Nutritional Evaluation and Treatment of the Cirrhotic Patient

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KEYWORDS

• Malnutrition • Cirrhosis • Sarcopenia • Nutritional support • Late-evening snack

KEY POINTS

- Sarcopenia is one of the most common complications of cirrhosis, leading to functional deterioration and frailty.
- Sarcopenia also may occur in obese patients, but, due to the coexistence of obesity, it might be overlooked.
- Sarcopenia and frailty predict lower survival in patients with cirrhosis and patients undergoing liver transplantation, independent of the Model for End-Stage Liver Disease score.
- Dietary and moderate exercise interventions in patients with cirrhosis are consistently beneficial and safe, but large long-term studies are needed.
- Lifestyle intervention with a goal of moderate weight reduction can be offered to compensate obese cirrhotic patients, with diet consisting of reduced caloric intake, achieved by reduction of carbohydrate and fat intake, while maintaining high protein intake.

NUTRITIONAL STATUS OF THE CIRRHOTIC PATIENT

Malnutrition in liver cirrhosis is common, occurring in 20% of patients with compensated cirrhosis and more than 50% of patients with decompensated liver disease.[1] Among cirrhotic patients awaiting liver transplantation (LT), there is a high prevalence of malnutrition and sarcopenia, affecting more than 50% to 60% of patients,[2–4] associated with higher rates of waiting list morbidity and mortality.[5] The preoperative nutritional status is predictive of a longer post-LT intensive care unit and hospital stay, need for mechanical ventilation, and higher risk of infections. Sarcopenia also is suggested to have an impact on post-LT mortality, emphasizing the importance of

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considering the nutritional status while planning patients' perioperative management and placement.[6,7]

Sarcopenia, defined by a progressive decline in skeletal muscle mass and function, is a major component of malnutrition and is associated with a higher rate of complications, such as susceptibility to infections, hepatic encephalopathy (HE), and ascites. Furthermore, sarcopenia independently predicts lower survival in patients with cirrhosis and patients undergoing LT.[1] Sarcopenic obesity, in which low skeletal muscle mass is associated with high adipose tissue mass, may be overlooked due to the coexistence of obesity. It occurs mostly in nonalcoholic steatohepatitis (NASH) cirrhosis and is found in a significant number of patients with cirrhosis pre-LT and post-LT.[8–10] Post-transplant obesity and metabolic syndrome are common, and weight gain after transplantation has been considered primarily due to an increase in the adipose tissue, with a concomitant loss in skeletal muscle mass and function.[9,11] Obesity and sarcopenic obesity worsen the prognosis of patients with liver cirrhosis.[10,12,13] Importantly, decreased muscle mass and function are more prevalent among cirrhotic patients with either minimal HE (MHE) or overt HE (OHE) compared with no HE, and protein malnutrition is an independent risk factor for both OHE (odds ratio [OR] 3.4; 95% CI, 1.4–6.9) and MHE (OR 2.15; 95% CI, 1.1–4.1).[14]

SCREENING AND ASSESSMENT OF MALNUTRITION SARCOPENIA AND FRAILTY

Given the worse prognosis associated with malnutrition, all patients with advanced chronic liver disease are advised to undergo a rapid nutritional screen; those identified at risk of malnutrition should complete a more detailed nutritional assessment to confirm its presence and severity,[15] as summarized in European Association for the Study of the Liver (EASL) clinical practice guidelines[1] (**Fig. 1**). Briefly, most screening tools for malnutrition were not validated in cirrhotic patients and are prone to bias in cases of fluid retention. The Royal Free Hospital (RFH)–Nutritional Prioritizing Tool score was designed for liver disease patients and reported to correlate with the severity of disease, clinical complications, and survival.[16] The components of a detailed nutritional assessment include evaluation of muscle mass, muscle contractile function, frailty and an option to utilize global assessment tools.

Sarcopenia is defined as loss of skeletal muscle mass and function. Quantification of muscle can be accomplished by computed tomographic (CT) image analysis. Cross-sectional imaging of abdominal skeletal muscle area at the level of the L3 vertebra provides an accurate assessment of muscle mass and is normalized to stature as skeletal muscle index (cm^2/m^2). Although the use of CT specifically for this purpose is limited by cost and concerns regarding radiation exposure, it still can be utilized in clinical practice because it frequently is performed in cirrhotic patients for other reasons (screening for hepatocellular carcinoma or evaluation of vascular shunts and portal vein thrombosis). Suggested cutoff values to define sarcopenia by CT (<50 cm^2/m^2 for men and <39 cm^2/m^2 for women) are based on clinical outcomes of cirrhotic patients on the LT waiting list.[17]

In a meta-analysis of 19 studies (3803 patients) with CT-assessed skeletal muscle mass, the prevalence of sarcopenia ranged from 22% to 70% across studies. The pooled hazard ratios (HRs) of sarcopenia independent of Model for End-Stage Liver Disease (MELD) score were 1.84 (95% CI, 1.11–3.05) and 1.72 (95% CI, 0.99–3.00) for post-transplantation and waiting list mortality, respectively.[18] Additionally, in 452 patients with cirrhosis (42% with sarcopenia) during a median follow-up period of 21.2 months, after adjusting for MELD and Child–Pugh scores (CPSs), sarcopenia was associated with higher mortality (HR 2.253; 95% CI, 1.442–3.519). The impact

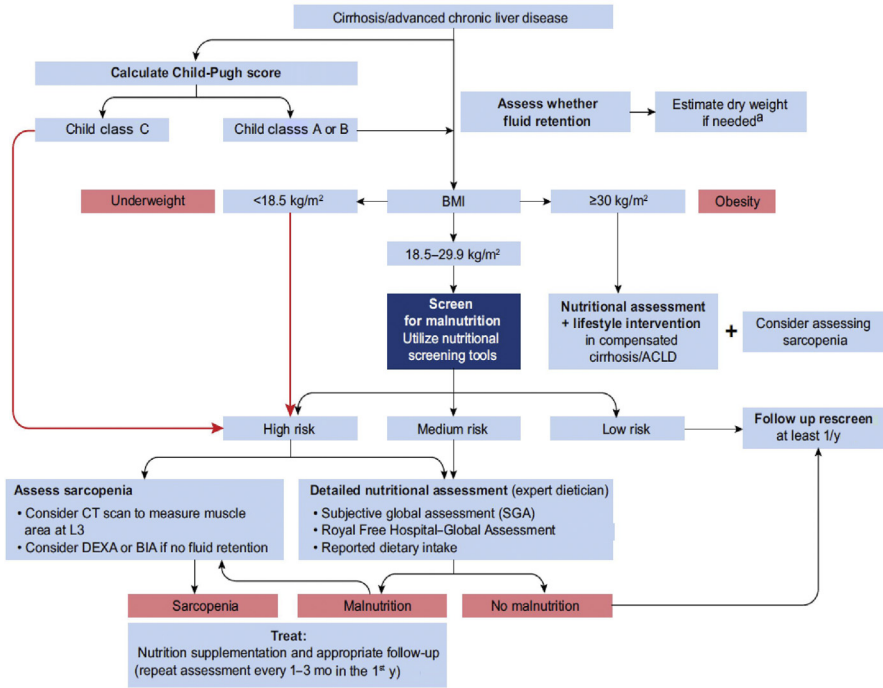

Fig. 1. Nutritional screening and assessment in patients with cirrhosis. [a]In cases of fluid retention, BW should be corrected by evaluating the patient's dry weight by post-paracentesis BW or weight recorded before fluid retention if available or by subtracting a percentage of weight based on severity of ascites (mild, 5%; moderate, 10%; and severe, 15%), with an additional 5% subtracted if bilateral pedal edema is present. ACLD, advanced chronic liver disease; BIA, bioelectrical impedance analysis; BW, body weight; DEXA, dual-energy X-ray absorptiometry. (*From* European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol.* 2019;70(1):172-193.)

