

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Nutrition in Patients With Cirrhosis



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G&H What are the most significant nutritional concerns in patients with cirrhosis?

CM Patients with cirrhosis frequently have either global malnutrition or alterations in specific aspects of nutritional status, such as micronutrient deficiencies, due to multiple mechanisms, including poor nutritional intake, poor absorption, and increased losses. Malnutrition is present in almost every patient with alcoholic cirrhosis and is frequent in most other types of cirrhosis. Poor nutritional intake is often seen in cirrhotic patients, especially in patients with alcoholic liver disease, which is a large cause of cirrhosis in the United States and worldwide. Clinical trials conducted by my colleagues and I found that the average number of drinks these patients had each day was approximately 15, which is equivalent to over 2000 calories without most critical nutrients and approximately the same number of calories recommended each day for many adults.

Cirrhotic patients often have multiple micronutrient deficiencies. (The Table displays a select list of micronutrient deficiencies and their manifestations in patients with cirrhosis.) One of the most common deficiencies involves zinc, which is critical for the function of a host of zinc finger transcription factors; with inadequate zinc, patients can develop many metabolic abnormalities. In addition to poor intake and decreased absorption, patients often lose a lot of zinc in their urine. Therefore, supplementing patients with zinc is often helpful in many types of cirrhosis.

Table. Signs and Symptoms of Select Micronutrient Deficiencies in Patients With Cirrhosis

Micronutrient Deficiency	Signs/Symptoms
Magnesium	Insulin resistance, muscle cramps
Selenium	Myopathy, cardiomyopathy
Vitamin B1/thiamine	Wernicke-Korsakoff syndrome, neurologic symptoms
Vitamin B2/riboflavin	Glossitis, cheilitis, lingual papillae atrophy
Vitamin A/retinol	Abnormal dark adaptation, rough skin
Vitamin C	Scurvy with purpura and petechiae
Vitamin D	Altered bone metabolism, altered gut barrier/immune function
Vitamin E	Oxidative stress
Niacin	Skin photosensitivity, confusion, pellagra
Folate, s-adenosylmethionine	Anemia, altered methylation, epigenetic effects

In addition, one of the most significant nutritional problems in cirrhotic patients is muscle wasting and sarcopenia. Patients with cirrhosis often go into a catabolic phase overnight due to limited glycogen stores in the liver. Thus, it is critically important for cirrhotic patients to maintain their muscle mass. One way to do this is by having a late-night snack, which helps prevent the development of a catabolic phase with muscle loss.

G&H How can nutrition be assessed in patients with cirrhosis?

CM Assessment is very difficult because many of the standard tests used to evaluate a patient's nutritional state are altered by liver disease. For example, visceral proteins, such as albumin or retinol-binding protein, are often used to assess nutritional status. However, these proteins become altered by liver disease because they are produced in the liver. Another test is the examination of skin folds; however, edema often occurs with liver disease and can affect skin fold thickness. Therefore, many of the simple tests that doctors use clinically are less useful in the setting of liver disease. Perhaps the best test in this setting is the Subjective Global Assessment, which evaluates nutritional status based upon features of a patient's medical history and physical examination and rates him or her on a scale ranging from well nourished to severely malnourished.

G&H How does diet affect cirrhosis?

CM Diet can play a large role in the development and progression of liver disease. Overnutrition can cause patients to become overweight, which can lead to fatty liver disease and nonalcoholic steatohepatitis (NASH), and then cirrhosis in some patients. Alcohol and alcohol metabolism can interact with nutrients such as omega-6 fatty acids (eg, linoleic acid) and cause lipid peroxidation with oxidative stress and production of certain highly reactive toxic lipid metabolites. When cirrhotic patients consume alcohol instead of drinking and/or eating food with nutritional value, they can become malnourished and have difficulty moving around and performing their daily routines (reduced functional activity), which often leads to a downward spiral.

G&H Are there specific dietary guidelines for patients with cirrhosis?

CM Yes. Cirrhotic patients are almost always on a low-sodium diet if they have decompensated disease with ascites. It is important that patients be educated regarding a low-sodium diet, especially patients with poorly responsive ascites. In addition, cirrhotic patients

need adequate protein intake to prevent muscle wasting. However, many clinicians and dietitians often erroneously recommend a low-protein diet to these patients to try to prevent the development of hepatic encephalopathy. It is important to emphasize that patients with cirrhosis generally should not be on a low-protein diet; recommending low-protein diets is one of the most common errors that health providers make.

