve both quality of life and overall clinical survival. All patients should undergo nutritional evaluation, be given a "prescription" for nutrition, and then be re-assessed at regular intervals to ensure that objective goals are being met. High-quality studies are still lacking in this field given uncertainties in definitions, lack of standardized interventions, and small groups with variable follow-up. Future research should focus on these deficiencies to help reinforce and/or modify our current practices of nutritional therapy in chronic liver disease.

ACKNOWLEDGMENTS

Both authors conceived the manuscript idea; Dr Shah performed the literature review and collected the data, and wrote the first draft of the paper; and both authors edited and refined the final manuscript. Both authors approved of the final manuscript.

DECLARATION OF INTEREST

None declared.

REFERENCES

1. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition inpatients with advanced liver disease, and nutrition management strategies. *Clin Gastroenterol Hepatol*. 2012;10:117–125.
2. Lai JC, Tandon P, Bernal W, Tapper EB. Malnutrition, frailty, and sarcopenia in patients with cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;74:1611–1644.
3. Barrera F, George J. The role of diet and nutritional intervention for the management of patients with NAFLD. *Clin Liver Dis*. 2014;18:91–112.
4. Rinella ME. Nonalcoholic fatty liver disease: A systematic review. *JAMA*. 2015;313:2263–2273.
5. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of randomised trials. *Diabetologia*. 2012;55:885–904.
6. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A. Weight loss via lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015;149:367–378.
7. Malespin MH, Barritt ASt, Watkins SE, Schoen C, Tincopa MA, Corbin KD, Mospan AR, et al. Weight loss and weight regain in usual clinical practice: results from the TARGET-NASH Observational Cohort [published online ahead of print January 21, 2021]. Clin Gastroenterol Hepatol
8. Ahn J, Jun DW, Lee HY, Moon JH. Critical appraisal for low-carbohydrate diet in nonalcoholic fatty liver disease: Review and meta-analyses. *Clin Nutr*. 2019;38:2023–2030.
9. Kirk E, Reeds DN, Finck BN, Mayurranjan SM, Patterson BW, Klein S. Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. *Gastroenterology*. 2009;136:1152–1160.
10. Haufe S, Engeli S, Kast P, B€ohnke J, Utz W, Haas V. Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat in overweight and obese human subjects. *Hepatology*. 2011;53:1504–1514.
11. Franz MJ, VanWormer JJ, Crain AL. Weight-loss outcomes: A systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Am Diet Assoc*. 2007;107:1755–1767.
12. D'Albuquerque LA, Gonzalez AM, Wahle RC. Liver transplantation for sub-acute hepatocellular failure due to massive steatohepatitis after bariatric surgery. *Liver Transpl*. 2008;14:881–885.
13. European Association for the Study of the Liver (EASL)European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO). "EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol*. 2016;64:1388–1402.
14. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67:328–357.
15. Plauth M, Bernal W, Dasarathy S, Merli M, Plank LD, Schütz T, Bischoff SC. ESPEN guideline on clinical nutrition in liver disease. *Clin Nutr*. 2019;38:485–521.
16. Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: A systematic review and meta-analysis. *J Hepatol*. 2012;57:157–166.
17. Wong VW, Wong GL, Chan RS, Shu SS, Cheung BH, Li LS, Chim AM, et al. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. *J Hepatol*. 2018;69:1349–1356.
18. Zelber-Sagi S. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): A population based study. *J Hepatol*. 2007;47:711–717.
19. Zelber-Sagi S, Ivancovsky-Wajcman D, Fliss Isakov N, Webb M, Orenstein D, Shibolet O, Kariv R. High red and processed meat consumption is associated with non-alcoholic fatty liver disease and insulin resistance. *J Hepatol*. 2018;68:1239–1246.
20. Noureddin M, Zelber-Sagi S, Wilkens LR, Porcel J, Boushey CJ, Le Marchand L, Rosen HR, et al. Diet associations with nonalcoholic fatty liver disease in an ethnically diverse population: The Multiethnic Cohort. *Hepatology*. 2020;71:1940–1952.
21. Soleimani D, Ranjbar G, Rezvani R, Goshayeshi L, Razmpour F, Nematy M. Dietary patterns in relation to hepatic fibrosis among patients with nonalcoholic fatty liver disease. *Diabetes Metab Syndr Obes*. 2019;12:315–324.
22. Oddy WH, Herbison CE, Jacoby P, Ambrosini GL, O'Sullivan TA, Ayonrinde OT, Olynyk JK, et al. The Western dietary pattern is prospectively associated with nonalcoholic fatty liver disease in adolescence. *Am J Gastroenterol*. 2013;108:778–785.

