Hepatic Encephalopathy and Sarcopenia: Two Faces of the Same Metabolic Alteration

Barbara Lattanzi, Daria D'Ambrosio, Manuela Merli

Department of Clinical Medicine, Gastroenterology, Sapienza University of Rome, Italy

Sarcopenia is an important burden in liver cirrhosis representing a negative prognostic factor for mortality. Moreover, sarcopenia is an independent predictor of complications in patients with liver cirrhosis, including Hepatic Encephalopathy (HE). An association between sarcopenia and HE in liver cirrhosis has been reported in recent studies, indeed both these complications often affect patients with advanced liver cirrhosis and may exert a synergic effect in deteriorating patients' outcome. Episodes of HE occur more often in patients with muscle depletion. The rationale for these finding is based on the role played by muscle in ammonia detoxification due to the inability of urea synthesis in the cirrhotic liver. Consequently, muscle depletion may have relevant implications in favoring hyperammonemia and HE. At the same time hyperammonemia has been found to impair muscle protein synthesis through myostatin down-regulation. From this point of view, modulation of diet and amelioration of nutritional status and muscle mass can be considered a potential goal to prevent this vicious circle and improve the cognitive impairment in cirrhotic patients. (J CLIN EXP HEPATOL 2019;9:125–130)

Alterations in nutritional status are a frequent complication associated with liver cirrhosis. The prevalence of malnutrition is related to the severity of liver disease and has been reported to be as high as 65–90% in advanced cirrhosis.^{1,2} A number of factors are involved in malnutrition in liver cirrhosis such as inadequate dietary intake, impaired nutrient absorption and alterations in substrate utilization due to liver disease.^{3–7} Moreover, a variety of acute events and complications may decrease the ability of the patient to care about their dietary intake.⁴ The most relevant component of malnutrition in cirrhotic patients is a progressive and generalized loss of muscle mass and strength.^{8,9} This condition, which is physiologic in aging, is known as sarcopenia.¹⁰ The exact mechanisms causing sarcopenia in cirrhosis are still not completely clarified; one of the major reasons has been the difficulty in identifying the mediator(s) of the liver-muscle axis. Indeed, several potential mediators have been proposed including increased ammonia¹¹; decreased testosterone¹² and growth hormone,¹³ and chronic inflammation due to endotoxemia^{14–17} but more studies are still needed to

understand the relative contribution and the possible interaction of these concomitant factors.

Computed Tomography (CT) and magnetic resonance image analysis are considered at present the gold standard technique to quantify muscle mass.^{9,18–20} The major limitations of these tools, despite their accuracy in identifying skeletal muscle mass, is due to their cost, radiation exposure and logistics.^{15,21} Usually sarcopenia is CT assessed when a CT scan, performed by the patient for other reasons, is already available. Further limitations derive from non-homogeneous methods applied by different studies (either whole muscle area, or psoas area or psoas diameter have been utilized in different studies) which also provide the identification of uniform cut offs.^{22,23}

Other techniques, although less accurate, are also utilized for the assessment of sarcopenia in cirrhotic patients: anthropometry (Triceps-Skinfold-Thickness and Mid-Arm-Muscle-Circumference), non-invasive, rapid, easy to perform and cost-effective²⁴; bioelectrical impedance analysis that estimates total body water, fat-free mass, and body fat²⁵; dual-energy X-ray absorptiometry an easy, reproducible and accurate method to analyze body composition which also allows a regional body composition analysis to study fat mass and fat free mass of selected body sites.²⁴ The evaluation of muscle function has also been proposed, to measure sarcopenia in liver cirrhosis, through the Hand Grip test^{10,26} and other more composite tests such the six-minute walk test.^{22,26}

Keywords: sarcopenia, hepatic encephalopathy, malnutrition

Received: 17 January 2018; **Accepted:** 25 April 2018; **Available online:** 5 May 2018

Address for correspondence: Manuela Merli, Department of Clinical Medicine, Gastroenterology Unit, La Sapienza University of Rome, Italy. Tel.: +39 0649972002; fax: +39 0649972002.

