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LIVER (S COTLER AND E KALLWITZ, SECTION EDITORS)

Nutrition in Cirrhosis

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Abstract

Purpose of Review This review discusses the prevalence of malnutrition in cirrhosis, metabolic functions of the liver and alterations in cirrhosis, malnutrition screening tools, and common macronutrient and micronutrient deficiencies encountered in individuals with chronic liver disease and their impact on morbidity and mortality.

Recent Findings Several meta-analyses and international society guidelines recommend malnutrition screening and nutrition interventions to improve outcomes in all patients with chronic liver disease given their high risk of malnutrition which is often under recognized.

Summary Malnutrition is common in individuals with chronic liver disease and has a significant impact on patient outcomes. Thus, it is critical that validated malnutrition screening tools are used routinely in this patient population in order to identify high-risk patients and implement nutrition and exercise interventions early.

Keywords Nutrition · Malnutrition · Cirrhosis · Sarcopenia · Branched-chain amino acids

Introduction

It is estimated that over one million people die from cirrhosis worldwide each year [1]. Alcohol abuse and chronic viral hepatitis are common causes; however, over the last two decades, there has been a significant rise in cirrhosis secondary to nonalcoholic steatohepatitis (NASH) [2].

Malnutrition is seen in as high as 75–90% of patients with cirrhosis, and the prevalence increases in those with more advanced states of liver disease [3]. Patients with alcoholic liver disease are more likely to have poor nutrition compared to other etiologies of cirrhosis [4, 5]. Carvalho and Parise showed increased rates of malnutrition with worsening Child-Turcotte-Pugh (CTP) class score with 46% of CTP class A, 84% of CTP class B, and 95% of CTP class C patients being malnourished [3].

Malnutrition is associated with complications of cirrhosis, including ascites, hepatic encephalopathy, variceal bleeding, poor wound healing, poor hepatic function, and increased mortality [6, 7]. Nutritional status is an important predictor of morbidity and mortality in cirrhosis, and it has important implications in selection for liver transplant as poorer nutritional status correlates with higher postoperative complications [8••, 9]. Therefore, it is of critical importance to assess nutritional status and start appropriate interventions early in order to minimize hepatic decompensation and death.

In this review, we describe the liver's role in nutrition and metabolism, how cirrhosis leads to malnutrition, common macronutrient and micronutrient deficiencies, and interventions that can be used to improve patient outcomes in those with chronic liver disease.

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The Liver's Role in Nutrition and Metabolism

Given the liver's essential role in macronutrient synthesis, storage, metabolism, and detoxification, it is of no surprise that end stage liver disease (ESLD) causes a wide variety of derangements. The liver is a key storage site for several macro and micronutrients including vitamin A, copper, manganese, iron, fatty acids, and glycogen among others (Table 1). The

Table 1 Essential nutrients that are stored, produced, metabolized, and regulated in the liver

Stored	Produced	Metabolized or processed	Regulated
Glycogen/glucose	Bile salts	Fatty acids	Acute phase response
Fatty acids	Heme	Amino acids	Global metabolism
Copper	Non-essential amino acids	Glycogen/glucose	Cholesterol homeostasis
Iron	Urea	Fructose	Glucose homeostasis
Vitamin A	Glycogen	Galactose	
Vitamin D	Ammonia	Certain hormones (thyroxine and steroid hormones)	
Vitamin B12	Carnitine		
Manganese	Plasma proteins		
	Cholesterol		
	Phospholipids		
	Lipoproteins		
	Fats and fatty acids		
	Coagulation factors		
	Cytokines, chemokines, and complement proteins		

liver is the second largest storage site of glycogen after skeletal muscle, and lack of glycogen storage capacity in cirrhosis plays a significant role in glucose homeostasis and insulin resistance. Over 90% of plasma proteins and approximately 15% of the total protein mass of the body are produced in the liver. The liver produces numerous cytokines and chemokines, plays a central role in the acute phase response, and serves as the primary site of fatty acid metabolism [10]. The liver's role in metabolism and storage of carbohydrates and fatty acids makes it a primary driver of the energy production that fuels basic cellular functions. Additionally, the liver produces and excretes bile salts which are essential for absorption of dietary fats and fat-soluble vitamins within the intestinal lumen. Lastly, the liver is a principal site for detoxification of substances and metabolites that are ingested as part of a normal diet [11, 12].

