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Nutrition and Obesity (O Pickett-Blakely, Section Editor)

Nutrition in Chronic Liver Disease

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Abbreviations *ALD* Alcoholic liver disease · *ASMI* Appendicular skeletal muscle index · *BCAAs* Branch chain amino acids · *BMI* Body mass index · *CLD* Chronic liver disease · *CT* Computed tomography · *DEXA* Dual energy X-ray absorptiometry · *HCC* Hepatocellular carcinoma · *HE* Hepatic encephalopathy · *HMB* β-Hydroxy β-methylbutyrate · *mTOR* Mammalian target of rapamycin · *NAFLD* Non-alcoholic fatty liver disease · *NASH* Non-alcoholic steatohepatitis · *NEAT* Non-exercise activity thermogenesis · *PN* Parenteral nutrition · *REE* Resting energy expenditure · *SBP* Spontaneous bacterial peritonitis · *SMI* Skeletal muscle index

Abstract

Purpose of review Malnutrition is a common finding in patients with chronic advanced liver disease (CLD) and is an important prognostic predictor for morbidity and mortality. This review aims to summarize the latest evidence-based guidelines and expert opinion regarding diagnosing malnutrition in patients with CLD and providing optimal solutions.
Recent findings In addition to diet, evidence demonstrates sarcopenia and frailty are emerging concepts critical to outcomes in those with CLD. Thus, adequate assessment of nutritional status incorporates the interplay of nutrient intake, sarcopenia, and frailty.
Summary Addressing malnutrition in patients with CLD requires understanding the multifactorial mechanisms contributing to nutritional deficiencies, but also careful assessment of functional capacity. Interventions mitigating or reversing sarcopenia and frailty are equally important to nutritional supplementation. While the latency period between compensated and decompensated cirrhosis provides a good window for fruitful interventions, we believe providers need to be vigilant early on the course of CLD to maximize nutritional gains and halt muscle loss.

Introduction

Malnutrition in chronic advanced liver disease (CLD) occurs in 20–50% of patients [1•] reaching close to 80% in patients with alcoholic liver disease (ALD) [2]. Cirrhotic patients, especially those with a body mass index (BMI) of < 18.5 kg/m^2 or with Child-Pugh score of C are malnourished [3]. The progression of liver failure parallels the progression of malnutrition, as evidenced by nutritional parameter such as caloric consumption [4•] and is manifested more in decompensated cirrhosis as compared to compensated cirrhosis. In fact, malnutrition is present in up to 80% of patients with decompensated liver disease [5], and it, along with sarcopenia and frailty, is an important prognostic indicator in those with CLD [6]. It is recommended that all patients with CLD be screened for malnutrition in order to prevent complications [7], as the early initiation of aggressive nutritional therapy along with correction of vitamin and micronutrient deficiencies has the potential to not only reduce the risk of such complications, but also improve the patient's overall mortality [1•, 3, 7]. Hence, timely assessment of nutritional status and appropriate treatment is imperative. For the majority of this review, we will focus on those with chronic advanced liver disease, which we will refer to as CLD.

Malnutrition

According to the European Association for the Study of the Liver (EASL) clinical practice guidelines 2019, "malnutrition" refers to "undernutrition" [1•]. The definition of malnutrition varies with societies and is outlined in Table 1 [3]. Frailty and sarcopenia are separate, yet closely related indices assessing nutritional status. Frailty represents a global construct signifying loss of physical, social, and cognitive functioning resulting in a vulnerable state unable to withstand stressors [6, 8, 9] and remains strongly and independently associated with an increased risk of hospitalization [10] and/or mortality in patients with cirrhosis [10, 11]. The European Working Group on Sarcopenia in Older People defined sarcopenia as progressive and generalized loss of skeletal muscle mass along with low muscle strength and function [9]. Sarcopenia may result from aging (primary sarcopenia), as well as from pathogenic mechanisms (secondary sarcopenia) [8, 9].

Sarcopenia is recognized as an important manifestation of cirrhosis [12, 13] and has been shown to be present in up to 40% of subjects evaluated for liver transplantation [12]. Studies have shown that sarcopenia is associated with worse outcomes in patients with cirrhosis, independent of the model for end-stage liver disease (MELD) score [14] and with rising healthcare costs [15]. Malnutrition and sarcopenia are associated with increased complications such as susceptibility to infections, sepsis, wound dehiscence, hepatic encephalopathy (HE), ascites, and increased mortality in patients with cirrhosis and those undergoing liver transplantation [12, 16]. Sarcopenia correlates with cognitive impairment in cirrhosis due the involvement of muscle with ammonia metabolism. In the setting of hepatic impairment, skeletal muscle plays a key role in buffering ammonia in the form of glutamine. Thus, muscle mass depletion worsens hyperammonemia [13].