E-mail: manuela.merli@uniroma1.it

Abbreviations: BCAA: Branched Chain Amino Acids; CT: Computed Tomography; HE: Hepatic Encephalopathy; MELD: Model for End-stage Liver Disease; MHE: Minimal Hepatic Encephalopathy; TIPS: Transjugular Intrahepatic Portosystemic Shunt
<https://doi.org/10.1016/j.jceh.2018.04.007>

SARCOPENIA AND COGNITIVE IMPAIRMENT

A number of cross sectional and longitudinal studies, using various methods to quantify muscle mass, have

Table 1 Studies Evaluating the Possible Association Between Muscle Wasting and Neurocognitive Impairment in Cirrhotic Patients.

Author (year)	Number of patients	Methods to identify sarcopenia	Aims	Results
Hanai (2017) ³⁷	120 cirrhotic patients	Bioelectrical impedance analysis and handgrip strength	To investigate the relationship between sarcopenia and MHE and to identify the predictors of MHE in cirrhotic patients.	The prevalence of MHE was higher in patients with sarcopenia than in those without sarcopenia ($P = 0.01$). In the multivariate analysis, sarcopenia (odds ratio = 3.31, 95% confidence interval = 1.19–9.42; $P = 0.02$) was found to be associated with MHE.
Nardelli (2017) ³⁹	46 cirrhotic patients selected for TIPS placement	Skeletal muscle index at CT scan lumbar 3	To investigate the relationship between sarcopenia and the incidence of HE in cirrhotic patients submitted to TIPS.	All the patients with HE after TIPS were sarcopenic and there was an increased occurrence of HE after TIPS in cirrhotic patients with sarcopenia ($P < 0.0001$).
Augusti (2016) ³⁸	54 cirrhotic outpatients with subclinical or clinical HE	Anthropometric measurements	To study the association between HE and measures related to muscle mass and strength.	Reductions of 1 mm of adductor pollicis muscle thickness and 1 kg in handgrip strength were associated with odds of 30.7% ($P = 0.0177$) and 12.2% ($P = 0.023$) of increasing HE grade, respectively.
Merli (2013) ³³	300 consecutive hospitalized cirrhotic patients	Anthropometric measurements (MAMC) and handgrip strength	To investigate whether a decrease in muscle mass or function may independently influence the prevalence of neurocognitive alterations in cirrhosis.	Muscle depletion and decreased muscle function are associated with higher prevalence of overt HE ($P = 0.0005$). and minimal HE ($P < 0.001$).
Meza-Junco (2013) ³⁶	116 patients with HCC consecutively evaluated for liver transplant	Skeletal muscle index measured by CT scan lumbar 3	To investigate the prevalence and prognostic significance of sarcopenia as a marker of nutritional status in patients with hepatocellular carcinoma.	No significant differences in the prevalence of HE in patients with and without sarcopenia (23% vs. 12%, $P = 0.2$).
Montano-Loza (2012) ⁹	112 cirrhotic patients consecutively evaluated for liver transplantation	Skeletal muscle index measured at CT scan lumbar 3	To investigate associations between sarcopenia and mortality and prognosis in cirrhotic patients.	Sarcopenia correlates with death and complication of cirrhosis, but not with HE (50% vs. 33%, $P = 0.6$).
Huisman (2011) ³²	84 cirrhotic patients	Handgrip strength	To determine whether protein energy malnutrition affects complication risk.	Increased complications in cirrhotic patients with lower muscle function, including HE (18% vs. 48%, $P = 0.007$).
Ndraha (2011) ⁶²	34 cirrhotic patients	Anthropometric measurements (MAMC)	To evaluate the influence of L-ornithine-L-aspartate together with the nutritional improvement to encephalopathy in liver cirrhosis with malnutrition.	Improvement of cognitive status after in the group treated by L-ornithine-L-aspartate ($P < 0.016$).
Kalaitzakis (2007) ³⁴	128 cirrhotic patients	BMI, weight loss, MAMC and triceps skinfold	To investigate the effects of malnutrition and diabetes mellitus on HE in unselected patients with liver cirrhosis.	Patients with vs. without malnutrition had more frequently HE (46 vs. 27%; $P = 0.031$). Multivariate analysis showed that the time needed to perform number connection test was independently associated to age, the Child–Pugh score, diabetes and malnutrition ($P < 0.05$).
Sörös (2008) ³⁵	223 histologically confirmed non-alcoholic cirrhotic patients	Anthropometric measurements and bioelectrical impedance analysis	To investigate whether malnutrition (and muscle depletion) could be associated with HE.	The nutritional status was not significantly different between patients with and without hepatic encephalopathy (grades 1–3).