Mechanisms of Malnutrition in Cirrhosis

Malnutrition is estimated to affect 20% to 95% of cirrhotic patients, and its prevalence and severity correlates with the degree of liver disease [13••]. The mechanisms of malnutrition in cirrhosis and chronic liver disease are complex and multifactorial.

Cytokine Effects Cytokine activation, as evidenced by elevated levels of TNF-alpha, interleukin-1, and interleukin-6, is partly responsible for decreased appetite which is exceedingly common in cirrhosis [14, 15]. Cytokine activation influences malnutrition in several ways: cytokine levels are inversely related to nutrient intake, cytokines have the potential to decrease appetite, and increased levels can contribute to hypermetabolism [14].

Poor Intake There are several etiologies that contribute to poor oral intake in cirrhosis. Cirrhotic patients commonly have anorexia of chronic disease and decreased sense of smell and/or dysgeusia, the latter of which can be caused or exacerbated by micronutrient deficiencies such as zinc and magnesium. Nausea and vomiting may be present due to ascites, intestinal edema, gastrointestinal (GI) dysmotility, small intestinal bacterial overgrowth, or unpalatable medications such as lactulose that also increase intestinal gas.

Complications of decompensated cirrhosis such as hepatic encephalopathy can contribute to poor appetite, limited access to food, difficulty swallowing and chewing, and lack of volition to eat. Large volume ascites can cause early satiety because of extrinsic compression of the GI tract. Gastrointestinal bleeding from varices, gastric antral vascular ectasias, or portal hypertensive gastropathy may require prolonged or frequent periods of fasting if the patient is having an active hemorrhage.

It is also common for external factors to contribute to poor oral intake. For example, cirrhotic patients undergo frequent medical procedures and imaging that require periods of nil per os. Cirrhotic patients have decreased glycogen stores; fasting for even 2 h can induce a starvation state leading to fat oxidation and gluconeogenesis resulting in increased proteolysis [16]. Additionally, patients with cirrhosis are frequently given dietary restrictions—both appropriate in the case of sodium limitations and often inappropriate in the case of protein restriction—together leading to less palatable diets.

Diarrhea, Malabsorption, and Small Intestine Bacterial Overgrowth Malabsorption is also a factor for malnutrition in cirrhosis. Disturbances in bile acid metabolism affect the formation of micelles which are necessary for fat digestion and fat-soluble vitamin absorption [17]. Small intestinal bacterial overgrowth (SIBO) can lead to diarrhea and malabsorption, and in one study, it was found to be present in 61% of cirrhotic patients based on small intestine cultures [18]. The prevalence of chronic pancreatitis and exocrine pancreatic insufficiency are higher in alcoholic cirrhosis and can result in fat malabsorption. Lastly, protein-losing enteropathies have been described in cirrhosis as a result of portal hypertension [19].

Dysmotility Impaired GI motility can affect multiple parts of the GI tract and adversely affect the nutritional status of affected individuals. Increased nitric oxide, autonomic neuropathy, and gut hormonal changes have been implicated as possible contributing factors. Delayed gastric emptying and impaired accommodation can be seen in cirrhosis and may result in early satiety. Small intestinal dysmotility is common in cirrhosis and can predispose to bacterial translocation, SIBO, and malabsorption [18, 20].

Metabolic Disturbances Patients with cirrhosis also display hypermetabolic states. By measuring the resting energy expenditure (REE), one study showed that 34% of clinically stable cirrhotic patients had an REE that exceeded the predicted REE by more than 20% [21]. Hypermetabolism is associated with malnutrition and worse outcomes. It may be mediated by cytokine activation and intermittent episodes of endotoxemia which are all factors that also contribute to anorexia.

Defining Malnutrition in Cirrhosis

The criteria for malnutrition in adults can be quite variable and are even more difficult to ascertain in those with liver disease and synthetic dysfunction. In the general population, the Academy of Nutrition and Dietetics (AND) defines malnutrition as meeting any two of the following parameters: insufficient energy intake, weight loss, loss of muscle mass or subcutaneous tissue, fluid accumulation, and/or decreased functional status as measured by hand grip strength [22]. In those with cirrhosis, malnutrition is most commonly defined as a loss in skeletal muscle mass and/or strength as well as decreased subcutaneous and visceral fat mass. Alterations in these structural components often occur in the setting of decreased protein and total energy consumption [23, 24]. Serum proteins like albumin and prealbumin are considered by many to be a surrogate for an individual's nutrition status. Data however suggest that these hepatic proteins are not in fact accurate indicators of one's nutritional status but more indicative of recovery from acute and/or chronic disease states [22, 25, 26].