Table 1. Society guidelines for defining malnutrition. Used with permission from John Wiley and Sons and [3]

	Food Intake	Weight loss	Muscle mass loss	Subcutaneous fat loss	Fluid accumulation	Functional status	BMI	Inflammation	SGA
General ASPEN	X	X	X	X	X	X		X	
Hospitalized inpatient			X				X		
General ESPEN		X	X				X		
Cirrhosis ESPEN		X	X	X			X		X
Cirrhosis ISHEN	X	X	X		X		X	X	

Abbreviations: *ASPEN* American Society for Parental and Enteral Nutrition, *BMI* body mass index, *ESPEN* European Society for Parental and Enteral Nutrition, *ISHEN* International Society for Hepatic Encephalopathy and Nitrogen Metabolism, *SGA* subjective global assessment

Mechanism of malnutrition in chronic liver disease

Various processes contribute to malnutrition in patients with advanced liver disease, particularly cirrhosis. Oral flora dysbiosis, xerostomia, and antibiotic use often alter taste. Frequently, patients with cirrhosis may have decreased energy intake due to unpalatable low-salt diets recommended for patients with ascites, abdominal distention from ascites leading to early satiety, and frequent testing necessitating fasting periods among hospitalized patients with cirrhosis [3]. Altered motility in cirrhosis also leads to early satiety [17, 18] and development of small intestinal bacterial overgrowth (SIBO) [17, 19]. Furthermore, micronutrient abnormalities, such as zinc deficiency and to a lesser extent hypomagnesemia, can lead to altered taste and smell, further resulting in anorexia [18]. Additionally, hormonal alterations can also influence energy intake, as patients with cirrhosis have been noted to have lower levels of ghrelin, the only orexigenic hormone with increased insulin resistance and postprandial hyperglycemia [20].

Another factor affecting nutritional status in subjects with liver disease is altered macronutrient metabolism. In CLD, the liver's ability to store glycogen is impaired requiring other sources for energy. Thus, subcutaneous fat and muscle depletion occurs in the setting of lipid peroxidation and utilization of amino acids to protein as the building blocks for gluconeogenesis [3, 7, 16, 21]. In cirrhosis, both hypercatabolism and starvation mechanisms occur simultaneously, as energy is harnessed from lipids and muscle during the fed or post-absorptive state. In fact, the term "accelerated starvation" has been used to characterize cirrhosis since there is an earlier than expected utilization of lipids and protein for energy utilization in the post-absorptive state compared to healthy adults. Anabolic resistance ensues since supplementing protein and caloric intake is insufficient to increase muscle mass. Ideally, therapeutic interventions should focus on decreasing the duration of time spent in the post-absorptive state to prevent muscle breakdown [22]. Additionally in the setting of sepsis, or decompensating events as in spontaneous bacterial peritonitis (SBP) or gastrointestinal bleeding, catecholamines are released with breakdown of tissue, further exacerbating catabolism. Hyperammonemia, itself, contributes to muscle breakdown and sarcopenia via upregulation of myostatin, a protein that impairs protein synthesis [13]. Decreased testosterone inherent in cirrhosis can potentially be worsened by the use of spironolactone, particularly in men, which can contribute to sarcopenia. Catabolism may also differ by sex, as women with liver disease have been found to have depletion of fat deposits while men with liver disease rapidly lose muscle mass [23].