reported that median survival and probability of survival are lower in cirrhotic patients with sarcopenia than in those without sarcopenia.^{9,27} For this reason, it has been suggested that sarcopenia may improve the prognostic value of the Model for End-stage Liver Disease (MELD) scoring system. However, data are still controversial and a recent study analysing 585 cirrhotic patients waiting for LT found that the MELD-Sarcopenia score²⁸ had a discriminative performance which was not superior than that of the original MELD score.²⁹ Further studies have shown that sarcopenia is an independent predictor of complications in patients with liver cirrhosis.³⁰⁻³²

A limited number of studies evaluated the possible association between muscle wasting and neurocognitive alterations in cirrhotic patients (Table 1).

A reduction in Handgrip strength, utilized for the assessment of muscle function in 84 cirrhotic patients, was found to be an independent predictor of complications, including Hepatic Encephalopathy (HE).³⁰ Similarly, in a prospective study including 300 hospitalized cirrhotic patients, muscle depletion evaluated by anthropometry, and impaired muscle function assessed by handgrip strength, were both independently associated with clinically overt HE at admission, previous HE in the last 12 months, covert HE diagnosed by psychometric tests.³³ In a further study, including 128 unselected cirrhotic patients in whom the presence of HE was evaluated according to West-Haven criteria, cognitive alterations were more frequent in patients with malnutrition, and a multivariate analysis showed that the time needed to perform number connection test A was independently correlated to age, Child-Pugh class, malnutrition and diabetes.³⁴ However, in this study, malnutrition was not strictly based on the evaluation of muscle mass but also included BMI, weight loss in the last 6 months and triceps skinfold. At variance with this finding, other authors have reported that the

prevalence of malnutrition (including muscle mass evaluated by Bioelectric Impedance Analysis) was not different between non-alcoholic cirrhotic patients with and without HE.³⁵ Likewise, in further investigations, the prevalence of HE was similar in sarcopenic and non sarcopenic patients with cirrhosis evaluated by CT-scan.^{9,36} These controversial results could be due to difference in patients' characteristics and lack of information that could better define the episode of HE such as timing, etiology and severity.

The relationship between sarcopenia and HE was also reported in a recent retrospective study including a cohort of 120 Japanese cirrhotic patients; the prevalence of Minimal Hepatic Encephalopathy (MHE) was found to be higher in patients with sarcopenia than in those without sarcopenia and sarcopenia was shown to be an independent predictor of MHE at multivariate analysis.³⁷ A further study showed that lower values of adductor pollicis muscle thickness and handgrip strength both correlated with the presence of HE in cirrhotic patient.³⁸

The presence of an interaction between muscle and cognitive alterations in cirrhotic patients is in agreement with the results of a recent study, in which muscle wasting in cirrhotic patients constitutes a strong and independent risk factor for the occurrence of HE after Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement.³⁹ In this series, all patients with an episode of overt HE during the follow up after TIPS were sarcopenic before TIPS placement while the prevalence of sarcopenia in the patients without post TIPS HE was only 20%.

AMMONIA METABOLISM AND TRAFFICKING

The rationale for an association between muscle depletion and HE derives from the possible involvement of muscle tissue in ammonia metabolism and trafficking (Figure 1). Ammonia is a crucial metabolite in the pathogenesis of

Figure 1 The ammonia metabolism and trafficking in liver cirrhosis.

cognitive impairment in liver cirrhosis and its concentrations are increased in these patients because of the inability of the impaired liver in removing ammonia through urea synthesis.⁴⁰ In this scenario the muscle mass acquires importance because it contributes, through glutaminase, to remove ammonia by incorporating it into glutamine.⁴¹ Although this metabolic pathway does not result in a definitive ammonia disposal, it has been proposed that muscle depletion may have relevant implications in favoring hyperammonemia.⁴² Furthermore, the enhanced muscle protein catabolism, which contributes to muscle wasting, increases glutamine release from muscle. Glutamine is drained to the small intestine and kidney where it is converted to glutamic acid and ammonia, further contributing to increase the whole-body ammonia availability.^{41,42}

Moreover, studies investigating the molecular mechanism of sarcopenia in liver cirrhosis revealed that ammonia itself impairs muscle protein synthesis in part through the up-regulation of myostatin production.^{7,11,43}