Measures of Body Composition Sarcopenia is one of the major components of frailty; however, frailty involves loss of skeletal mass as well as a loss of performance [27]. Body composition assessment in cirrhotic patients should include the use of BMI in conjunction with identification of volume overload, sarcopenia, and lipopenia. There is no validated method to adjust the BMI calculation in cirrhotic patients, and this is often overestimated in the setting of volume overload [28]. Prior studies have utilized post paracentesis weight or calculated dry weights based on the severity of ascites and lower extremity edema to calculate the corrected BMI [28, 29].

Not only is BMI affected, but sarcopenia and lipopenia may also be underestimated in cirrhotic patients with volume overload and/or obesity [30]. Sarcopenia can be assessed using a variety of modalities including computed tomography (CT), dual-energy X-ray absorptiometry (DEXA), and bioelectrical impedance analysis (BIA). When using CT, the skeletal muscle area (SMA) is calculated (in cm^2) as the cross-sectional area of the abdominal muscles at the top of the L3 vertebral level including the psoas, paraspinal, and abdominal wall muscles. The skeletal muscle index (SMI) is calculated by dividing the SMA by height squared (in m^2). An SMI of less than 50 cm^2/m^2 for men or less than 39 cm^2/m^2 for women meets criteria for sarcopenia and is associated with increased mortality [31]. DEXA scans can be used to assess sarcopenia and have the capability to measure bone, fat mass, and fat-free mass content which is usually used as a surrogate for lean muscle mass [32]. However, the limitations of using DEXA technology in cirrhotic patients include the inability to distinguish water mass from muscle mass in patients with ascites and volume overload as well as the limited ability to measure visceral abdominal fat which is an important in cirrhotic patients with NASH [33]. BIA uses principles of electrical current impedance through various body tissues to estimate total body water, and from there, fat mass and fat-free mass. Fat-free mass is taken as a surrogate of muscle mass [34]. BIA has the advantage of being easy to obtain at the point-of-care as it is a portable technology with rapid results. The phase-angle measurement in BIA has been showing in some studies to be a reliable marker of nutrition risk in cirrhotic patients, with a proposed level of ≤ 4.9° used as the cutoff for increased risk [35]. BIA has the same limitations as DEXA technology, however, in the setting of fluctuations in total body water.

In addition to sarcopenia, alterations in muscle function also correlate with mortality. Muscle strength can be assessed by measuring handgrip strength (HS). HS can be assessed in less than 1 min with a Jamar dynamometer with the mean of three readings taken with the dominant hand. In men, HS of less than 29 kg (BMI ≤ 24), less than 30 kg (BMI 24.1–28), and less than 32 kg (BMI > 28.1) is considered weak, whereas in women, HS of less than 17 kg (BMI ≤ 23), less than 17.3 kg (BMI 23.1–26), less than 18 kg (BMI 26.1–29), and less than 21 kg (BMI > 29) is considered weak.

Functional status and frailty may also be assessed with the Short Physical Performance Battery (SPPB), the 6-min walk test, or the Clinical Frailty Scale (CFS) [39–43]. The SPPB consists of timed repeated chair stands, balance testing, and a timed 13-ft walk. The SPPB takes approximately 3 min to complete, and patients are given up to four points for each task with a maximum score of 12. Scores of nine or lower were associated with increased waitlist mortality [36, 37]. A 6-min walking distance of less than 250 m was also associated with increased mortality [38]. Lastly, the CFS is a 10-point descriptive scale that assesses overall performance status with a score of 5 or greater associated with an increased risk of hospitalization and death [39].