23. Yki-Järvinen H, Luukkonen PK, Hodson L, Moore JB. Dietary carbohydrates and fats in nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol*. 2021;18:770–786.
24. Abdelmalek MF, Suzuki A, Guy C, Unalp-Arida A, Colvin R, Johnson RJ, Diehl AM. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. *Hepatology*. 2010;51:1961–1971.
25. Geidl-Flueck B, Hochuli M, Németh Á, Eberl A, Derron N, Köfeler HC, Tappy L, et al. Fructose- and sucrose- but not glucose-sweetened beverages promote hepatic de novo lipogenesis: A randomized controlled trial. *J Hepatol*. 2021;75:46–54.
26. Zhang S, Gu Y, Bian S, Lu Z, Zhang Q, Liu L, Meng G, et al. Soft drink consumption and risk of nonalcoholic fatty liver disease: results from the Tianjin Chronic Low-Grade Systemic Inflammation and Health (TCLSIH) cohort study. *Am J Clin Nutr*. 2021;113:1265–1274.
27. Kawaguchi T, Charlton M, Kawaguchi A, Yamamura S, Nakano D, Tsutsumi T, Zafer M, et al. Effects of Mediterranean diet in patients with nonalcoholic fatty liver disease: A systematic review, meta-analysis, and meta-regression analysis of randomized controlled trials. *Semin Liver Dis*. 2021;41:225–234.
28. Yaskolka Meir A, Rinott E, Tsaban G, Zelicha H, Kaplan A, Rosen P, Shelef I, et al. Effect of green-Mediterranean diet on intrahepatic fat: The DIRECT PLUS randomised controlled trial. *Gut*. 2021;70:2085–2095.
29. Younossi ZM, Corey KE, Lim JK. AGA clinical practice update on lifestyle modification using diet and exercise to achieve weight loss in the management of nonalcoholic fatty liver disease: Expert review. *Gastroenterology*. 2021;160:912–918.
30. Memel ZN, Wang J, Corey KE. Intermittent fasting as a treatment for nonalcoholic fatty liver disease: What is the evidence? *Clin Liver Dis*. 2022;19:101–105.
31. Johari MI, Yusoff K, Haron J, Nadarajan C, Ibrahim KN, Wong MS, Hafidz MIA, et al. A randomised controlled trial on the effectiveness and adherence of modified alternate-day calorie restriction in improving activity of non-alcoholic fatty liver disease. *Sci Rep*. 2019;9:11232.
32. Holmer M, Lindqvist C, Petersson S, Moshtaghi-Svensson J, Tillander V, Brismar TB, Hagström H, et al. Treatment of NAFLD with intermittent calorie restriction or low-carb high-fat diet - a randomised controlled trial. *JHEP Rep*. 2021;3:100256.
33. Watanabe M, Tozzi R, Risi R, Tuccinardi D, Mariani S, Basciani S, Spera G, et al. Beneficial effects of the ketogenic diet on nonalcoholic fatty liver disease: A comprehensive review of the literature. *Obes Rev*. 2020;21:13024.
34. Browning JD, Baker JA, Rogers T, Davis J, Satapati S, Burgess SC. Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction. *Am J Clin Nutr*. 2011;93:1048–1052.
35. Abe RM, Masroor A, Khorochkov A. The role of vitamins in non-alcoholic fatty liver disease: A systematic review. *Cureus*. 2021;13:16855.
36. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med*. 2010;362:1675–1685.
37. Moriya A, Iwasaki Y, Ohguchi S, Kayashima E, Mitsumune T, Taniguchi H, Ando M, et al. Roles of alcohol consumption in fatty liver: A longitudinal study. *J Hepatol*. 2015;62:921–927.
38. Dunn W, Sanyal AJ, Brunt EM, Unalp-Arida A, Donohue M, McCullough AJ, Schwimmer JB. Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with non-alcoholic fatty liver disease (NAFLD). *J Hepatol*. 2012;57:384–391.
39. Åberg F, Puukka P, Salomaa V, Männistö S, Lundqvist A, Valsta L, Perola M, et al. Risks of light and moderate alcohol use in fatty liver disease: Follow-up of population cohorts. *Hepatology*. 2020;71:835–848.
40. Kennedy OJ, Fallowfield JA, Poole R. All coffee types decrease the risk of adverse clinical outcomes in chronic liver disease: A UK Biobank study. *BMC Public Health*. 2021;21:970.
41. 2nd Saab S, Mallam D, Cox GA, Tong MJ. Impact of coffee on liver diseases: A systematic review. *Liver Int*. 2014;34:495–504.
42. Ebadi M, Ip S, Bhanji RA, Montano-Loza AJ. Effect of coffee consumption on non-alcoholic fatty liver disease incidence, prevalence and risk of significant liver fibrosis: Systematic review with meta-analysis of observational studies. *Nutrients*. 2021;13:3042.
43. Singal AK, Charlton MR. Nutrition in alcoholic liver disease. *Clin Liver Dis*. 2012;16:805–826.
44. Lieber CS. Relationships between nutrition, alcohol use, and liver disease. *Alcohol Res Health*. 2003;27: 220–231.
45. Roggin GM, Iber FL, Kater RM. Malabsorption in the chronic alcoholic. *Johns Hopkins Med J*. 1969;125: 321–330.
46. Parlesak A, Schäfer C, Schütz T, Bode JC, Bode C. Increased intestinal permeability to macromolecules and endotoxemia in patients with chronic alcohol abuse in different stages of alcohol-induced liver disease. *J Hepatol*. 2000;32:742–747.
47. Jhangiani SS, Agarwal N, Holmes R, Cayten CG, Pitchumoni CS. Energy expenditure in chronic alcoholics with and without liver disease. *Am J Clin Nutr*. 1986;44:323–329.