Indeed, in cirrhosis, the skeletal muscle by removing large quantities of ammonia from the circulation, is exposed to high intramuscular concentration of this metabolite causing transcriptional up-regulation of myostatin in a p65 NF- κ B-dependent manner.⁴⁴

Myostatin, a member of the TGF β superfamily, is a powerful catabolic signal that inhibits protein synthesis and satellite cells proliferation and differentiation. Myostatin, binding to its muscle surface receptor, leads to activation of Smad2/3 promoting muscle proteolysis and wasting via activation of ubiquitin-proteasome system.^{45,46} Levels of myostatin have been found to be increased in experimental models of liver cirrhosis^{47,48} and cirrhotic patients.⁴⁹

Moreover, the ammonia disposal in non-hepatic tissue results in loss of α -Ketoglutarate (α KG), an intermediate of Tricarboxylic Acid (TCA) cycle, leading to cataplerosis, which contributes to mitochondrial dysfunction.⁵⁰ As protein synthesis is a highly energy-requiring cellular process, mitochondrial dysfunction with low ATP content contributes to dysregulated proteostasis. In addition to mitochondrial dysfunction, because of cataplerosis of α KG, hyperammonemia also results in increase of reactive oxygen species leading to autophagy.⁵⁰ Furthermore, hyperammonemia also induces muscle damage thought a cellular stress response, which is mediated by an eIF2 α kinase.⁵¹

These pathways lead to imagine the existence of a vicious circle: on one side hyperammonemia is generated by sarcopenia due to the inability of the depleted muscle to metabolize ammonia, on the other hand, increased ammonia concentrations, through myostatin up-regulation, mitochondrial dysfunction and cellular stress response, induces further muscle wasting. From this viewpoint, an improvement in nutritional status and muscle

mass can be considered a potential goal to ameliorate the cognitive function in cirrhotic patients and a modulation of diet may represent a promising option when seeking to prevent HE.⁵² At the same time, a reduction in ammonia levels may ameliorate muscle wasting.⁵³

NUTRITIONAL MEASURES

Restriction of protein intake has been abandoned as a therapy in patients with acute HE. Indeed, in a randomized controlled study, in addition to standard treatment of HE, a protein-restricted diet vs. a normal protein diet for 14 days was found to have no advantage in cognitive recovery. The protein restricted diet caused an increased protein catabolism which is detrimental for these patients.⁵⁴ In a more recent study, a high protein meal in decompensated cirrhotic patients did not precipitate HE, despite of the accumulation of some amino acids.⁵⁵ These results support the current nutritional guidelines that recommend a protein intake of 1.2–1.5 g/kg body weight/day for patients with cirrhosis and HE.⁵⁶

While a low protein diet does not seem to be beneficial in HE, selection of protein quality should be considered as an opportunity. In patients with recurrent HE it has been shown that vegetable proteins are better tolerated.⁵⁷ A higher intestinal clearance of nitrogen-waste products, a shortened transit time, a reduced colonic pH, a higher ornithine and arginine and a lower methionine and tryptophan content compared to animal proteins are among the proposed beneficial effects. Additional benefits of a vegetal-enriched diet may derive from the modulation of gut microbiota.⁵² In decompensated cirrhosis alterations in gut microbiota are frequent, and modulation of gut microbiota may be effective for treating and preventing HE.⁵⁸ Prebiotics and probiotics have also been proposed to be useful in preventing HE and MHE, but more studies are required.^{58,59}

In a recent randomized controlled trial performed in India, six-month nutritional therapy (30–35 kcal/kg/day, 1.0–1.5 g vegetable protein/kg/day) was effective to ameliorate MHE score and was associated with an improvement in health-related quality of life. The authors suggest that multiple factors (improvement in liver functions, recovery of muscle mass, positive nitrogen metabolism, and modifications in gut flora) may have contributed to the improvement in MHE. Moreover, episodes of overt HE appeared to be lower in the group on nutritional therapy than in controls.⁶⁰

Nutritional supplements have been shown to improve cognitive status in cirrhotic patients. Oral supplementation with Branched Chain Amino Acids (BCAA) also has a role for its effect in reducing the risk of recurrence of HE. Indeed, a Cochrane database systematic review, examining clinical trials on BCAA supplement vs. standard therapy in cirrhotic patients with HE, reported that BCAA had a

significant beneficial effect on HE either overt or minimal.⁶¹ Another study reported positive effect on cognitive impairment in cirrhotic patients with the introduction of L-Ornithine-L-aspartate.⁶²

Theoretically even, physical exercise might improve cognitive status by its effect on sarcopenia but at present, no studies have explored this opportunity.