Additionally, if cirrhotic patients are overweight and have NASH, they should be on calorie (but not protein) restriction. They should also avoid fructose and sugared beverages, as such beverages are a frequent cause of weight gain and can be easily removed from their diet. Smaller portion size is also important in NASH patients as a way of facilitating weight reduction.

G&H Are there any dietary guidelines involving carbohydrates and fats for cirrhotic patients in general?

CM Fructose should be avoided if possible. There has been controversy in the literature regarding whether fructose is worse than glucose as a carbohydrate source. Our research team thinks that it is and thus recommends limiting it, especially in sugared drinks.

As for dietary fats, omega-6 fatty acids (which are found in corn oil, for example) should be avoided in patients with alcohol-related liver disease. This type of fat can lead to toxic lipid metabolites. Moreover, with increased omega-6 fatty acid intake, the amount of omega-3 fats is usually reduced. Omega-3 lipids are usually anti-inflammatory and have a beneficial effect on the liver. Some omega-3 fats become metabolized to specialized pro-resolving mediators that help turn off inflammation and injury.

G&H Are there any recommendations regarding fluid intake?

CM Some patients with more advanced liver disease must be on a fluid-restricted diet, which is difficult because they often feel thirsty. However, if they drink too much fluid, they will retain it and develop more ascites.

G&H When is nutritional supplementation necessary in cirrhotic patients?

CM It depends on the individual patient. For most cirrhotic patients, a nighttime snack of approximately 700 calories and approximately 25 grams of protein is recommended for maintenance of muscle mass and prevention of catabolism. I also recommend that patients with cirrhosis take a multivitamin, and in some patients,

supplementation is recommended for select micronutrients such as zinc. The standard daily dose of zinc is 50 mg/day of elemental zinc, which is the amount of zinc in a 220-mg zinc sulfate tablet. I recommend taking this tablet with a meal to avoid an upset stomach.

G&H Are there any risks associated with supplementation?

CM Some of the nutrients that cirrhotic patients can be deficient in also have potential toxicity. Vitamin A is an example. Many patients with more advanced liver disease, especially those with cholestatic liver disease, can develop vitamin A deficiency. If patients receive too much vitamin A supplementation, they can develop liver injury. Certain other nutrients, such as selenium, also have potential toxicity. A patient can be deficient in selenium but can develop toxicity if he or she receives too much supplementation. Importantly, some of these micronutrients, such as vitamin A, have a relatively narrow window between deficiency and toxicity.

G&H Are herbal supplements safe in patients with cirrhosis?

CM Many patients use complementary and alternative medicine, such as herbal supplements. The one that is most widely used is milk thistle, or silymarin. It has beneficial antioxidant properties and is probably safe in liver disease. However, it is unclear whether this supplement actually improves liver function.

A number of other herbal agents can cause liver disease. For example, certain weight loss supplements are among the most prominent herbal agents causing liver toxicity. There also is the possibility of an herbal agent affecting another drug's metabolism. Thus, it is important that clinicians always ask cirrhotic patients whether they are using any herbal agents. It is common practice to ask patients about their prescription medications, but over-the-counter agents and supplements may be overlooked or not considered to be medicines. Patients also may feel embarrassed about taking supplements and may not readily volunteer information about their use.

G&H How common is leg cramping in cirrhotic patients, and how should this problem be managed?

CM A large percentage of cirrhotic patients experience leg cramping that can be quite severe. Cirrhotic patients often complain that leg cramps are the most annoying problem that they have. Unfortunately, leg cramps are generally unrecognized by primary care doctors and even

many liver specialists. In addition to being highly annoying, leg cramps can stop cirrhotic patients from sleeping at night. These patients should undergo monitoring of their potassium levels, as low levels can cause leg cramps. My colleagues and I frequently recommend that these patients take zinc and magnesium supplementation, as both zinc deficiency and magnesium deficiency can also cause leg cramps. Some clinicians also recommend supplementation of carnitine to help with leg cramps. Vitamin D is another deficiency in cirrhotics, and so some clinicians think that vitamin D may be associated with this problem. Unfortunately, it is not known exactly why leg cramping occurs in cirrhotic patients.