48. Mitchell MC, Friedman LS, McClain CJ. Medical management of severe alcoholic hepatitis: Expert review from the Clinical Practice Updates Committee of the AGA Institute. *Clin Gastroentrol Hepatol*. 2017;15:5–12.
49. Fialla AD, Israelsen M, Hamberg O, Krag A, Gluud LL. Nutritional therapy in cirrhosis or alcoholic hepatitis: A systematic review and meta-analysis. *Liver Int*. 2015;35:2072–2078.
50. Koretz RL, Avenell A, Lipman TO. Nutritional support for liver disease. *Cochrane Database Syst Rev*. 2012;2012:CD008344.
51. Moreno C, Deltenre P, Senterre C. Intensive enteral nutrition is ineffective for patients with severe alcoholic hepatitis treated with corticosteroids. *Gastroenterology*. 2016;150:903–910.
52. Medici V, Mendoza M, Kappus M. Liver Disease. *The ASPEN Adult Nutrition Support Core Curriculum*. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017:532–542.
53. Sorokin A, Brown JL, Thompson PD. Primary biliary cirrhosis, hyperlipidemia, and atherosclerotic risk: A systematic review. *Atherosclerosis*. 2007;194:292–299.
54. Solaymani-Dodaran M, Aithal GP, Card T, West J. Risk of cardiovascular and cerebrovascular events in primary biliary cirrhosis: A population-based cohort study. *Am J Gastroenterol*. 2008;103:2784–2788.
55. JR Angulo P, Petterson T, Lindor KD. Fat-soluble vitamin levels in patients with primary biliary cirrhosis. *Am J Gastroentol*. 2001;96:2745–2750.
56. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2019;69:394–419.
57. Send S. Nutritional management of cholestasis. *Clin Liver Dis (Hoboken)*. 2020;15:9–12.
58. Menon KV, Angulo P, Weston S, Dickson ER, Lindor KD. Bone disease in primary biliary cirrhosis: independent indicators and rate of progression. *J Hepatol*. 2001;35:316–323.
59. Angulo P, Grandison GA, Fong DG, Keach JC, Lindor KD, Bjornsson E, Koch A. Bone disease in patients with primary sclerosing cholangitis. *Gastroenterolgy*. 2011;140:180–188.
60. Traub J, Reiss L, Aliwa B, Stadlbauer V. Malnutrition in patients with liver cirrhosis. *Nutrients*. 2021;13:540.
61. Borhofen SM, Gerner C, Lehmann J, Fimmers R, Görtzen J, Hey B, Geiser F, et al. The Royal Free Hospital-Nutritional Prioritizing Tool is an independent predictor of deterioration of liver function and survival in cirrhosis. *Dig Dis Sci*. 2016;61:1735–1743.
62. Carey EJ, Lai JC, Sonnenday C, Tapper EB, Tandon P, North Duarte-Rojo AA. American expert opinion statement on sarcopenia in liver transplantation. *Hepatology*. 2019;70:1816–1829.
63. Tapper EB, Finkelstein D, Mittleman MA, Piatkowski G, Lai M. Standard assessments of frailty are validated predictors of mortality in hospitalized patients with cirrhosis. *Hepatology*. 2015;62:584–590.
64. Thuluvath PJ, Thuluvath AJ, Savva Y. Karnofsky performance status before and after liver transplantation predicts graft and patient survival. *J Hepatol*. 2018;69:818–825.
65. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, Feng S. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. *Hepatology*. 2017;66:564–574.
66. Lai JC, Dodge JL, Kappus MR, Dunn MA, Volk ML, Duarte-Rojo A, Ganger DR, et al. Changes in frailty are associated with waitlist mortality in patients with cirrhosis. *J Hepatol*. 2020;73:575–581.
67. Gu XB, Yang XJ, Zhu HY, Xu BY. Effect of a diet with unrestricted sodium on ascites in patients with hepatic cirrhosis. *Gut Liver*. 2012;6:355–361.
68. Sorrentino P, Castaldo G, Tarantino L, Bracigliano A, Perrella A, Perrella O, Fiorentino F, et al. Preservation of nutritional-status in patients with refractory ascites due to hepatic cirrhosis who are undergoing repeated paracentesis. *J Gastroenterol Hepatol*. 2012;27:813–822.
69. Amodio P, Bemeur C, Butterworth R, Cordoba J, Kato A, Montagnese S, Uribe M, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. *Hepatology*. 2013;58:325–336.
70. Maharshi S, Sharma BC, Sachdeva S, Srivastava S, Sharma P. Efficacy of nutritional therapy for patients with cirrhosis and minimal hepatic encephalopathy in a randomized trial. *Clin Gastroenterol Hepatol*. 2016;14:454–460.
71. Córdoba J, López-Hellín J, Planas M, Sabín P, Sanpedro F, Castro F, Esteban R, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. *J Hepatol*. 2004;41:38–43.
72. Uribe M, Marquez MA, Ramos GG, Ramos-Uribe MH, Vargas F, Villalobos A. Treatment of chronic portal—systemic encephalopathy with vegetable and animal protein diets: A controlled crossover study. *Dig Dis Sci*. 1982;27:1109–1116.
73. Bianchi GP, Marchesini G, Fabbri A, Rondelli A, Bugianesi E, Zoli M. Vegetable versus animal protein diet in cirrhotic patients with chronic encephalopathy. A randomized cross-over comparison. *J Intern Med*. 1993;233:385–392.
74. Plank LD, Gane EJ, Peng S, Muthu C, Mathur S, Gillanders L, McIlroy K, et al. Nocturnal nutritional supplementation improves total body protein status of