CONCLUSION

In conclusion, sarcopenia is an important burden in liver cirrhosis and evidences support that it is strictly correlated with cognitive impairment in cirrhotic patients. This gives a glimpse of the relationship between muscle and brain in liver cirrhosis which is mediated by metabolic changes in which the role of hyperammonemia is of great importance.²¹

Few evidences showed beneficial effect of nutritional supplementation in cognitive impairment in cirrhotic patients but more extensive studies are still needed. Taking into account the improving knowledge about molecular mechanism of sarcopenia in liver cirrhosis, target therapies, through myostatin antagonists, direct mTORC1 activators, antioxidants, and mitochondrial protective agents, might have the potential to benefit the brain-muscle axis in liver cirrhosis.⁶³

Understanding the complexity of this correlation can lead to a better strategy of treatment of these two important complications of liver cirrhosis that negatively affect morbidity and mortality.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

- 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):325–336.
- Merli M, Riggio O, Dally L. Does malnutrition affect survival in cirrhosis? PINC (Policentrica Italiana Nutrizione Cirrosi). *Hepatology*. 1996;23(5):1041–1046.
- Tandon P, Raman M, Mourtzakis M, Merli M. A practical approach to nutritional screening and assessment in cirrhosis. *Hepatology*. 2017;65(3):1044–1057.
- Plauth M, Schütz ET. Cachexia in liver cirrhosis. *Int J Cardiol*. 2002;85(1):83–87.
- Schutz ET, Gerstner C, Lochs H, Plauth M. Effects of disease severity, ascites and transjugular intrahepatic porto-systemic shunt (TIPS) on food intake in patients with liver cirrhosis. *Clin Nutr*. 1998;17(suppl 1):19.
- Plauth M, Merli M, Kondrup J, et al. ESPEN guidelines for nutrition in liver disease and transplantation. *Clin Nutr*. 1997;16(2):43–55.
- Anand AC. Nutrition and muscle in cirrhosis. *J Clin Exp Hepatol*. 2017;7(4):340–357.
- Dasarathy S. Consilience in sarcopenia of cirrhosis. *J Cachexia Sarcopenia Muscle*. 2012;3(4):225–237.
- Montano-Loza AJ, Meza-Junco J, Prado CM, et al. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2012;10(2):166–173. 173.
- Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. European Working Group on sarcopenia in older people. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing*. 2010;39(4):412–423.
- Qiu J, Tsien C, Thapalaya S, et al. Hyperammonemia-mediated autophagy in skeletal muscle contributes to sarcopenia of cirrhosis. *Am J Physiol Endocrinol Metab*. 2012;303:E983–E993.
- Sinclair M, Grossmann M, Hoermann R, Angus PW, Gow PJ. Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: a randomised controlled trial. *J Hepatol*. 2016;65(5):906–913.
- Liu W, Thomas SG, Asa SL, Gonzalez-Cadavid N, Bhasin S, Ezzat S. Myostatin is a skeletal muscle target of growth hormone anabolic action. *J Clin Endocrinol Metab*. 2003;88:5490–5496.
- Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. *J Hepatol*. 2015;63(5):1272–1284.
- Merli M, Dasarathy S. Sarcopenia in non-alcoholic fatty liver disease: targeting the real culprit? *J Hepatol*. 2015;63(2):309–311.
- Tilg H, Wilmer A, Vogel W, et al. Serum levels of cytokines in chronic liver diseases. *Gastroenterology*. 1993;105:310–311.
- Deviere J, Content J, Denys C, et al. Immunoglobulin A and interleukin 6 form a positive secretory feedback loop: a study of normalsubjects and alcoholic cirrhotics. *Gastroenterology*. 1992;103(4):1296–1301.
- Giusto M, Lattanzi B, Di Gregorio V, Giannelli V, Lucidi C, Merli M. Changes in nutritional status after liver transplantation. *World J Gastroenterol*. 2014;20(31):10682–10690.
- Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* (1985). 2004;97(6):2333–2338.
- Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol* (1985). 1998;85:115–122.
- Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol*. 2016;65(6):1232–1244.
- Carey EJ, Lai JC, Wang CW, et al. Fitness, Life Enhancement, and Exercise in Liver Transplantation Consortium. A multicenter study to define sarcopenia in patients with end-stage liver disease. *Liver Transpl*. 2017;23(5):625–633.
- Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol*. 2013;31(12):1539–1547.
- Giusto M, Lattanzi N, Albanese C, et al. Sarcopenia in liver cirrhosis: the role of computed tomography scan for the assessment of muscle mass compared with dual-energy X-ray absorptiometry and anthropometry. *Eur J Gastroenterol Hepatol*. 2015;27(3):328–334.
- Dazzani F, Micati M, Caraceni P, et al. Transthoracic electrical bioimpedance: a non-invasive technique for the evaluation of the haemodynamic alterations in patients with liver cirrhosis. *Dig Liver Dis*. 2005;37(10):786–792.
- Bhanji RA, Narayanan P, Allen AM, Malhi H, Watt KD. Sarcopenia in hiding: the risk and consequence of underestimating muscle