of sarcopenia was more pronounced in patients with MELD score less than 15 or CPS class A or class B.[19]

Body mass assessment by simple bedside anthropometric methods of midarm muscle circumference is low cost and not affected by fluid retention. Whole-body dual-energy x-ray absorptiometry (DEXA) allows the measurement of bone mineral density, fat mass, and fat-free mass, but cost and availability limit its use. Tetrapolar bioelectrical impedance analysis (BIA) is a low-cost, portable modality; however, it is inaccurate in the presence of fluid retention.[1]

A reduction in muscle function has been used as an indirect measure of sarcopenia. The new European consensus on definition and diagnosis of sarcopenia states that sarcopenia is considered a muscle disease, with low muscle strength overtaking the role of low muscle mass as the principal determinant. This change is expected to facilitate prompt identification of sarcopenia in practice because in contrast to muscle mass and muscle quality (eg, myosteatosis), which are technically difficult to measure, muscle strength easily can be measured using simple tools.[20] Handgrip strength is a simple, inexpensive, and reliable method to detect reduction of muscle function. In cirrhotic patients, it can be used to detect malnutrition and predict major complications and mortality.[21,22]

Frailty, defined as a patient's vulnerability to stress and decreased physiologic reserve, also can be used for assessment of cirrhotic patients.[23,24] The Short Physical

Performance Battery, which consists of timed repeated chair stands, balance testing, and a timed 4 meters walk, is a predictor of LT waiting list mortality.[22]

The Liver Frailty Index, derived specifically to capture the construct of physical frailty in LT candidates, consists of handgrip strength, chair stands, and balance testing. In a large cohort, it was found to strongly predict waiting list mortality more accurately than the MELD sodium score.[25] The American Society of Transplantation advocates for longitudinal assessments of the Liver Frailty Index in LT candidates, aiming at standardizing incorporation of frailty into transplant decision making.[23]

The RFH–Global Assessment,[26] based on dry weight–based body mass index (BMI), midarm muscle circumference, and dietary intake, is reproducible and correlates with other measures of body composition in determining nutritional status in patients with cirrhosis. The RFH–Global Assessment stratifies patients as adequately nourished, moderately malnourished (or suspected to be), and severely malnourished. It predicts pretransplant survival and post-transplant complications, but its wide application might be limited by time requirements and the need for trained personnel for consistent results.

NUTRITIONAL AND LIFESTYLE SUPPORT OF THE CIRRHOTIC PATIENT

The first step of a productive nutritional treatment is a detailed dietary interview, identifying what and how much a patient is willing to eat and capable of eating as well as determining whether specific nutrient deficiencies need to be addressed. A detailed dietary intake assessment should include food, fluids, supplements, and number of meals and their timing throughout the day (eg, intervals between meals and if a patient follows recommendations regarding eating breakfast and late-evening snacks [LES]). It also should include barriers to eating: nausea, vomiting, specific food aversion, change in taste, low-sodium diet, early satiety, abdominal pain or discomfort, and diarrhea or constipation.[27] Evaluation of the dietary intake is time consuming, requires skilled personnel, and relies on patient recall and cooperation. At a minimum, patients should be asked about changes in their relative food intake, including quantity (eg, reduced by half) and over what period of time.

Cirrhosis is a state of accelerated starvation in which protein synthesis is decreased and gluconeogenesis from amino acids is increased. The accelerated starvation is aggravated by reduced dietary intake due to a variety of factors, including dysgeusia, anorexia of chronic disease, dislike for salt-restricted food, portal hypertension that contributes to impaired gut motility, decreased nutrient absorption, and protein-losing enteropathy.[28] Additional factors that result in decreased dietary intake include inappropriate dietary protein restriction, hospitalization with periods of fasting for diagnostic and therapeutic procedures, encephalopathy, and gastrointestinal bleeding.[1]

A meta-analysis of 13 randomized controlled trials (RCTs), including both enteral and parenteral nutritional interventions among patients with cirrhosis and alcoholic hepatitis, suggested a beneficial effect on morbidity and mortality. The data were not sufficiently strong, however, to conclude any treatment recommendations.[29] Because nutritional intervention improves survival and quality of life,[30] dietary management should be implemented for every malnourished patient, with regular follow-up to evaluate response, preferably by a dedicated nutritional team.[1,31] The EASL clinical practice guidelines on nutrition in chronic liver disease provide a comprehensive review of the recommended nutritional intake.[1] The approach of the majority of nutritional interventions in cirrhosis is to supply at least 35 kcal/kg/body weight (BW)/d, with a daily recommended protein intake of 1.2 g/kg/BW/d to 1.5 g/

kg/BW/d to prevent muscle mass loss and reverse it in those who are sarcopenic. Similar recommendations also were provided by the European Society for Clinical Nutrition and Metabolism (ESPEN) 2019 guidelines[2] and by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) 2013 consensus[32] (**Table 1**).

Obesity is an independent risk factor for clinical decompensation in cirrhotic patients.[12] In the obese patient with compensated cirrhosis, a reduction in BW through lifestyle interventions, including nutritional therapy and supervised moderate-intensity physical exercise, may prevent clinical decompensation and improve portal pressure.[12,33]

All recent guidelines provide specific recommendations for the obese cirrhotic patients, indicating that moderate caloric restriction to promote weight loss should be encouraged in obese patients with compensated cirrhosis (see **Table 1**). Nevertheless, over-restriction can result in endogenous muscle breakdown. In the ISHEN 2013 consensus, Amodio and colleagues[32] recommend careful monitoring alongside increased physical activity and caloric intake of 25 kcal/kg/d to 35 kcal/kg/d in obese patients (30–40 kg/m^2) and not less than 20 kcal/kg/d to 25 kcal/kg/d in morbidly obese patients (>40 kg/m^2).