patients with liver cirrhosis: A randomized 12-month trial. *Hepatology*. 2008;48:557–566.
75. Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. *J Gastroenterol Hepatol*. 2012;27:430–441.
76. Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CM, Sawyer MB, Beaumont C, Esfandiari N, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. *J Cachexia Sarcopenia Muscle*. 2016;7:126–135.
77. Hara N, Iwasa M, Sugimoto R, Mifuji-Moroka R, Yoshikawa K, Terasaka E, Hattori A, et al. Sarcopenia and sarcopenic obesity are prognostic factors for overall survival in patients with cirrhosis. *Intern Med*. 2016;55:863–870.
78. Nishikawa H, Nishiguchi S. Sarcopenia and sarcopenic obesity are prognostic factors for overall survival in patients with cirrhosis. *Intern Med*. 2016;55:855–856.
79. Kashiwagi K, Takayama M, Fukuhara K, Shimizu-Hirota R, Chu PS, Nakamoto N, Inoue N, et al. A significant association of non-obese non-alcoholic fatty liver disease with sarcopenic obesity. *Clin Nutr ESPEN*. 2020;38:86–93.
80. Carias S, Castellanos AL, Vilchez V, Nair R, Dela Cruz AC, Watkins J, Barrett T, et al. Nonalcoholic steatohepatitis is strongly associated with sarcopenic obesity in patients with cirrhosis undergoing liver transplant evaluation. *J Gastroenterol Hepatol*. 2016;31:628–633.
81. Berzigotti A, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Morillas R, Escorsell A, et al. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. *Hepatology*. 2011;54:555–561.
82. Berzigotti A, Albillos A, Villanueva C, Genescá J, Ardevol A, Augustín S, Calleja JL, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The SportDiet study. *Hepatology*. 2017;65:1293–1305.
83. McCullough D, Kirwan R, Butler T, Heredia F, Thijssen D, Lip GYH, Mills J, et al. Feasibility of a high-PRotein Mediterranean-style diet and resistance Exercise in cardiac Rehabilitation patients with sarcopenic obesity (PRiMER): Study protocol for a randomised control trial. *Clin Nutr ESPEN*. 2021;498:45.

Address correspondence to: Neil D. Shah, MD, UNC Liver Center, Campus Box 7584, University of North Carolina, Chapel Hill, NC 27599–7584. E-mail: neil_shah@med.unc.edu.