- dysfunction in nonalcoholic steatohepatitis. *Hepatology*. 2017;66(6):2055–2065.
27. Tandon P, Ney M, Irwin I, et al. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. *Liver Transpl*. 2012;18(10):1209–1216.
 28. Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, et al. Inclusion of sarcopenia within MELD (MELD-Sarcopenia) and the prediction of mortality in patients with cirrhosis. *Clin Transl Gastroenterol*. 2015;6:e102.
 29. Van Vugt JL, Alferink LJM, Buettner S, et al. A model including sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant candidates. *J Hepatol*. 2017. S0168-8278(17)32474-1.
 30. Lucidi C, Lattanzi L, Di Gregorio V, et al. A low muscle mass increases mortality in compensated cirrhotic patients with sepsis. *Liver Int*. 2018 [Epub ahead of print].
 31. Merli M, Lucidi C, Giannelli V, et al. Cirrhotic patients are at risk for health care-associated bacterial infections. *Clin Gastroenterol Hepatol*. 2010;8:979–985.
 32. Huisman EJ, Trip EJ, Siersema PD, van Hoek B, van Erpecum KJ. Protein energy malnutrition predicts complications in liver cirrhosis. *Eur J Gastroenterol Hepatol*. 2011;23(11):982–989.
 33. 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;28:281–284.
 34. Kalaitzakis E, Olsson R, Henfridsson P, et al. Malnutrition and diabetes mellitus are related to hepatic encephalopathy in patients with liver cirrhosis. *Liver Int*. 2007;27(9):1194–1201.
 35. Sörös P, Böttcher J, Weissenborn K, Selberg O, Müller MJ. Malnutrition and hypermetabolism are not risk factors for the presence of hepatic encephalopathy: a cross-sectional study. *J Gastroenterol Hepatol*. 2008;23(4):606–610.
 36. Meza-Junco J, Montano-Loza AJ, Baracos VE, et al. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. *J Clin Gastroenterol*. 2013;47(10):861–870.
 37. Hanai T, Shiraki M, Watanabe S, et al. Sarcopenia predicts minimal hepatic encephalopathy in patients with liver cirrhosis. *Hepatology Res*. 2017;47(13):1359–1367.
 38. Augusti L, Franzoni LC, Santos LA, et al. Lower values of handgrip strength and adductor pollicis muscle thickness are associated with hepatic encephalopathy manifestations in cirrhotic patients. *Metab Brain Dis*. 2016;31(4):909–915.
 39. Nardelli S, Lattanzi B, Torrisi S, et al. Sarcopenia is risk factor for development of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt placement. *Clin Gastroenterol Hepatol*. 2017;15(6):934–936.
 40. Ganda OP, Ruderman NB. Muscle nitrogen metabolism in chronic hepatic insufficiency. *Metabolism*. 1976;25:427–435.
 41. Wright G, Noiret L, Olde Damink SW, Jalan R. Interorgan ammonia metabolism in liver failure: the basis of current and future therapies. *Liver Int*. 2011;31(2):163–175.
 42. Olde Damink SW, Jalan R, Redhead DN, Hayes PC, Deutz NE, Soeters PB. Interorgan ammonia and amino acid metabolism in metabolically stable patients with cirrhosis and a TIPSS. *Hepatology*. 2002;36(5):1163–1171.
 43. Dasarthy S. Myostatin and beyond in cirrhosis: all roads lead to sarcopenia. *J Cachexia Sarcopenia Muscle*. 2017;8(6):864–869.
 44. Qiu J, Tsien C, Thapalaya S, et al. Hyperammonemia-mediated autophagy in skeletal muscle contributes to sarcopenia of cirrhosis. *Am J Physiol Endocrinol Metab*. 2012;303:E983–E993.