The importance of substantial daily protein intake for sustaining adequate muscle mass has become clear, and tolerance of proteins is higher than previously believed.[32,34] Cordoba and colleagues[34] showed that administration of a low-protein diet (0.5 g/kg/d) worsened HE and exacerbated protein breakdown compared with a daily protein intake of 1.2 g/kg/d. Currently, the recommended daily protein intake is 1.2 g/kg/d to 1.5 g/kg/d.[1,2,32] For obese cirrhotic patients, the moderately hypocaloric diet must include adequate amounts of protein (1.2–1.5 g/kg/d) in order to achieve weight loss without muscle or lean mass depletion.[32] The EASL guidelines suggest a greater intake of protein of greater than 1.5 g/kg ideal BW (IBW) for obese patients undergoing caloric restriction for weight reduction (meaning a caloric reduction mostly from fat and carbohydrates)[1] (see **Table 1**).

In a small fraction of cirrhotic patients, there may be a variable tolerance to different dietary proteins according to their source. Some uncontrolled studies showed better tolerance to vegetable protein over meat protein and to dairy protein over mixed sources protein.[35–38] In an RCT among 120 patients with MHE treated with a 6-month, high-protein diet based on vegetable and dairy protein (1.0–1.5 g/kg ideal BW/d) versus nutrition education, a higher proportion of patients in the nutritional therapy group had reversal of MHE (71.1% vs 22.8%, respectively), and a lower proportion developed OHE (10% vs 21.7%, respectively). In addition, the nutritional therapy group had greater improvement in skeletal muscle mass and handgrip strength, correlating with MHE improvement.[39]

Branched-chain amino acids (BCAAs) supplementation can induce tolerability to meat protein and enable adequate protein intake.[40] Moreover, substituting meat with dairy or vegetable protein along with BCAA supplements is better than reducing total protein intake.[32] In a meta-analysis of 16 RCTs, BCAAs had a beneficial effect on HE compared with placebo or best supportive care (diet, lactulose, or neomycin); however, no conclusions could be drawn regarding its nutritional effects.[41]

Physical activity and exercise are anabolic stimuli that can improve muscle mass and function. The pathogenesis of sarcopenia and frailty in cirrhotic patients includes a low level of physical activity.[23] Despite the lack of robust evidence, consistent benefits of exercise in these patients include reversal of sarcopenia and improvements in aerobic capacity, muscle mass and strength, health-related quality of life, and hepatic

Table 1
Summary of protein and energy, sodium, and dietary pattern recommendations for patients with cirrhosis, as indicated by different associations

Society/ association	ISHEN, 2013,[32] and AASLD and EASL, 2014[73] for hepatic encephalopathy; and AASLD for ascites, 2012[69]			EASL, 2019[1]		ESPEN, 2019[2]	
BMI status[a]	Normal/overweight BMI (20–30 kg/m^2)	Obese (30–40 kg/m^2)	Morbid Obese (>40 kg/m^2)	Mixed BMIs	Obese (BMI > 30 kg/m^2)	Mixed BMIs	Obese (BMI > 30 kg/m^2)
Daily energy	35–40 kcal/kg IBW	25–35 kcal/kg IBW	20–25 kcal/kg IBW	35 kcal/kg ABW (in nonobese individuals)	>5%–10% WR, moderately hypocaloric diet (−500–800 kcal/d)	30–35 kcal/kg only for DC Regular energy requirements in CC	WR No need for increased energy intake
Daily protein	1.2–1.5 g/kg IBW	1.2–1.5 g/ kg IBW	1.2–1.5 g/ kg IBW	1.2–1.5 g/ kg ABW	>1.5 g/kg IBW	1.2 (for nonmalnourished patients with CC) −1.5 (to malnourished and/or sarcopenic cirrhotic patients)	—
Meal patterns	Small frequent meals throughout the waking hours			Split food intake into 3 main meals and 3 snacks		Three to 5 meals a day and LES	
LES	50 g of complex carbohydrate			No specific composition		No specific composition	
Dietary protein source in cases of HE	High protein intake per patient preference. Substitution of milk-based or vegetable protein is preferable to reduction of total protein intake.			Patients may tolerate animal protein (meat) less well than vegetable protein (beans, peas, etc.) and dairy proteins		In patients who are protein "intolerant," vegetable proteins should be used.	
Sodium restriction in cases of ascites	88 mmol/d, although the evidence is poor and debated. Intakes should not be reduced below 60 mmol/ d because the diet becomes unpalatable.			80 mmol/d = 2 g of sodium, corresponding to 5 g of salt Take care to improve diet palatability.		When prescribing a low sodium diet, the increased risk of even lower food consumption should be balanced against its moderate advantage.	

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ABW, actual BW; BW, body weight; CC, compensated cirrhosis; DC, decompensated cirrhosis; EASL, European Association for the Study of the Liver; ESPEN, European Society for Clinical Nutrition and Metabolism; HE, hepatic encephalopathy; IBW, ideal BW; ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; LC, liver cirrhosis; LES, late-evening snack; WR, weight reduction.

[a] In cases of fluid retention, BW should be corrected by evaluating the patient's dry weight.

venous pressure gradient.[33,42–44] Exercise must be tailored to a patient's ability, beginning with moderate intensity and maintained for the long term.[1] Two recent comprehensive reviews and meta-analyses on exercise in cirrhotics generally agree on the importance, benefit, safety, and applicability of moderate-intensity exercise and provide practical advice.[31,45,46] In a recent RCT, patients with cirrhosis (CPS class A or class B; ages 62 y ± 7 y) who performed 1-hour sessions of supervised resistance training (1 h, 3 times/wk, for 12 weeks) compared with no change in daily activity level had increased muscle strength and mass alongside beneficial effects on general performance measures.[47] Patients with cirrhosis on the transplant waiting list are advised, if possible, to perform 30-minute to 60-minute exercise sessions, combining both aerobic and resistance training, to achieve greater than or equal to 150 min/wk, along with a parallel increase in activities of daily living.[31]

Recommended Eating Pattern and Late-Evening Snack

One of the most important strategies to prevent accelerated starvation and the related proteolysis is to shorten fasting intervals between meals by eating every 4 hours to 6 hours.[1] Because the longest intermeal duration is at night, the efficacy of a LES has been studied extensively. An LES containing complex carbohydrates as well as protein reduces lipid oxidation, improves nitrogen balance, reduces skeletal muscle proteolysis, increases muscle mass, reduces HE, and improves quality of life; however, a reduction in mortality or need for transplantation has not been reported.[48,49] Although an LES containing at least 50 g of complex carbohydrate[32] was suggested by the ISHEN 2013 consensus article, a variety of night meal compositions appear to be effective as long as they include a reasonable amount of complex carbohydrates and protein (in most studies, the LES contained approximately 200–250 kcal and approximately 13.5 g protein) (**Table 2**), thus suggesting that the meal compositions can be decided according to patient preferences.