Liver-Specific Nutrition Screening Tools Any patient with cirrhosis should undergo nutritional assessment, particularly those at highest risk which includes those with a BMI of less than 18.5 or CTP class C cirrhosis [30, 40]. The 2019 EASL guidelines for clinical nutrition in liver disease recommend screening all patients with chronic liver disease for malnutrition [13••]. However, obtaining an accurate and reliable nutritional assessment in cirrhotic patients presents unique challenges. Typical nutrition biomarkers are skewed in cirrhosis because of decreased hepatic protein synthesis and volume overload leading to fluctuations in body weight. Currently, there are sparse validated malnutrition screening tools (MST) in this patient population [30]. Validated MSTs for the general population include the Nutritional Risk Screening 2002 (NRS-2002), the Malnutrition Universal Screening Tool (MUST), and the Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT). The RFH-NPT was shown to have a higher sensitivity when compared to the NRS-2002 [41–44]. A recent study evaluating 1146 hospitalized patients demonstrated that the MUST screening method had a better correlation with the ESPEN criteria for malnutrition when compared to the NRS-2002 [45].

Two screening tools have been developed for patients with liver disease and include the RFH-NPT and the Liver Disease Undernutrition Screening Tool (LDUST). The RFH-NPT is an independent predictor of hepatic decompensation and transplant-free survival [42]. The RFH-NPT score is based on several elements including volume overload, BMI, recent weight loss, and decreased oral intake. Patients are then categorized as being at low, moderate, or high risk for malnutrition [44]. The LDUST is a six-item questionnaire that incorporates oral intake, weight loss, loss of subcutaneous fat or muscle mass, volume overload, and functional status [46, 47]. Further studies are still warranted to evaluate the effectiveness of these liver disease-specific screening tools.

The authors' experience is that screening cirrhotic patients for malnutrition varies widely by clinical practice and resource availability. It is more common to use general malnutrition screening tools such as the ADA guidelines for malnutrition classification, but if a trained Registered Dietitian Nutritionist (RDN) is available, liver disease-specific tools may be used. Additionally, some RDN's are trained to use hand grip dynamometers which can enhance detection of frailty and malnutrition. Generally, malnutrition risk is assessed at every clinic visit with nutrition support personnel (physicians and RDNs) and more frequently in high-risk patients.

Nutrition Interventions

General Calorie and Protein Targets Individuals with cirrhosis often have increased caloric and protein requirements due to metabolic disturbances including hypercatabolism and increased proteolysis. Recent EASL guidelines recommend that non-obese individuals with cirrhosis consume at least 35 kcal/kg of body weight per day, while optimal protein intake should be between 1.2 and 1.5 g/kg of body weight per day [13••]. Critically ill cirrhotic patients should receive between 35 and 40 kcal/kg/day or 1.3 times the measured REE by indirect calorimetry. Protein intake in these patients should be between 1.2 and 1.3 g/kg/day. Protein-calorie malnutrition is associated with increased muscle catabolism and sarcopenia and should thus be treated early on in the disease process. Sarcopenic obesity is common and represents a challenge in regard to nutrition support recommendations. Generally accepted practice for sarcopenic obesity and/or malnourished obese patients is to maximize the protein recommendations at the level of actual body weight but to lower total calorie targets to ideal body weight or to 15 to 20 kcal/kg/day of actual body weight.

With increasing rates of NAFLD, as well as the global obesity epidemic, it is estimated that 20–35% of cirrhotic patients are obese, even after adjustment for fluid retention [13••]. Obese cirrhotic patients may have worse clinical outcomes including higher risk for clinical decompensation and higher rates of postoperative liver transplant complications [52, 53]. Dietary principles for obese, cirrhotic patients include moderate caloric restriction with a deficit of 500–800 kcal/day and adequate protein intake of > 1.5 g of protein per kg of ideal body weight per day [13••]. Furthermore, weight loss of 5–10% in the HALT-C trial was associated with a reduced rate of disease progression and is a reasonable goal for this patient population. For those undergoing surgery, expert guidelines recommend energy intake of 25 kcal/kg of ideal body weight per day and protein intake of 2 g/kg of ideal body weight per day [48].

Timing of Nutrients As previously discussed, cirrhosis is a state of accelerated starvation with increased rates of fat oxidation and gluconeogenesis during periods of fasting. These alterations in metabolism contribute to protein-calorie malnutrition which is associated with worse outcomes [49, 50]. Inter-meal snacks are well studied and recommended to mitigate the accelerated starvation and proteolysis found in cirrhosis.