Decreased nutrient absorption is also a factor that negatively affects nutritional status in those with liver disease. Portal hypertension secondary to cirrhosis can cause mucosal pathological changes throughout the entire gastrointestinal tract, termed portal hypertensive gastroenteropathy. This can present as inflammatory-like lesions (edema, erythema, friable lesions) and vascular lesions (cherry red spots, telangiectasias, or angiodysplasia-like lesions and varices) [24]. These lesions are associated with acute or chronic blood loss leading to anemia and associated with intestinal mucosal atrophy worsening hypoalbuminemia. Cirrhotics with decompensations have been shown to have altered small bowel motility time contributing to the development of SIBO compared to cirrhotics without decompensating events. SIBO may increase

bacterial translocation, which can culminate in SBP or other infections [19]. Patients with cirrhosis are also treated with lactulose, an osmotic laxative that often causes symptoms such as bloating, flatulence, and intestinal hurry, the latter can further decrease absorption of fats and proteins. In some patients, lactulose prepared in a powder form (Kristalose) may have better tolerance [25]. Systemic antibiotics used for SBP prophylaxis (oral quinolones, trimethoprim-sulfamethoxazole) have been associated with disruption of intestinal microbiota and development of antibiotic-resistant bacterial infections. Fortunately, rifaximin has the potential advantage of being poorly absorbed resulting in high fecal concentrations, preventing SIBO and translocation without the systemic side effects of broad-spectrum antibiotics [26, 27].

Assessment of nutritional status

All patients with CLD should be evaluated for malnutrition, sarcopenia, and frailty. A careful past medical history should be conducted to document weight loss, nausea, vomiting, anorexia, eating patterns, dietary intake, and the use of dietary supplements. Physical examination should include the assessment of oral mucosa, hair, skin, subcutaneous fat, muscle wasting, and other stigmata of CLD. Laboratory studies including plasma pre-albumin, serum transferrin, and retinol-binding protein can be used to determine nutritional status, although may not be accurate in critically ill patients or those with CLD, as they vary with the severity of liver disease [28, 29•]. Levels of minerals such as phosphorus, magnesium, iron, zinc, fat-soluble vitamins, and water-soluble vitamins should be assessed [3, 7]. As always, it remains critical to tailor laboratory studies in the setting of each individual patient's underlying liver disease etiology and comorbid conditions.

Successful nutritional interventions require calculation of energy expenditure such that the requisite energy needs are recommended. Resting energy expenditure (REE) represents the majority of total energy expenditure [1•, 30] and is defined as the energy expended at rest by a fasted individual in a thermo-neutral environment [30]. Indirect calorimetry is the most accurate, clinically available tool to measure REE, however, due to limitations of accessibility and cost, is often replaced by mathematical equations [1•, 30] such as the Harris-Benedict [5, 18, 28]. The accuracy of calculated REE versus measured REE has not been extensively studied in liver disease, although literature indicates that the predictive equations calculating REE tend to underestimate energy requirements. As such, the use of indirect calorimetry when available is preferred [5, 7].

The assessment of body mass can be achieved by simple, cheap, and non-invasive anthropometric measurements, although these methods often are limited by critical illness, volume overload, and inter-observer reliability [1•, 3, 7, 9, 28]. These include BMI, mid-arm muscle circumference (MAMC), mid-arm muscular area, triceps skin fold thickness, and biceps or subscapular skin fold thickness. MAMC has a high prognostic value in patients with cirrhosis comparable to the assessment of sarcopenia assessed using computed tomography (CT) scan with an area under the receiver operating characteristic curve ranging from 0.75 to 0.84, depending on sex [31].

Other modalities measuring sarcopenia include CT, magnetic resonance imaging (MRI), bioelectrical impedance analysis (BIA), and dual-energy X-ray absorptiometry (DEXA) [1•]. CT and MRI images are superior tools to quantify total body skeletal muscle mass for the assessment of sarcopenia, and have the added benefit for screening for hepatocellular carcinoma (HCC) [13]. The cross-sectional area of the muscle at the third or fourth vertebrae is normalized to the individual's height squared to calculate the skeletal muscle index (SMI) measured in cm^2/m^2. A multicenter study involving 396 end-stage liver disease patients listed SMI cutoff values for sarcopenia as SMI < 50.0 cm^2/m^2 in men and < 39.0 cm^2/m^2 in women [32]. Another study by Ebadi et al. [23] noted that sarcopenia was predictive of mortality in males, but not in females. Instead, subcutaneous adipose tissue index, defined as cross-sectional area of subcutaneous adipose tissue at L3 level measured by CT scan and adjusted for height squared and measured as cm^2/m^2 was used as a prognostic tool to predict outcomes in female patients with cirrhosis females [23]. CT scan, however, has some drawbacks including radiation exposure and contrast-induced nephropathy [33]. The use of MRI avoids these risks and has been shown to be superior over CT for improved detection of HCC in the setting of CLD [34] and additionally can differentiate muscle tissue from adipose tissue [33].