Micronutrients Requirements in the Cirrhotic Patient

Specific evidence regarding the beneficial effect of micronutrients and vitamin supplementation in cirrhotic patients is lacking. EASL guidelines suggest that clinically suspected or confirmed deficiency should be treated based on accepted general recommendations and common practice.[1] Because vitamin status is not assessed easily and multivitamin supplements are cheap and largely free of side effects, a course of oral multivitamin supplementation could be justified in decompensated patients.[1]

As for specific micronutrients, the most relevant ones with up-to-date literature are described. Vitamin D insufficiency, defined as less than 30 ng/mL, can be found in most patients.[50] Vitamin D deficiency (VDD), defined as less than 20 ng/mL, is the most common deficiency, affecting 70% to 90% of patients with liver disease.[50–52] Moreover, VDD severity corresponds with the severity of liver disease,[53–55] whether expressed as CPS class A, B or C, MELD score, or liver stiffness evaluated by transient elastography.[54,56,57] In a prospective study, including more than 300 cirrhotic patients, severe VDD at baseline was an independent risk factor for hepatic decompensation during 3 months to 12 months of follow-up (OR 3.25; 95% CI, 1.30–8.2).[58] The patients with severe VDD also had elevated inflammatory markers (eg, C-reactive protein and interleukin-6).[58] More so, in a cross-sectional study, vitamin D levels in hospitalized cirrhotic patients inversely correlated with the presence of infection, regardless of CPS class A,B or C or MELD score (OR 0.93; 95% CI, 0.894–0.959).[59] VDD also is a general predictor of liver disease–related mortality. In a prospective study spanning 22 years, higher serum 25(OH) vitamin D levels were associated with lower rates of chronic liver disease–related mortality, regardless of the

Table 2
Description of studies testing a variety of late-evening snacks in cirrhotic patients, indicating efficacy in improved survival, liver metabolism, muscle volume and strength, and quality of life; reduction of protein catabolism; and abnormal fuel metabolism

				Late-evening Snack Nutritional Composition			
First Author, Year	Study Design	Study Population	Intervention	Energy (kcal/meal)	Protein (g/meal)	Carbohydrate (g/meal)	Fat (g/meal)
Hanai et al,[74] 2020	Retrospective cohort study	523 cirrhotic patients (CPS classes A–C)	Daily use of a BCAA-enriched supplement (Aminoleban) before bedtime or as LES Follow-up of 2.4 y	213	13.5 protein, including 6.1 g BCAA	31.5	3.7
Maki et al,[75] 2019	Randomized crossover trial	10 cirrhotic patients	BCAA-enriched supplement (Aminoleban) as LES vs BCAA-enriched supplement (Aminoleban) during daytime vs no supplement (control) for 1 mo	210	13.5 protein, including 6.1 g BCAA	31.05	3.5
Hiraoka et al,[76] 2017	Noncontrolled trial	33 cirrhotic patients (CPS classes A–B)	BCAA-enriched supplement (Aminoleban) (average period 2.7 mo $\pm$ 0.7 mo) and walking exercise (additional 2000 steps/d)	210	13.5	31.5	3.5
Hidaka et al,[77] 2013	RCT	40 cirrhotic patients (CPS classes A–B)	BCAA granules (Livact) supplement after breakfast (4 g) + as LES (8 g) vs BCAA granules (Livact) supplement after each meal (4 g) for 3 mo	NM	L-isoleucine 952 mg, L-leucine 1904 mg, L-valine 1144 mg per 4 g of BCAA granules	NM	NM

Koreeda et al,[78] 2011	Noncontrolled trial	17 cirrhotic patients (CPS classes A–C)	Low-protein diet with 2 BCAA-enriched supplement (Aminoleban): 1 during daytime and 1 as LES for 6 mo	210	13.5 (BCAA 6 g)	NM	3.5
Yamanaka-Okumura et al,[79] 2010	RCT	39 cirrhotic patients (CPS class A)	High-CHO LES (rice ball, rice cake, sweet potato, cup of noodles, roll, crackers, banana, or 1 slice of bread with strawberry jam) vs controls without LES for 12 mo	149	3.6	NM	NM
Plank et al,[48] 2008	RCT	103 cirrhotic patients (CPS classes A–C)	2 cans of Ensure Plus or diabetic formula as LES vs during the day for 12 mo	710 (or 500 in the diabetic formula)	26 (or 30 g in the diabetic formula)	94 (or 45 in the diabetic formula)	25 (or 22.2 in the diabetic formula)
Nakaya et al,[80] 2007	RCT	48 cirrhotic patients (CPS classes A–C)	BCAA-enriched supplement as LES (Aminoleban) vs ordinary food as LES (rice ball, bread, or cookies) for 3 mo	210	13.5 vs 9 in the ordinary food	NM	3.5 vs 5 in the ordinary food
Yamanaka-Okumura et al,[81] 2006	Randomized crossover trial	21 hospitalized cirrhotic patients (CPS class A)	3 meals/d + LES (rice ball) vs 3 regular meals/d for 1 wk	200	4.3	44	0.9

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Table 2
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First Author, Year	Study Design	Study Population	Intervention	Late-evening Snack Nutritional Composition			
				Energy (kcal/meal)	Protein (g/meal)	Carbohydrate (g/meal)	Fat (g/meal)
Sakaida et al,[82] 2004	Noncontrolled trial	11 hospitalized cirrhotic patients	2 packs of BCAA-enriched supplement (Aminoleban): 1 as LES and the other during daytime for 1 wk	210	13.7	NM	3.5
Sako,[83] 2003	Noncontrolled trial	8 cirrhotic patients (CPS classes B–C)	BCAA-enriched supplement (Aminoleban) for 3 mo	210	13.7	NM	3.5
Fukushima et al,[84] 2003	Randomized crossover trial	12 cirrhotic patients (CPS classes A–B)	BCAA granules after breakfast (4 g) + as LES (8 g) vs BCAA granules after each meal (4 g) vs no supplement for 1 wk	320	8 g amino acids	NM	NM
Nakaya et al,[85] 2002	Noncontrolled trial	30 cirrhotic patients (CPS classes A–C)	2 BCAA-enriched supplement (Aminoleban): 1 during daytime and 2 as LES for 1 wk	210	13.5	31.1	3.5
Yamauchi et al,[86] 2001	Randomized crossover trial	14 hospitalized cirrhotic patients (CPS classes A–C)	BCAA-enriched supplements (Aminoleban) as LES (22:30) days vs after dinner (19:00) for 14 d	210	13.7	NM	3.5

Miwa et al,[87] 2000	Noncontrolled trial	12 hospitalized cirrhotic patients (CPS classes A–C)	250 mL liquid nutrient (Ensure Liquid) at bedtime for 1 d	250	14% of meal kcal	54.5% of meal kcal	31.5% of meal kcal
Chang et al,[88] 1997	Noncontrolled trial	16 hospitalized cirrhotic patients (CPS classes A–C)	Two slices of bread with strawberry jam as LES (intervention duration is NM)	Approximately 200	NM	50	NM
Verboeket-van de Venne et al,[89] 1995	Randomized crossover trial	8 cirrhotic patients (CPS classes A–B)	4 meals at 07:30, 12:00, 18:00, and 22:30 (considered as LES) vs 2 meals at 12:00 and 18:00 for 2 d	20% of daily kcal	12% of LES kcal	50% of LES kcal	38% of LES kcal
Zillikens et al,[90] 1993	RCT	8 cirrhotic patients	100 g polymeric glucose as LES vs water (control) for 2 d	Approximately 400	NM	100	NM
Swart et al,[91] 1989	Randomized crossover trial	9 cirrhotic patients (CPS class B)	4 or 6 meals/d, including LES vs 3 meals/d for 5 d. The LES was designed to contain approximately 20% of the total daily energy and protein intake.	349 (17% of total kcal)	13.2 g (20% of total daily protein)	NM	NM