Consuming a protein-rich snack prior to bedtime shortens the longest fasting interval between meals, and studies have shown this to be the most important for improved clinical outcomes. In a study that included over 100 cirrhotic patients randomized to a nighttime or daytime snack of 710 kcal/day, the nighttime group had significantly increased total body protein at 3, 6, and 12 months compared to baseline [51]. There was no significant change in total body protein compared to baseline over a 12-month period in the daytime group. Furthermore, health-related quality of life (QOL) measures were assessed in both nighttime and daytime snack groups, with significant increases in scores for physical, social functioning, emotional, and health distress in the nighttime group at 6 months. By 12 months, both daytime and nighttime snack groups had significant increases in QOL scores.

The optimal composition of the recommended nighttime snack has not yet been established. A meta-analysis evaluating the late evening snack in cirrhosis showed decreased fat oxidation and improved nitrogen balance regardless of snack composition [52]. Most guidelines therefore recommend a nutrient dense snack [50]. However, given the increased protein needs in cirrhosis, it may be prudent to include some protein in an otherwise nutrient dense nighttime snack. The authors generally recommend either a low sugar, protein-enhanced commercial liquid nutrition supplement or a snack similar to a nut butter sandwich on multigrain bread as a source of high-quality protein and complex carbohydrates.

Oral/Enteral/Parenteral Supplementation Oral nutrition is the preferred route of nutrition for most cirrhotic patients, but many will have difficulty achieving caloric goals by oral intake alone. When oral nutrition is inadequate or not feasible, enteral or parenteral nutrition should be considered. Enteral nutrition (EN) is largely preferred over parenteral nutrition (PN) due to lower rates of complications, particularly infection, and decreased cost [53]. Therefore, PN should be reserved for patients in whom EN has failed or is contraindicated (i.e., ileus, small bowel obstruction, gastrointestinal bleeding, discontinuous intestine) [50]. While nasoenteric and nasogastric tubes should be avoided in the setting of active or recent variceal bleeding, the ESPEN guidelines indicate that it is probably safe to use nasoenteric and nasogastric tubes for nutrition in the presence of non-bleeding esophageal varices [41, 54]. Conversely, cirrhosis and the presence of ascites is not an absolute contraindication for PEG placement but should be avoided given the increased risk for bleeding as well as increased risk of complications from ascites including buried bumper, leakage, and peritonitis [55].

Although meta-analyses have not shown a survival benefit for EN or PN in the malnourished cirrhotic patient, there are specific clinical circumstances in which there is evidence for nutrition support in the patient with chronic liver disease. In several randomized controlled trials (RCTs), EN and oral nutrition support have been shown to have a mortality benefit in patients with alcoholic hepatitis [56–58]. Cabre at al. showed similar 28-day mortality in patients with severe alcoholic hepatitis treated with EN compared to prednisone, but the mortality rate due to infectious complications was higher in the steroid group during the following year [57]. Additionally, in the VA cooperative study, 6-month mortality rates were lower in moderately malnourished, but not severely malnourished patients with severe alcoholic hepatitis who were receiving combined treatment with EN supplementation and oxandrolone versus placebo. This suggests the importance of early, sustained nutrition support. Mendenhall et al. compared these results with those from the subjects in the VA cooperative study who were treated with oxandrolone without food supplementation and found that oxandrolone reduced 6-month mortality in patients with moderate malnutrition and adequate calorie intake. Conversely, oxandrolone had no effect on mortality in patients with moderate malnutrition and inadequate caloric intake [58]. Similarly, a small study showed that EN may improve liver function indices and improve hepatic encephalopathy more rapidly than regular diet alone in patients with alcoholic liver disease [59]. Hirsch et al. found significantly decreased hospitalizations in patients with decompensated alcoholic cirrhosis receiving EN supplementation with 1000 kcal and 34 g protein compared to the control group which received a placebo capsule [60].

In the preoperative cirrhotic patient, nutrition is essential to ensure good outcomes after surgery. In the preoperative cirrhotic patient, nil per os time should be minimized when possible given reduced glycogen stores [13••]. Furthermore, meta-analyses have demonstrated that enhanced recovery after surgery (ERAS) measures, including a clear liquid carbohydrate drink 2 h prior to surgery, improves morbidity and is associated with decreased length of stay (LOS) after liver surgery [61, 62]. Post-liver transplantation, both EN and PN have been shown to decrease ICU LOS, ventilator duration, and risk of bacterial infections [13••, 63]. Moreover, EN initiated within 12 h of transplant is associated with improved outcomes when compared to PN [63]. After liver transplantation, early EN or oral nutrition should be initiated within 12 to 24 h postoperative when possible [13••].