DEXA offers the opportunity to evaluate sarcopenia, in addition to bone mineral density. Unlike anthropometry or BIA, which both can be impaired by volume retention such as ascites or edema, DEXA with measurement of the appendicular skeletal muscle mass index (ASMI) is not affected by volume overload. Additionally, DEXA-ASMI in combination with non-dominant handgrip strength can be reliably used for skeletal muscle mass estimation and in predicting mortality in cirrhosis [35].

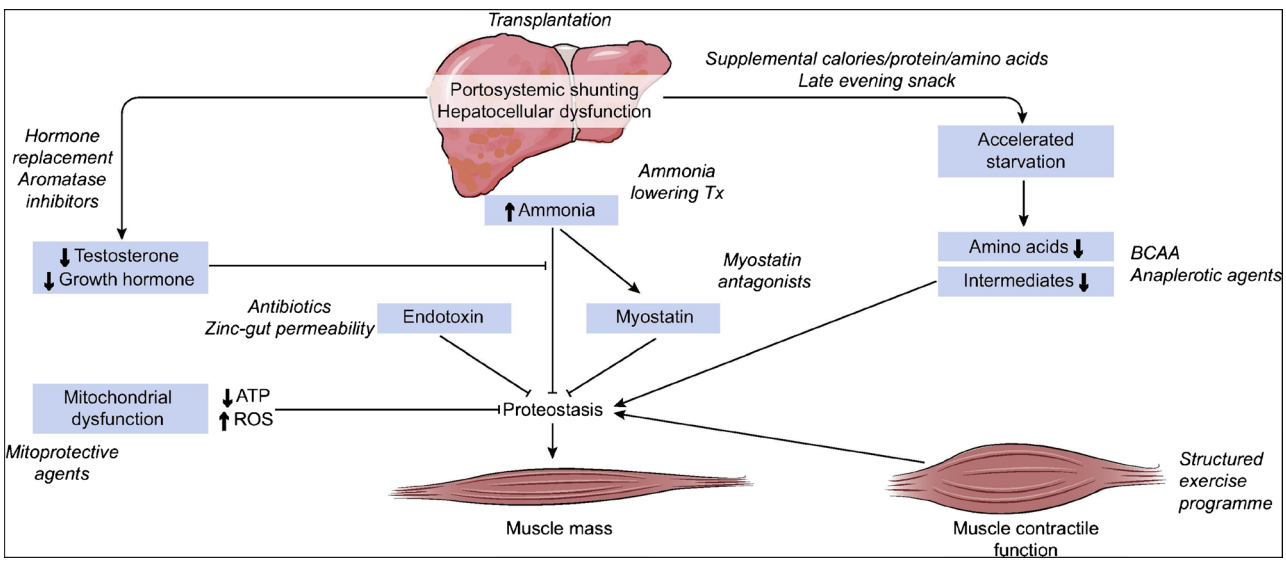

Fig. 1. The interconnectivity between physical fitness and nutrition, mechanisms of muscle wasting, and the treatment options available to mitigate nutritional deficiencies and functional impairments. Used with permission from Elsevier.

Table 2. Summary of Society Guidelines on Enteral Nutrition for patients with liver disease

Society	Guideline statements specific to EN or nutritional support	Reference
EASL (2019)	• In cirrhosis patients with malnutrition who are unable to maintain adequate nutritional intake with oral diet, a period of enteral nutrition is recommended. • Post liver transplantation, oral or enteral feeding should be resumed 12–24 h postoperatively. If this is not possible, parenteral nutrition should be used to reduce complication rates, need for mechanical ventilation, and ICU stay. • In obese patients, enteral feeding and/or PN with a reduced target energy intake (25 kcal/kg BW/day) and an increased target protein intake (2.0 g/kg BW/day) should be utilized.	[1•]
ESPEN guideline (2019)	• Non-malnourished patients with compensated cirrhosis should ingest 1.2 g/kg/day of protein. • In cirrhotic patients who do not achieve nutritional target through the oral diet, EN should be performed. • To replenish malnourished and/or sarcopenic cirrhotic patients, the amount of 1.5 g/kg/day protein should be ingested. • In malnourished ALF patients, enteral nutrition and/or PN should be initiated promptly. • After transplantation, enteral formula together with selected probiotics should be used to reduce infection rate.	[7]
AASLD-Alcoholic liver disease (2010)	• Diets rich in polyunsaturated fats promote alcohol-induced liver disease, whereas diets high in saturated fats may be protective. • Patients with alcoholic cirrhosis should receive frequent interval feedings with a regular oral diet at higher-than-usual dietary intakes (1.2–1.5 g/kg of protein and 35–40 kcal/kg of energy) along with a night time snack and morning breakfast, to improve nitrogen balance.	[52]
ISHEN (2013)	• Patients with cirrhosis, with or without HE, should be provided with high-energy, high-protein diets. • Energy requirements are 35–45 kcal/g and nitrogen requirements are 1.2–1.5 g/kg protein daily in patients with HE. Ingestion of 25–45 g fiber daily should be encouraged. • In patients with decompensated cirrhosis, attempts to reduce body weight should be done by reducing the carbohydrate and fat content of the diet while maintaining a high-protein intake of up to 2 g/kg daily. • Patients should avoid fasting for longer than 3–6 h during the daytime and should be encouraged to take small, frequent meals throughout the day. • The late evening snack should contain at least 50 g of complex carbohydrate.	[71]