Abbreviations: BCAA, branched-chain amino acids; CHO, carbohydrates; CPS, Child-Pugh score; LES, late evening snack; NM, not mentioned; RCT, randomized controled trial.

presence of hepatitis B.[60] A meta-analysis of 1339 patients with cirrhosis found increased risk of mortality in the presence of severe VDD (relative risk 1.79; 95% CI, 1.44–2.22).[61]

Despite this evidence, the efficacy of vitamin D supplementation in cirrhosis has not been demonstrated convincingly. Among advanced decompensated cirrhotic patients (CPS score $\geq$10) randomly assigned to vitamin D treatment compared with standard care for 6 months, survival rates as well as CPS and MELD scores were comparable between the groups.[62] In a Cochrane review of 15 RCTs, including 1034 adult participants, vitamin D supplementation for chronic liver diseases had no beneficial or harmful effects on all-cause mortality (OR 0.69; 95% CI, 0.09–5.40), and the investigators' conclusion was that there is no convincing evidence for a therapeutic benefit in patients with chronic liver disease as a result of vitamin D supplementation.[63] Selected recent studies describing vitamin D in patients with chronic liver disease are summarized in **Table 3**. The ESPEN guidelines[2] conclude that according to the currently available evidence, micronutrients supplementation, including vitamin D, has no proved benefit aside from correction of deficiency state, similar to the general population. The EASL recommends assessment of plasma 25(OH) vitamin D levels in all patients with chronic liver disease, especially in advanced disease, cholestatic liver disease, or fatty liver disease.[1] Oral vitamin D supplementation is recommended in all patients with chronic liver disease who have vitamin D levels below 20 ng/mL until reaching a serum vitamin D level above 30 ng/mL. No specific dosage was recommended.[1]

Vitamin E is a lipid-soluble antioxidant that mainly prevents peroxidation of lipids. The dietary reference intakes for adult men and women is 15 mg/d (35 μmol/d or 22.4 IU/d) of α-tocopherol.[64] In a cross-sectional study of approximately 800 patients, there was an inverse association between reaching the recommended vitamin E intake and presence of nonalcoholic fatty liver disease (NAFLD) on ultrasound and NASH serum marker.[65] In a propensity score–adjusted study of patients with advanced liver fibrosis and cirrhosis, a dose of 800 IU/d for greater than or equal to 2 years was associated with reduced risk for mortality, LT, and hepatic decompensation.[66] In an RCT, 800 IU/d of vitamin E given to NASH patients, without diabetes or cirrhosis, reduced steatosis and lobular inflammation but not fibrosis.[67] According to the ESPEN, vitamin E supplement (800 IU/d) should be prescribed to nondiabetic adults with histologically confirmed NASH,[2] but there is no recommendation with regard to patients with cirrhosis.

The evidence regarding sodium restriction in cirrhotic patients is limited and conflicting. For example, in an RCT of cirrhotic patients with ascites, 98 patients were on a sodium-unrestricted diet and 102 patients on a sodium-restricted diet for 10 days, resulting in low blood sodium and renal impairment only in the restricted group. Furthermore, the time for ascites resolution was significantly shorter in the unrestricted group compared to the sodium-restricted group (30.24 d $\pm$ 3.12 d vs 47.19 d $\pm$ 9.22 d, respectively).[68] Nevertheless, the EASL recommends a reduction in dietary sodium intake in patients with ascites: 80 mmol/d of sodium, which corresponds to 2 g/d of sodium and a total of 5 g/d of salt, and not below 60 mmol/d, because this may render the diet unpalatable, compromising energy and protein intake.[1] The American Association for the Study of Liver Diseases (AASLD) recommendation regarding daily salt intake is similar.[69] The ESPEN does not specify the recommended intake but rather states that a moderate dietary sodium intake (60 mmol/d) usually is recommended[2] (see **Table 1**). In reality, following the recommendations is difficult and adherence is poor. In a prospective cohort study among 120 outpatients with cirrhosis and ascites, approximately 70% did not follow a moderately low-salt diet in practice, whereas 65% of them thought that they were following it.[70] The adherent patients had a 20% reduction in their mean daily calorie intake compared with nonadherent patients,

Table 3
Selected recent published studies describing vitamin D serum levels in patients with chronic liver disease

Authors, Year	Study Design	Study Population	Results Summary
Ramadan et al,[59] 2019	Cross-sectional	87 hospitalized cirrhotic patients (45 with infection/42 without infection)	• 71.4% with sufficient vitamin D levels in the group without infection and 11.1% in the group with infection • VDD was an independent predictor of infection in cirrhotic patients regardless of the CPS or MELD
Khan et al,[56] 2019	Case-control study	75 cirrhotic patients/75 controls	• 18.7% of patients and 45.3% of controls with sufficient vitamin D levels • Cirrhosis, CPS and MELD score associated with a low level of vitamin D adjusted for age, gender, BMI, residence, and education level
Buonomo et al,[92] 2019	Prospective cohort	345 cirrhotic patients (23/345 with active HCC)	• In cirrhotic patients severe VDD associated with poor survival irrespective of the presence of HCC
Kubesch et al,[58] 2018	Prospective cohort	338 patients with advanced liver fibrosis or cirrhosis	• 39% with sufficient vitamin D levels • Severe VDD an independent risk factor for hepatic decompensation • Inflammatory markers higher among patients with severe VDD
Jamil et al,[57] 2018	Prospective cohort	125 cirrhotic patients	• 12.8% with sufficient vitamin D levels • Age, female sex, MELD and CPS predictors of low vitamin D levels
Putz-Bankuti et al,[54] 2012	Prospective cohort	75 cirrhotic patients	• 71% of patients with vitamin D levels <20 ng/mL • Vitamin D levels inversely correlated with MELD score and CPS
Skaaby et al,[55] 2014	Prospective cohort	2649 subjects with a median follow-up of 16.5 y	• Vitamin D levels inversely associated with incident liver disease

Abbreviation: BMI, body mass index; CPS, Child -Pugh score; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; VDD, Vitamin D deficiency.

without any difference in hyponatremia occurrence.[70] Besides nutritional intake, sodium can be found in substantial amounts in intravenous solutions, in particular antibacterial and antifungal treatments commonly used in hospitalized patients with liver cirrhosis and active infection, reaching up to 8 g of sodium per day.[71]