 45. Sandri M. Signaling in muscle atrophy and hypertrophy. *Physiology (Bethesda)*. 2008;23:160–170.
 46. Zhou X, Wang JL, Lu J, et al. Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. *Cell*. 2010;142:531–543.
 47. Qiu J, Thapaliya S, Runkana A, et al. Hyperammonemia in cirrhosis induces transcriptional regulation of myostatin by an NF-kappaB-mediated mechanism. *Proc Natl Acad Sci U S A*. 2013;110:18162–18167.
 48. Merli M, Giusto M, Molfino A, et al. MuRF-1 and pGSK3beta expression in muscle atrophy of cirrhosis. *Liver Int*. 2013;33:714–721.
 49. Garcia PS, Cabbabe A, Kambadur R, Nicholas G, Csete M. Brief reports: elevated myostatin levels in patients with liver disease: a potential contributor to skeletal muscle wasting. *Anesth Analg*. 2010;111:707–709.
 50. Davuluri G, Allaway A, Thapaliya S, et al. Hyperammonemia-induced skeletal muscle mitochondrial dysfunction results in cataplerosis and oxidative stress. *J Physiol*. 2016;594:7341–7360.
 51. Davuluri G, Krokowski D, Guan BJ, et al. Metabolic adaptation of skeletal muscle to hyperammonemia drives the beneficial effects of L-leucine in cirrhosis. *J Hepatol*. 2016;65:929–937.
 52. Merli M, Iebba V, Giusto M. What is new about diet in hepatic encephalopathy. *Metab Brain Dis*. 2016;31(6):1289–1294.
 53. Kumar A, Davuluri G, Silva RNE, et al. Ammonia lowering reverses sarcopenia of cirrhosis by restoring skeletal muscle proteostasis. *Hepatology*. 2017;65(6):2045–2058.
 54. Córdoba J, López-Hellín J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. *J Hepatol*. 2004;41(1):38–43.
 55. Campollo O, Sprengers D, Dam G, Vilstrup H, McIntyre N. Protein tolerance to standard and high protein meals in patients with liver cirrhosis. *World J Hepatol*. 2017;9(14):667–676.
 56. Amodio P, Canesso F, Montagnese S. Dietary management of hepatic encephalopathy revisited. *Curr Opin Clin Nutr Metab Care*. 2014;17(5):448–452.
 57. Amodio P, Caregaro L, Pattenò E, Marcon M, Del Piccolo F, Gatta A. Vegetarian diets in hepatic encephalopathy: facts or fantasies? *Dig Liver Dis*. 2001;33(6):492–500.
 58. Zhao LN, Yu T, Lan SY, et al. Probiotics can improve the clinical outcomes of hepatic encephalopathy: an update meta-analysis. *Clin Res Hepatol Gastroenterol*. 2015;39(6):674–682.
 59. Lunia MK, Sharma BC, Sharma P, Sachdeva S, Srivastava S. Probiotics prevent hepatic encephalopathy in patients with cirrhosis: a randomized controlled trial. *Clin Gastroenterol Hepatol*. 2014;12(6):1003–8.e1.
 60. Maharshi S, Sharma BC, Sachdeva S, Srivastava S, Sharma P. Efficacy of nutritional therapy for patients with cirrhosis and minimal hepatic encephalopathy in a randomized trial. *Clin Gastroenterol Hepatol*. 2016;14(3):454–60.e3.
 61. Gluud LL, Dam G, Les I, et al. Branched-chain amino acids for people with hepatic encephalopathy. *Cochrane Database Syst Rev*. 2017;5:CD001939.
 62. Ndraha S, Hasan I, Simadibrata M. The effect of L-ornithine L-aspartate and branch chain amino acids on encephalopathy and nutritional status in liver cirrhosis with malnutrition. *Acta Med Indones*. 2011;43(1):18–22.
 63. Han HQ, Zhou X, Mitch WE, Goldberg AL. Myostatin/activin pathway antagonism: molecular basis and therapeutic potential. *Int J Biochem Cell Biol*. 2013;45:2333–2347.