G&H Do probiotics have a role in patients with cirrhosis?

CM The role of probiotics, live bacteria that provide a health benefit to the host, is not well documented in humans with cirrhosis. There is a wealth of experimental data in animals suggesting that probiotics are beneficial, especially certain types of probiotics. My colleagues and I have extensively studied *Lactobacillus rhamnosus* GG and have found that it provides many benefits for liver disease, including stabilizing the gut barrier function, improving the gut flora, decreasing endotoxin levels, and improving liver enzymes. Whether all of these benefits will translate into humans is not known, but many studies are currently investigating this issue.

G&H Overall, does improving nutritional status lead to improved outcomes in these patients?

CM It is clearly documented that the use of nutritional supplementation can improve nutritional status. Whether that improves overall outcomes is a little more controversial, but there are data suggesting that outpatient nutritional supplementation decreases hospitalization and improves immune function. As previously mentioned, we know that having a late-night snack can help maintain lean muscle mass in patients with cirrhosis. There has also been a study in patients with severe alcoholic hepatitis in which nutritional supplementation improved short-term mortality to a degree similar to corticosteroids, and had a better effect on long-term survival than corticosteroids.

G&H Do you have any nutritional advice for clinicians managing cirrhotic patients?

CM The most important advice I have is for clinicians to think about nutrition. We are always worried about what medicines we can give. It is important to maintain the nutritional status of our patients; in fact, nutritional

status should be one of the first things that we think about. Unfortunately, nutrition is often overlooked right now.

G&H What are the next steps in research?

CM One of the most important areas of research is the interaction between the gut and the liver (ie, the gut-liver axis) in the development and progression of liver disease, as well as factors that improve gut flora and gut metabolites, such as prebiotics or probiotics, and that stabilize gut barrier function. Also undergoing active investigation are factors that can decrease endotoxin translocation and nutrients that may have beneficial effects, such as antioxidant function.

Dr McClain has no relevant conflicts of interest to disclose.

Suggested Reading

Bharadwaj S, Ginoya S, Tandon P, et al. Malnutrition: laboratory markers vs nutritional assessment [published online May 11, 2016]. *Gastroenterol Rep (Oxf)*.

doi:10.1093/gastro/gow013.

Hanje AJ, Fortune B, Song M, Hill D, McClain C. The use of selected nutrition supplements and complementary and alternative medicine in liver disease. *Nutr Clin Pract*. 2006;21(3):255-272.

Jin R, Willment A, Patel SS, et al. Fructose induced endotoxemia in pediatric nonalcoholic fatty liver disease. *Int J Hepatol*. 2014;2014:560620.

Johnson TM, Overgard EB, Cohen AE, DiBaise JK. Nutrition assessment and management in advanced liver disease. *Nutr Clin Pract*. 2013;28(1):15-29.

Kirpich IA, Marsano LS, McClain CJ. Gut-liver axis, nutrition, and non-alcoholic fatty liver disease. *Clin Biochem*. 2015;48(13-14):923-930.

Kirpich IA, Miller ME, Cave MC, Joshi-Barve S, McClain CJ. Alcoholic liver disease: update on the role of dietary fat. *Biomolecules*. 2016;6(1):1.

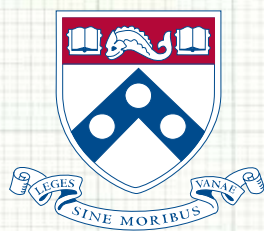
Kirpich IA, Petrosino J, Ajami N, et al. Saturated and unsaturated dietary fats differentially modulate ethanol-induced changes in gut microbiome and metabolome in a mouse model of alcoholic liver disease. *Am J Pathol*. 2016;186(4):765-776.

Li F, Duan K, Wang C, McClain C, Feng W. Probiotics and alcoholic liver disease: treatment and potential mechanisms. *Gastroenterol Res Pract*. 2016;2016:5491465.

Mohammad MK, Zhou Z, Cave M, Barve A, McClain CJ. Zinc and liver disease. *Nutr Clin Pract*. 2012;27(1):8-20.

Plank LD, Gane EJ, Peng S, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. *Hepatology*. 2008;48(2):557-566.

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