SUMMARY

Sarcopenia is a common complication of cirrhosis, which also may occur in obese patients. Dietary and moderate exercise interventions in patients with cirrhosis are consistently beneficial and safe, but large long-term studies are needed to test potential reversibility of sarcopenia and improved survival. Structured nutritional counseling should be performed in cirrhotic patients with malnutrition and all patients should be encouraged to avoid hypomobility and try exercise. The exercise should be practical, appropriate to their abilities, and always accompanied by nutritional intervention. Lifestyle intervention aiming at moderate weight reduction can be offered to compensated obese cirrhotic patients, with diet consisting of reduced caloric intake, achieved by reduction of carbohydrate and fat intake, while maintaining high protein intake. In practical terms, when addressing the topic of nutrition with patients with cirrhosis, it is advisable to keep it simple and combine nutritional education, motivation, and behavioral skills. Dedicated education around nutrition empowers patients to take control of their health and increases patient engagement.[72]

CLINICS CARE POINTS

- The first step of a productive nutritional treatment is a detailed dietary interview, to identify the type and quantity of foods the patient can eat, and if unintentional weight reduction has occurred.
- A detailed dietary intake assessment should include the timing and number of meals, meal composition (food, fluids, and supplements) and barriers for eating.
- Eating breakfast and late-evening snack is a relatively easy way to improve nutritional status, compliance may improve if the logic behind this recommendation is shared with the patient.
- Malnutrition and sarcopenia should be considered in every cirrhotic patient, including those with obesity.
- Regardless of the patient's BMI or recommended caloric intake (even if restricted to achieve weight reduction), high protein intake should be maintained.

CASE STUDY

A case study of nutritional advice provided for cirrhotic patient

The patient is a 55-year-old man with liver cirrhosis. Previously, he had an episode of HE approximately 1 month ago; he has no ascites and no varices. His anthropometrics are height 175 cm, weight 76 kg, and BMI 25 kg/m^2. He has a good appetite.

Treatment plan: optimal daily energy intake should be no less than the recommended 35 kcal/kg/actual BW/d (for nonobese individuals). Optimal daily protein intake should be no less than the recommended 1.2 g/kg/actual BW/d to 1.5 g/kg/actual BW/d.[1]

$76 \times 1.2 = 91$ g protein

$76 \times 35 = 2660$ kcal

General instructions (partially adopted from EASL guidelines[1])

- Split the food intake into 3 main meals (breakfast, lunch, and dinner) and 3 snacks (midmorning, midafternoon, and late evening). The LES is the most important one, because it covers the long interval between dinner and breakfast.
- If there are recurrent episodes of HE, it may be advised to eat less meat and instead to increase the intake of plant-sourced protein (beans, peas, etc.) and dairy-based proteins. The total protein intake should not be reduced. Any changes to the protein intake always should be discussed with a doctor or dietician.
- Eat a variety of vegetables on a daily basis and try keep a healthy diet in general. This includes preferring unprocessed food that is rich in fiber and low in added sugars and sodium.

Sample menu (this menu in provided as example; specific menu and instructions should be tailored to individual patients, according to their health status and preferences)
Energy: 2553 kcal
Protein: 99 g (1.3 g/kg)
Carbohydrate: 181 g
Fat: 154 g
Saturated fat: 29 g (10% total kcal)
Sodium: approximately 2000 mg

Breakfast
Two slices of whole grain bread, cucumber, and tomato (eat as many vegetables as desired) with 1 spoon of olive oil, 2 spoons of cheese, and 1 egg (18 g protein)

Midmorning snack
1 pear or apple + 5 walnuts
(4 g protein)

Lunch
100 g salmon with olive oil and garlic in the oven
0.5 cup of rice and 0.5 cup of lentils (majadra)
1 cup of cauliflower with 1 zucchini sautéed with olive oil and 1 spoon of sesame seeds
(38 g protein)

Midlunch snack
Smoothie: 1 banana + 0.5 cup of milk + 1 spoon of almond spread or 5 almonds
(6 g protein)

Dinner
2 tortillas with guacamole (0.5 avocado and 1 tomato)
Tofu (100 g) in marinade (1 spoon of sesame oil, 1 teaspoon ginger, and 1 spoon of lemon juice)
Cabbage and carrot salad with and 1 spoon of sesame
(20 g protein)

LES
Muesli: 1 yogurt + 10 strawberries + 1 teaspoon of honey + 1 spoon of natural peanut butter
(13 g protein)
Hot beverages can be consumed, such as coffee or tea, throughout the day, but added sugar should be restricted as much as possible.

DISCLOSURE

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REFERENCES

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol 2019;70(1):172–93.
2. Plauth M, Bernal W, Dasarathy S, et al. ESPEN guideline on clinical nutrition in liver disease. Clin Nutr 2019;38(2):485–521.
3. Lattanzi B, Giusto M, Albanese C, et al. The effect of 12 weeks of β-hydroxy-β-methyl-butyrate supplementation after liver transplantation: a pilot randomized controlled study. Nutrients 2019;11(9):2259.
4. Tsien C, Garber A, Narayanan A, et al. Post-liver transplantation sarcopenia in cirrhosis: a prospective evaluation. J Gastroenterol Hepatol 2014;29(6):1250–7.
5. van Vugt JLA, Alferink LJM, Buettner S, et al. A model including sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant candidates: a competing risk analysis in a national cohort. J Hepatol 2018;68(4):707–14.
6. Montano-Loza AJ, Meza-Junco J, Baracos VE, et al. Severe muscle depletion predicts postoperative length of stay but is not associated with survival after liver transplantation. Liver Transpl 2014;20(6):640–8.
7. Kalafateli M, Mantzoukis K, Choi Yau Y, et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the model for end-stage liver disease score. J Cachexia Sarcopenia Muscle 2017;8(1):113–21.
8. Carias S, Castellanos AL, Vilchez V, et al. Nonalcoholic steatohepatitis is strongly associated with sarcopenic obesity in patients with cirrhosis undergoing liver transplant evaluation. J Gastroenterol Hepatol 2016;31(3):628–33.
9. Choudhary NS, Saigal S, Saraf N, et al. Sarcopenic obesity with metabolic syndrome: a newly recognized entity following living donor liver transplantation. Clin Transplant 2015;29(3):211–5.
10. Montano-Loza AJ, Angulo P, Meza-Junco J, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle 2016;7(2):126–35.
11. Dasarathy S. Posttransplant sarcopenia: an underrecognized early consequence of liver transplantation. Dig Dis Sci 2013;58(11):3103–11.
12. Berzigotti A, Garcia-Tsao G, Bosch J, et al. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. Hepatology 2011;54(2):555–61.
13. Nishikawa H, Nishiguchi S. Sarcopenia and sarcopenic obesity are prognostic factors for overall survival in patients with cirrhosis. Intern Med 2016;55(8):855–6.
14. Merli M, Giusto M, Lucidi C, et al. Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. Metab Brain Dis 2013;28(2):281–4.
15. Tandon P, Raman M, Mourtzakis M, et al. A practical approach to nutritional screening and assessment in cirrhosis. Hepatology 2017;65(3):1044–57.
16. Borhofen SM, Gerner C, Lehmann J, 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(6):1735–43.
17. Carey EJ, Lai JC, Wang CW, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver Transpl 2017;23(5):625–33.
18. van Vugt JL, Levolger S, de Bruin RW, et al. Systematic review and meta-analysis of the impact of computed tomography-assessed skeletal muscle mass on outcome in patients awaiting or undergoing liver transplantation. Am J Transplant 2016;16(8):2277–92.