Abbreviations: *AASLD* American Association for the Study of the Liver, *ALF* acute liver failure, *EASL* European Association for the Study of the Liver, *EN* enteral nutrition, *ESPEN* European Society for Parenteral and Enteral Nutrition, *HE* hepatic encephalopathy, *ICU* intensive care unit, *ISHEN* International Society for Hepatic Encephalopathy and Nitrogen Metabolism, *PN* total parenteral nutrition

Multiple tools exist to assess frailty by subjective or objective parameters such as the Clinical Frailty Score, Fried Frailty Criteria, 6-min walk test, and Short Physical Performance Battery [1•, 10, 36], although decision aids specific to those with CLD are lacking. One such tool, the Liver Frailty Index, evaluates three physical maneuvers: grip strength, timed chair stands, and balance testing; it has been associated with mortality in a multi-center study [11]. Other tools used in CLD include the Subjective Global Assessment [1•, 3, 4, 7, 8, 14] and protein-calorie malnutrition score [37].

Nutritional therapy

Nutritional therapy in patients with CLD involves caloric and protein supplementation (protein intake of 1.2–1.5 g/kg of dry body weight/day [1•, 7]), physical activity combined with resistance training, and ammonia-lowering strategies. In those with cirrhosis, energy requirement of 32–35 kcal/kg of dry body weight/daily is suggested, but specific requirements should be considered in the context of underlying and comorbid conditions [1•, 7, 38]. While the available data is not strong enough to recommend one particular nutritional plan over another [39], all patients with CLD should be placed on an aggressive, nutritious diet to maintain hepatic function. A multidisciplinary team that includes registered dieticians should be involved to help improve patients' quality of life by preventing nutrition-related complications. With the advancement of liver disease, patient's nutrition regimen should be adjusted accordingly. A retrospective study analyzing early nutrition therapy for patients with cirrhosis delivered by registered dieticians showed improvement in survival rates when compared to therapy of branched chain amino acids and late evening snacks by physicians alone [40]. It is paramount to initiate interventions to prevent physical deconditioning, halt sarcopenia, and reverse nutritional impairments *early* in the course of CLD, such that patients can build enough reserve to weather potential decompensations. Decompensated cirrhosis is characterized by protein anabolic resistance whereby protein supplementation fails to appropriately contribute to protein synthesis [22]. Often, practitioners remain focused on major complications and overlook nutritional status until patients have deteriorated. When the MELD score or Child-Pugh score are high, forced, excessive oral protein or caloric supplementation may not be useful for muscle protein synthesis and may lead to complications such as osmotic diarrhea.

Figure 1 demonstrates the interconnectivity between physical fitness and nutrition, mechanisms of muscle wasting, and the treatment options available to mitigate nutritional deficiencies and functional impairments [1•].

Route of nutritional support

Whenever possible, patients should be advised to consume a high-protein diet with adequate nutritional supplementation. Patients should be encouraged to consume a late evening and an early morning snack containing proteins to shorten the duration of fasting periods, as it has been shown to be beneficial in preventing continued muscle loss in cirrhosis during the post-absorptive or fed period, which is longest between the evening until morning [22, 41].