Modified Protein Intake

Plant Versus Animal-Based Proteins Cirrhotic patients are often inappropriately counseled to limit protein intake with concern for worsening hepatic encephalopathy. A recent RCT showed that a diet high in plant-based protein (1–1.5 g/day) as part of a nutritional intervention with 30–35 kcal/day can improve hepatic encephalopathy, QOL, nutritional parameters such as mid-arm circumference, and decrease subsequent hospitalizations [64, 65]. Improvement was greater in the CTP class B patients compared to those with CTP class C, suggesting that early nutritional intervention is more advantageous. Vegetable protein may be preferable to meat protein in patients with hepatic encephalopathy, but the data is based on small and non-blinded studies [66, 67].

Branched-Chain Amino Acids In cirrhosis, there is a reduction in circulating levels of the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine, which is thought to contribute to sarcopenia and hepatic encephalopathy. BCAAs are required for protein synthesis, and they serve as an alternative mode of ammonia detoxification in peripheral skeletal muscle. Early studies demonstrated improvements in hepatic encephalopathy and overall liver function when subjects were supplemented with BCAAs [68–70]. A 2016 Cochrane review of 16 RCTs evaluated the effects of oral and IV BCAAs on hepatic encephalopathy in cirrhosis. The review concluded that oral but not IV BCAAs can improve hepatic encephalopathy with a number needed to treat (NNT) of 5 and a relative risk reduction of 0.73 [71]. In addition to the beneficial effect on hepatic encephalopathy, supplementation with oral BCAAs can ensure adequate protein intake. There is also data, albeit limited, that long-term supplementation with oral BCAAs may improve clinical outcomes such as nutritional parameters, hospital readmission rates, and QOL measures [78]. Despite these benefits, BCAAs are sometimes poorly tolerated, and palatability and cost limit use in routine clinical practice [2, 72].

Vitamins, Minerals, and Other Nutrients

Cirrhotic patients often have protein-calorie malnutrition and certain micronutrient deficiencies because of decreased oral intake as well as impaired digestion and nutrient absorption.

Fat-Soluble Vitamins: A, D, E, K Fat-soluble vitamins including A, D, E, and K are often affected by cholestatic liver disease because of reduced intraluminal bile salt concentration needed for optimal absorption [73]. Vitamin A deficiency can lead to multiple skin abnormalities such as xerosis and acneiform lesions as well as night blindness. Vitamin A deficiency can be prevented with vitamin A monitoring and replacement; however, vitamin A has a narrow therapeutic window, and replacement should be monitored carefully [74]. Vitamin E deficiency can lead to hemolytic anemia, neuropathy, and kidney damage [75]. Vitamin K causes a prolonged prothrombin time and can increase bleeding risk. Replacement can be given in an outpatient setting with oral supplementation, but inpatients with an active GI hemorrhage often require more aggressive replacement with intramuscular or intravenous formulations [13••, 75]. Vitamin K is also a key cofactor in bone health, and metabolic bone disease is common in cirrhosis. As there is no standard of care for vitamin dosing and monitoring schedules, clinical practice varies widely. Given the narrow therapeutic windows of most fat-soluble vitamins in liver disease, however, the authors favor a conservative approach. Dosing recommendations generally fall on the lower end of dose, for example 10,000 to 20,000 units of vitamin A daily, as opposed to high-dose replacements. Serum levels are usually reassessed in 8- to 12-week intervals.

Vitamin D deficiency is extremely common in chronic liver disease, particularly cholestatic etiologies, affecting up to 92% of patients [76]. While low serum vitamin levels can reflect true nutritional deficiency, they can also be due to decreased plasma binding proteins present in cirrhosis. A recent study found that severe vitamin D deficiency in alcoholic liver disease was associated with increased liver damage and higher mortality, suggesting very low vitamin D levels can be a surrogate for liver disease severity [77]. There is also evidence that vitamin D deficiency may be associated with worse liver-related outcomes including lack of response to the now obsolete interferon-based hepatitis C treatment [78] and hepatocellular carcinoma, though causality has not been established [78, 79]. Vitamin D also has an immunomodulatory effect which is helpful to prevent spontaneous bacterial peritonitis, where an active version of vitamin D is locally made in response to the infection [80]. Vitamin D deficiency (< 20 ng/mL) can also lead to osteopenia and osteoporosis from calcium loss. Supplementation to target a 25-hydroxyvitamin D level > 30 ng/mL is recommended [13••]. It is reasonable to replete vitamin D levels, but whether this impacts liver-related outcomes is still unknown.