19. Kang SH, Jeong WK, Baik SK, et al. Impact of sarcopenia on prognostic value of cirrhosis: going beyond the hepatic venous pressure gradient and MELD score. J Cachexia Sarcopenia Muscle 2018;9(5):860–70.
20. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48(4):601.
21. Tandon P, Tangri N, Thomas L, et al. A rapid bedside screen to predict unplanned hospitalization and death in outpatients with cirrhosis: a prospective evaluation of the clinical frailty scale. Am J Gastroenterol 2016;111(12):1759–67.
22. Wang CW, Feng S, Covinsky KE, et al. A comparison of muscle function, mass, and quality in liver transplant candidates: results from the functional assessment in liver transplantation study. Transplantation 2016;100(8):1692–8.
23. Kobashigawa J, Dadhania D, Bhorade S, et al. Report from the American Society of Transplantation on frailty in solid organ transplantation. Am J Transplant 2019; 19(4):984–94.
24. Lai JC, Feng S, Terrault NA, et al. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant 2014;14(8):1870–9.
25. Lai JC, Covinsky KE, Dodge JL, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology 2017;66(2):564–74.
26. Morgan MY, Madden AM, Soulsby CT, et al. Derivation and validation of a new global method for assessing nutritional status in patients with cirrhosis. Hepatology 2006;44(4):823–35.
27. Gabrielson DK, Scaffidi D, Leung E, et al. Use of an abridged scored Patient-Generated Subjective Global Assessment (abPG-SGA) as a nutritional screening tool for cancer patients in an outpatient setting. Nutr Cancer 2013;65(2):234–9.
28. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. J Hepatol 2016;65(6):1232–44.
29. Fialla AD, Israelsen M, Hamberg O, et al. Nutritional therapy in cirrhosis or alcoholic hepatitis: a systematic review and meta-analysis. Liver Int 2015;35(9): 2072–8.
30. Iwasa M, Iwata K, Hara N, et al. Nutrition therapy using a multidisciplinary team improves survival rates in patients with liver cirrhosis. Nutrition 2013;29(11):1418–21.
31. Duarte-Rojo A, Ruiz-Margain A, Montano-Loza AJ, et al. Exercise and physical activity for patients with end-stage liver disease: improving functional status and sarcopenia while on the transplant waiting list. Liver Transpl 2018;24(1): 122–39.
32. Amodio P, Bemeur C, Butterworth R, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. Hepatology 2013;58(1):325–36.
33. Berzigotti A, Albillos A, Villanueva C, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: the SportDiet study. Hepatology 2017;65(4):1293–305.
34. Cordoba J, Lopez-Hellin J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 2004;41(1): 38–43.
35. Bessman AN, Mirick GS. Blood ammonia levels following the ingestion of casein and whole blood. J Clin Invest 1958;37(7):990.
36. Fenton J, Knight E, Humpherson P. Milk-and-cheese diet in portal-systemic encephalopathy. Lancet 1966;287(7430):164–6.
37. Greenberger NJ, Carley J, Schenker S, et al. Effect of vegetable and animal protein diets in chronic hepatic encephalopathy. Dig Dis Sci 1977;22(10):845–55.

38. Gheorghe L, Iacob R, Vadan R, et al. Improvement of hepatic encephalopathy using a modified high-calorie high-protein diet. Rom J Gastroenterol 2005; 14(3):231–8.
39. Maharshi S, Sharma BC, Sachdeva S, et al. Efficacy of nutritional therapy for patients with cirrhosis and minimal hepatic encephalopathy in a randomized trial. Clin Gastroenterol Hepatol 2016;14(3):454–60.e3 [quiz: e433].
40. Dam G, Ott P, Aagaard NK, et al. Branched-chain amino acids and muscle ammonia detoxification in cirrhosis. Metab Brain Dis 2013;28(2):217–20.
41. Gluud LL, Dam G, Les I, et al. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev 2017;5:CD001939.
42. Kruger C, McNeely ML, Bailey RJ, et al. Home exercise training improves exercise capacity in cirrhosis patients: role of exercise adherence. Sci Rep 2018; 8(1):99.
43. Berzigotti A, Saran U, Dufour JF. Physical activity and liver diseases. Hepatology 2016;63(3):1026–40.
44. Zenith L, Meena N, Ramadi A, et al. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. Clin Gastroenterol Hepatol 2014;12(11):1920–6.e2.
45. Tandon P, Ismond KP, Riess K, et al. Exercise in cirrhosis: translating evidence and experience to practice. J Hepatol 2018;69(5):1164–77.
46. Aamann L, Dam G, Rinnov AR, et al. Physical exercise for people with cirrhosis. Cochrane Database Syst Rev 2018;12:CD012678.
47. Aamann L, Dam G, Borre M, et al. Resistance training increases muscle strength and muscle size in patients with liver cirrhosis. Clin Gastroenterol Hepatol 2020; 18(5):1179–87.e6.
48. 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):557–66.
49. Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. J Gastroenterol Hepatol 2012;27(3):430–41.
50. Kitson MT, Roberts SK. D-livering the message: the importance of vitamin D status in chronic liver disease. J Hepatol 2012;57(4):897–909.
51. Hansen KE, Johnson MG. An update on vitamin D for clinicians. Curr Opin Endocrinol Diabetes Obes 2016;23(6):440–4.
52. Stokes CS, Krawczyk M, Reichel C, et al. Vitamin D deficiency is associated with mortality in patients with advanced liver cirrhosis. Eur J Clin Invest 2014;44(2): 176–83.
53. Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. Dig Dis Sci 2010;55(9):2624–8.
54. Putz-Bankuti C, Pilz S, Stojakovic T, et al. Association of 25-hydroxyvitamin D levels with liver dysfunction and mortality in chronic liver disease. Liver Int 2012;32(5):845–51.
55. Skaaby T, Husemoen LL, Borglykke A, et al. Vitamin D status, liver enzymes, and incident liver disease and mortality: a general population study. Endocrine 2014; 47(1):213–20.
56. Khan MA, Dar HA, Baba MA, et al. Impact of Vitamin D status in chronic liver disease. J Clin Exp Hepatol 2019;9(5):574–80.
57. Jamil Z, Arif S, Khan A, et al. Vitamin D deficiency and its relationship with childpugh class in patients with chronic liver disease. J Clin Transl Hepatol 2018;6(2): 135–40.