Enteral nutrition (EN) in the form of gastric or jejunal small-bore feeding tubes is the preferred route of nutrition delivery in patients who have poor oral intake due to dysgeusia since it is less expensive, and maintains the functional integrity of the gut by stimulating blood flow, inducing the release of endogenous chemicals (cholecystokinin, gastrin, bombesin, and bile salts) and the maintenance of secretory IgA-producing B cells and plasma cells [28]. Table 2 summarizes the different society guidelines for enteral nutrition in patients with CLD.

Furthermore, feeding is safer with EN when compared to parenteral nutrition (PN), as PN carries the risk of infection, electrolyte imbalance, and fluid overload [28]. The indications for PN use in the critically ill and in those with CLD have recently been reviewed and published by multiple societies; in general, it should be used when oral and enteral nutrition is not feasible [1•, 7, 8, 28].

Macronutrient supplementation

Specific macronutrient recommendations differ based on the etiology of liver disease. Overall, carbohydrate intake in the form of complex carbohydrates should make up 50–60% of non-protein energy requirements. Care must be taken not to induce hyperglycemia since a significant proportion of patients with CLD have diabetes mellitus (DM), particularly in the setting of non-alcoholic fatty liver disease (NAFLD) [16].

Patients with advanced cirrhosis have low levels of essential fatty acids. Lipid administration should be limited to 1 g/kg/day using dry weight [16]. In patients requiring PN, lipids in the form of fat emulsions should make up 40–50% of non-protein energy requirements. In cases of fat malabsorption, medium chain triglycerides may be used, as they do not require bile salts for absorption.

Protein restriction was long-hailed as an effective strategy to prevent HE. A randomized controlled study showed that restriction of dietary protein did not have any beneficial effect for cirrhotic patients [42]. Similarly in a study involving 136 patients with alcoholic hepatitis, low protein consumption was associated with worsening HE while patients with high-protein consumption were noted to have improved mental status [43]. Restriction of protein intake is no longer recommended in patients with liver disease given the predilection for muscle catabolism in cirrhosis. The European Society for Parenteral and Enteral Nutrition and EASL recommends caloric intake of 30–35 kcal/kg of dry body weight/day and protein intake of 1.2–1.5 g/kg of dry body weight/day in patients with cirrhosis [1•, 7]. In patients with alcoholic cirrhosis and HE grades I–III, 70 g protein per day is recommended for improvement in mental state [43]. Moreover, leucine, along with isoleucine and valine, are branched chain amino acids (BCAAs) that stimulate the mammalian target of rapamycin (mTOR) signaling pathway in muscle, a pathway critical for protein synthesis [13, 22]. Serum levels of BCAAs are decreased in patients with cirrhosis; thus, nutritional supplements in the form of BCAA may have a role in disease prognosis and reducing the risk of recurrence of HE and improve quality of life [7, 13, 22, 36].

Micronutrients and other supplementation

Micronutrient deficiencies are exceedingly common in those with CLD due to impaired absorption and decreased intake. Antioxidant micronutrient deficiencies (selenium, vitamin E, vitamin C) are secondary to oxidative stress. Thiamine, folate, zinc, selenium, and lipid soluble vitamin supplementation may provide benefit in reversing side effects of their deficiencies. In particular, zinc and vitamin A supplementation can help dysgeusia [7]. The finding of macrocytic anemia should prompt investigation into folate or B12 deficiency.

Changes in bone mineral density are prevalent in patients with CLD, particularly those treated with long-term glucocorticosteroids or those with cholestatic disease, and represent a major cause of morbidity. Changes in parathyroid hormone and calcitonin levels along with increased circulating levels of bilirubin and cytokines may contribute to this along with poor diet and decreased physical activity. Thus, patients at risk should be encouraged to consume foods rich in calcium and vitamin D, and those with osteopenia or osteoporosis require appropriate treatment with calcium, vitamin D supplementation, and/or bisphosphonates.

Interestingly, coffee has beneficial effects in patients with liver disease. A dose-dependent effect of coffee has been shown to decrease risk of HCC and CLD mortality in the Multi-Ethnic Study of Atherosclerosis cohort [44]. Studies of patients with NAFLD or viral hepatitis note those who consume coffee have decreased fibrosis as measured by histology and elastography compared to non-coffee drinkers. While the mechanism remains unclear, the prevailing thought is that coffee has beneficial antioxidant and anti-inflammatory effects on those with CLD [45, 46]. However, care must be taken in those with advanced liver disease or portal hypertension, particularly in those who are at risk for hepatic encephalopathy. While coffee is protective early in the course of liver disease, it may have counterproductive results in those with progressive disease and further alter their sleep/wake cycle.