B Vitamins B vitamin deficiencies are less common because they are commonly found in a wide array of foods, but when present, they can lead to a variety of complications. Left untreated, thiamine deficiency can lead to serious and irreversible complications including Wernicke's encephalopathy and Korsakoff's syndrome, as well as heart failure (wet beriberi) [13••, 75]. Prompt treatment with IV thiamine is warranted if either Wernicke's or Korsakoff's are suspected [13••]. Though less common, deficiencies in pyridoxine (B6), folate, and cobalamin (B12) can also be present leading to anemia and neuropathy [13••].

Trace Metals: Zinc, Copper, and Manganese Zinc deficiency is common in cirrhosis and has been implicated as a potential treatment target for hepatic encephalopathy. Zinc deficiency is a common mineral deficiency in cirrhotic patients and can manifest as dysgeusia; it has also been associated with hepatic encephalopathy, glossitis, hypogonadism, and poor wound healing. A randomized, controlled trial of 79 cirrhotic patients with hepatic encephalopathy refractory to lactulose and a 1.0 g/kg/day protein diet found that 225 mg of daily oral zinc supplementation significantly decreased hepatic encephalopathy grade, improved CTP scores, and improved QOL measures [81]. Other studies, however, have shown that zinc supplementation does not improve hepatic encephalopathy; therefore, the data is overall conflicting [75, 82, 83]. Some studies, including a small randomized, controlled trial [84], have shown an improvement in taste with oral zinc supplementation. Given the predisposition for zinc deficiency in cirrhosis, the lack of a reliable serum assessment, and the potential treatment benefits, it is reasonable to supplement with 25–50 mg of oral elemental zinc per day in symptomatic patients with careful monitoring and limited treatment duration in patients with chronic renal insufficiency [13••, 75, 85]. Copper and zinc interact competitively for absorption at the brush border of the small intestine. Therefore, precipitation of copper deficiency manifesting with findings such as microcytic anemia, neutropenia, and leukopenia should be considered when using long-term zinc supplementation for the above indications [86]. Copper is stored in the liver, and therefore monitoring is recommended prior to supplementation. Manganese levels are often high in patients with cirrhosis from impaired biliary excretion from portal shunting of blood. This leads to selective accumulation of manganese in parts of the brain. As a result, manganese supplementation should be avoided in cirrhosis [87]. Patients requiring long-term PN often receive trace metal supplementation as a compounded 5-element formulation including copper, zinc, manganese, selenium, and chromium; therefore, the entire additive is generally removed from PN in those with ESLD.

Magnesium Serum magnesium levels are frequently low in cirrhosis and can contribute to dysgeusia as well as decreased appetite, muscle cramps, weakness, and other symptoms. A study comparing 75 cirrhotic patients to healthy volunteers found a significant negative relationship between serum magnesium levels and gustatory function, particularly in the detection threshold for salt [88]. Oral magnesium repletion may be beneficial for appetite and dysgeusia. Magnesium can be supplemented by intravenous, intramuscular, or oral routes, and 400 mg magnesium oxide is often recommended [89, 90]. While oral therapy is most convenient, this can cause or exacerbate diarrhea, which may also contribute to further stool magnesium losses.

Carnitine Deficiencies in carnitine can also lead to muscle cramps. Nakanishi et al. showed high-dose supplementation can reduce rates of these cramps significantly [91]. Supplementation may also be helpful to improve energy metabolism and decrease ammonia levels [92, 93].

Conclusions

Malnutrition is exceedingly common among people with cirrhosis and has serious implications for clinical outcomes and QOL. The liver is a key organ in nutrition and metabolism, and ESLD has a broad impact on multiple metabolic states. Timely malnutrition screening is required in order to identify individuals with malnutrition who can benefit from early nutrition counseling and support to prevent decompensation and improve survival.

Compliance with Ethical Standards

Conflict of Interest Lena B. Palmer, Gabriela Kuftinec, Michelle Pearlman, and Caitlin Homberger Green declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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