58. Kubesch A, Quenstedt L, Saleh M, et al. Vitamin D deficiency is associated with hepatic decompensation and inflammation in patients with liver cirrhosis: a prospective cohort study. PLoS One 2018;13(11):e0207162.
59. Ramadan HK, Makhlouf NA, Mahmoud AA, et al. Role of vitamin D deficiency as a risk factor for infections in cirrhotic patients. Clin Res Hepatol Gastroenterol 2019; 43(1):51–7.
60. Wang JB, Abnet CC, Chen W, et al. Association between serum 25(OH) vitamin D, incident liver cancer and chronic liver disease mortality in the Linxian Nutrition Intervention Trials: a nested case-control study. Br J Cancer 2013;109(7): 1997–2004.
61. Yang F, Ren H, Gao Y, et al. The value of severe vitamin D deficiency in predicting the mortality risk of patients with liver cirrhosis: a meta-analysis. Clin Res Hepatol Gastroenterol 2019;43(6):722–9.
62. Jha AK, Jha SK, Kumar A, et al. Effect of replenishment of vitamin D on survival in patients with decompensated liver cirrhosis: a prospective study. World J Gastrointest Pathophysiol 2017;8(3):133–41.
63. Bjelakovic G, Nikolova D, Bjelakovic M, et al. Vitamin D supplementation for chronic liver diseases in adults. Cochrane Database Syst Rev 2017;11: CD011564.
64. Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: The National Academies Press; 2000.
65. Ivancovsky-Wajcman D, Fliss-Isakov N, Salomone F, et al. Dietary vitamin E and C intake is inversely associated with the severity of nonalcoholic fatty liver disease. Dig Liver Dis 2019;51(12):1698–705.
66. Vilar-Gomez E, Vuppalanchi R, Gawrieh S, et al. Vitamin E improves transplant-free survival and hepatic decompensation among patients with nonalcoholic steatohepatitis and advanced fibrosis. Hepatology 2020;71(2):495–509.
67. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362(18):1675–85.
68. Gu XB, Yang XJ, Zhu HY, et al. Effect of a diet with unrestricted sodium on ascites in patients with hepatic cirrhosis. Gut Liver 2012;6(3):355–61.
69. Runyon BA, AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013;57(4):1651–3.
70. Morando F, Rosi S, Gola E, et al. Adherence to a moderate sodium restriction diet in outpatients with cirrhosis and ascites: a real-life cross-sectional study. Liver Int 2015;35(5):1508–15.
71. Maimone S, Mazzeo AT, Squadrito G, et al. Sodium load and intravenous antimicrobials in patients with cirrhosis. Dig Liver Dis 2019;51(10):1490–2.
72. Lai JC, Tandon P. How I approach it: improving nutritional status in patients with cirrhosis. Am J Gastroenterol 2018;113(11):1574–6.
73. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60(2):715–35.
74. Hanai T, Shiraki M, Imai K, et al. Late evening snack with branched-chain amino acids supplementation improves survival in patients with cirrhosis. J Clin Med 2020;9(4):1013.

75. Maki H, Yamanaka-Okumura H, Katayama T, et al. Late evening snacks with branched-chain amino acids improve the Fischer ratio with patients liver cirrhosis at fasting in the next morning. Clin Nutr ESPEN 2019;30:138–44.
76. Hiraoka A, Michitaka K, Kiguchi D, et al. Efficacy of branched-chain amino acid supplementation and walking exercise for preventing sarcopenia in patients with liver cirrhosis. Eur J Gastroenterol Hepatol 2017;29(12):1416.
77. Hidaka H, Nakazawa T, Kutsukake S, et al. The efficacy of nocturnal administration of branched-chain amino acid granules to improve quality of life in patients with cirrhosis. J Gastroenterol 2013;48(2):269–76.
78. Koreeda C, Seki T, Okazaki K, et al. Effects of late evening snack including branched-chain amino acid on the function of hepatic parenchymal cells in patients with liver cirrhosis. Hepatol Res 2011;41(5):417–22.
79. Yamanaka-Okumura H, Nakamura T, Miyake H, et al. Effect of long-term late-evening snack on health-related quality of life in cirrhotic patients. Hepatol Res 2010; 40(5):470–6.
80. Nakaya Y, Okita K, Suzuki K, et al. BCAA-enriched snack improves nutritional state of cirrhosis. Nutrition 2007;23(2):113–20.
81. Yamanaka-Okumura H, Nakamura T, Takeuchi H, et al. Effect of late evening snack with rice ball on energy metabolism in liver cirrhosis. Eur J Clin Nutr 2006;60(9):1067–72.
82. Sakaida I, Tsuchiya M, Okamoto M, et al. Late evening snack and the change of blood glucose level in patients with liver cirrhosis. Hepatol Res 2004;30S:67–72.
83. Sako K. Branched-chain amino acids supplements in the late evening decrease the frequency of muscle cramps with advanced hepatic cirrhosis. Hepatol Res 2003;26(4):327–9.
84. Fukushima H, Miwa Y, Ida E, et al. Nocturnal branched-chain amino acid administration improves protein metabolism in patients with liver cirrhosis: comparison with daytime administration. JPEN J Parenter Enteral Nutr 2003;27(5):315–22.
85. Nakaya Y, Harada N, Kakui S, et al. Severe catabolic state after prolonged fasting in cirrhotic patients: effect of oral branched-chain amino-acid-enriched nutrient mixture. J Gastroenterol 2002;37(7):531–6.
86. Yamauchi M, Takeda K, Sakamoto K, et al. Effect of oral branched chain amino acid supplementation in the late evening on the nutritional state of patients with liver cirrhosis. Hepatol Res 2001;21(3):199–204.
87. Miwa Y, Shiraki M, Kato M, et al. Improvement of fuel metabolism by nocturnal energy supplementation in patients with liver cirrhosis. Hepatol Res 2000;18(3): 184–9.
88. Chang WK, Chao YC, Tang HS, et al. Effects of extra-carbohydrate supplementation in the late evening on energy expenditure and substrate oxidation in patients with liver cirrhosis. J Parenter Enteral Nutr 1997;21(2):96–9.
89. Verboeket-van de Venne W, Westerterp K, Van Hoek B, et al. Energy expenditure and substrate metabolism in patients with cirrhosis of the liver: effects of the pattern of food intake. Gut 1995;36(1):110–6.
90. Zillikens M, Van den Berg J, Wattimena J, et al. Nocturnal oral glucose supplementation: the effects on protein metabolism in cirrhotic patients and in healthy controls. J Hepatol 1993;17(3):377–83.
91. Swart G, Zillikens M, Van Vuure J, et al. Effect of a late evening meal on nitrogen balance in patients with cirrhosis of the liver. BMJ 1989;299(6709):1202–3.
92. Buonomo AR, Scotto R, Zappulo E, et al. Severe Vitamin D deficiency increases mortality among patients with liver cirrhosis regardless of the presence of HCC. In Vivo 2019;33(1):177–82.