Pharmacological therapy

Hormone replacement therapy with testosterone has been proposed to increase muscle mass in cirrhosis. Testosterone therapy may be used in men with cirrhosis to increase muscle mass, bone mass, and hemoglobin, as well as, reduce fat mass and glycosylated hemoglobin (HbA1c) [47]. Additionally, the use of aromatase inhibitors can increase testosterone levels [1•]. Caution must be used as it has been shown that HCC contains higher concentrations of androgen receptors which may take up exogenous testosterones [48]. Growth hormone signaling in the liver is decreased in patients with cirrhosis and those who have NAFLD and associated with decreased hepatic insulin sensitivity and insulin resistance [49].

β-Hydroxy β-methylbutyrate (HMB) is a bioactive metabolite formed from the breakdown of leucine, which has been shown to improve muscle mass and function [50, 51]. Furthermore, emerging evidence suggests myostatin antagonists can help prevent sarcopenia [13].

Physical activity

Physical exercise is beneficial in patients with CLD and cirrhosis in building muscle mass, strength, and functional capacity as well as increasing bone mineral density and insulin sensitivity. Emphasis on both aerobic activity, resistance exercise, and balance training remains important [29•, 36]. An exercise program should be divided into warm-up (5–10 min), an exercise phase with aerobic and resistance components (20–60 min) followed by stretching exercises (5–10 min) [36]. However, activities need tailoring to an individual's baseline function and consideration of portal hypertensive complications. While some concern exists regarding resistance exercise in those with varices [21, 29•], we believe significant varices should be eradicated prior to pursuing

regular resistance training. Passive mechanical tension causes myofibrils to stretch resulting in decreased myostatin; thus, gradual increase in resistance is important as tolerated, to stimulate muscle growth. As such, non-exercise activity thermogenesis (NEAT) deserves emphasis. NEAT including climbing stairs and parking further away from intended destination are pragmatic activities requiring few resources and are feasible for integration into one's daily routine [29•, 36•]. Innovative home-based physical therapy sessions may be beneficial to many of these patients. Furthermore, supplements containing HMB can be complementary to resistance training for muscle building [50, 51].

Management of specific liver diseases and complications

The following discusses management of specific liver diseases including strategies to optimize nutrition prior to development of advanced fibrosis.

Alcoholic liver disease

The cornerstone of management in those with ALD remains abstinence, as alcohol itself is a hepatotoxin and promotes anabolic resistance. Nutritional support remains paramount in patients with ALD since there is sufficient macro and micronutrient deficiencies due to their past habits. This is particularly true in patients presenting with alcoholic hepatitis. Specifically, their previous diet typically lacks sufficient protein, fats, vitamin A, vitamin B_{12}, thiamine, folate, vitamin D, and zinc [21]. Ingestion of alcohol can also promote bone loss and attention to bone density should be considered [52].

NAFLD

Comorbidities associated with NAFLD include obesity, DM, dyslipidemia, and metabolic syndrome; therefore, lifestyle optimization of these risk factors via weight loss and low-carb diet remains the mainstay of available treatment [53]. For highly motivated pre-cirrhotic patients, we recommend strategies such as incorporating approaches from the Dietary Approaches to Stop Hypertension nutrition plan, Mediterranean diet, intermittent fasting to help with weight loss in those without advanced fibrosis, or any healthy, structured nutrition plan resulting in weight loss. Interestingly, manipulating nutrient sequencing during meals (consuming carbohydrates last) can improve glucose control in diabetes [54, 55]. Additionally, vitamin E can be considered in a select group of patients with biopsy-proven non-alcoholic steatohepatitis (NASH), the inflammatory component of NAFLD, in the absence of DM or cirrhosis [53, 56].

Patients with cirrhosis secondary to NASH often exhibit sarcopenia, which is often masked by the coexistence of increased fat mass, termed "sarcopenic obesity" and myosteatosis, fat infiltration into muscle cells [7, 57–59]. Both are associated with higher mortality in patients with cirrhosis [57]. While weight loss in patients with NAFLD is paramount, it should be paired with resistance exercise in patients with sarcopenic obesity to avoid further loss of muscle mass [59]. Irisin, a protein responsible for the "browning" of white adipose tissue, is downregulated in sarcopenia [59], and recombinant irisin may be a treatment option for sarcopenic obesity in the future [60].

In patients who are unable to achieve weight loss through diet, bariatric surgery improves hepatic steatosis and steatohepatitis, but has variable effects on fibrosis [53, 61]. Care must be taken to ensure adequate weight loss without losing muscle mass. Bariatric surgery reduces resting metabolic rate and post-operative energy intake [62], but in the case of malabsorptive bariatric surgery (roux-en-y gastric bypass), it may also result in nutritional deficiencies. Hence, a thorough nutritional survey is required for individuals with CLD who have undergone bariatric surgery. Patients are encouraged to eat nutrient-dense foods with vitamin and mineral supplementation to compensate for changes in absorption after bariatric surgery.

Other liver diseases

Studies have shown that the outcome of chronic hepatitis B and hepatitis C patients can be affected comorbidities, such as dyslipidemia, DM, and hypertension, which may influence mortality [63, 64]. In the setting of chronic cholestasis, the paucity of bile acids can lead to fat and fat-soluble vitamin malabsorption, which can lead to hepatic osteodystrophy [18]. In patients requiring liver resection, nutritional therapy is essential to reduce postoperative morbidity and mortality.

Peri-liver transplant

In liver transplant candidates and recipients, malnutrition is associated with increased duration of hospitalization, lengthy intensive care unit stays, and higher rate of infections [65]. Moreover, in liver transplant recipients, sarcopenia may not reverse quickly, mandating specific interventions [13]. Glucocorticosteroids, commonly used for induction therapy, increase hepatic gluconeogenesis and reduce endogenous insulin secretion. In addition, other immunosuppressive medications often adversely alter lipid profile and blood pressure [66]. Resultant deleterious consequences of hyperglycemia as well as components of the metabolic syndrome affect not only graft survival but also mortality in transplant recipients [67]. The metabolic consequences of immunosuppression warrant strategies to optimize cardiometabolic disease.

Portal hypertensive complications

Initial treatment of ascites begins with a low-sodium diet and diuretics. Some require paracentesis, but a worrisome complication of large-volume paracentesis (LVP) is paracentesis-induced circulatory dysfunction, a disorder of systemic arterial vasodilatation, resulting in further sodium and water retention; this is associated with poor outcomes [68]. We recommend that patients with ascites be managed with a low-sodium diet, diuretics, and periodic parenteral albumin infusions to maintain a serum albumin > 3.5 mg/dL rather than scheduled paracentesis. If patients require LVPs, then they should be arranged on-demand basis as opposed to standing orders. Patients with treatment-refractory ascites may be offered transjugular intrahepatic portosystemic shunt. A study was conducted in which patients with cirrhosis and refractory ascites were treated with long-term human albumin 20 g twice per week. It was found that the incidence of 24-month mortality was significantly lower in patients treated with albumin than those treated with standard of care (41.6% vs 65.5%; $P = 0.032$) and also had lower incidence of HE, ascites, and SBP [69].

Hyperammonemia, which often manifests as HE, contributes to sarcopenia [13]. In an animal model, 4 weeks of ammonia-lowering therapy with L-ornithine L-aspartate and rifaximin resulted in significant increase in lean body mass, improved grip strength, higher skeletal muscle mass and diameter, and an increase in type 2 muscle fibers. The use of ammonia-lowering drugs to concomitantly treat HE and reverse sarcopenia of cirrhosis maybe a reliable treatment regimen in the future, but further investigation in humans is warranted before broad use [70].

Conclusion

CLD, particularly cirrhosis, is a prolonged illness complicated by malnutrition, sarcopenia, poor functional status, and frailty. Each of these conditions can independently affect a patient's disease prognosis and mortality. Appropriate assessment of nutritional, physical, and functional capacity is warranted in all patients. The key is early recognition and intervention since the systemic implications of malnutrition significantly influence the prognosis in CLD patients. A multidisciplinary team including registered dieticians should be involved early in the course to minimize nutrition-related complications. In those with cirrhosis, interventions should be implemented prior to decompensation to reap maximal benefit prior to the development of anabolic resistance or untoward complications from nutritional therapy from occurring. Above all, clinical judgment remains necessary to modify a nutritional and physical activity prescription with regard for the etiology of disease, an individual's baseline function and nutritional requirements, as well as individual preferences.

Compliance with Ethical Standards

Conflict of Interest
None.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
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