

Sarcopenia in cirrhosis: a systematic review

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Abstract

Introduction. Sarcopenia is a common complication and a frequently encountered feature in liver cirrhosis. Also, sarcopenia is a strong prognosis factor and a predictor of mortality in patients with advanced liver disease. However, in clinical practice, there are no well-established criteria for the diagnosis of this common complication of cirrhosis, the mechanisms which are involved are poorly understood and the possible therapeutic options are still undergoing randomized clinical trials.

Materials and methods. To summarize the actual understanding of sarcopenia in cirrhosis, a literature search was performed using PubMed, MedLine, and Web of Science, to find articles related to definition, physiopathology, and treatment of sarcopenia of these patients.

Results. A number of 30 papers that were suitable for this review were found. Most of them concluded that sarcopenia is a strong predictor of mortality, has a higher risk of hepatic encephalopathy and an increased health related cost in cirrhotic patients. The factors involved in this condition are far more complex than malnutrition and reduced protein intake, and include metabolic switch to the use of amino acids and fats to produce glucose. According to actual guidelines, beside moderate physical exercise and BCAA intake, therapeutic intervention with testosterone and ammonia-lowering therapies might have the potential to reverse sarcopenia in cirrhosis.

Conclusion. Improved understanding of factors such as underlying nutritional imbalances, amount of oral protein intake, dose, type and duration of supplementation and the compliance of physical exercise, should be the focus of further research with randomized controlled trials.

Keywords: sarcopenia, liver cirrhosis, muscles waste

Introduction

The root of the term "sarcopenia" originates in Greek culture, coming from –sarx- for flesh and –penia- for loss, and was used for the first time by Rosenbeg in 1988 [1]. European Society for Clinical Nutrition and Metabolism (ESPEN) defined sarcopenia as a syndrome

characterized by progressive and generalized loss of skeletal muscle mass, strength, and function (performance) with a consequent risk of adverse outcomes [2]. Primary sarcopenia is often linked with the ageing processes and precedes the onset of the condition named frailty, which is a state of vulnerability and non-resilience with limited reserve capacity in major

organ systems [2]. Secondary sarcopenia is a consequence of pathogenic mechanisms related to several diseases, lack of physical activity or nutritional deficits [3]. Advanced liver disease, like liver cirrhosis (LC), is, by far, the most prevalent condition that may lead to sarcopenia.

Kim et al. concluded in the most recent systematic review and meta-analysis on sarcopenia in LC, that sarcopenia is related to a poor prognosis, a lower survival rate (as assessed by Model for End-Stage Liver Disease - MELD score), and occurrence of cirrhotic complications [4]. According to this review, sarcopenia prevalence in LC ranges from 25% to 70%, far higher than in other gastrointestinal diseases, being a consequence of metabolic derangements caused by liver failure. Furthermore, sarcopenia is linked with an increased risk of infection and length of hospital stay [4].

However, in clinical practice, there are no well-established criteria for the diagnosis of this common complication of cirrhosis, the mechanisms that are involved being poorly understood and the possible therapeutic options being still undergoing randomized clinical trials.

To summarize the actual understanding of sarcopenia in cirrhosis, a literature search was performed using PubMed, MedLine, and Web of Science, to find articles related to definition, physiopathology, and treatment of sarcopenia in cirrhosis.

Clinical prognosis of sarcopenia in advanced liver disease

Emerging studies showed that sarcopenia, independent of liver function, is a strong prognosis factor and a predictor of mortality in patients with cirrhosis [5], has a higher risk of hepatic encephalopathy [6] and an increased health-related cost in patients waiting for liver transplant [7]. Furthermore, sarcopenia is correlated with lower survival rates in patients

with hepatocellular carcinoma [8]. Another risk factor associated with the development of sarcopenia is male gender [9]. This discrepancy between genders is explained by metabolism, fat distribution and hormonal characteristics.

Sarcopenia pathophysiology in cirrhosis

Sarcopenia is a consequence of the imbalance between muscle formation and muscle breakdown. Protein turnover, or the muscle mass metabolism, is regulated by two opposing factors, myostatin, and insulin-like growth factor 1 (IGF1). Myostatin is the predominant negative regulator of satellite cells (the precursors of new muscle fibers) proliferation; elevated myostatin levels being the main mechanisms underlying sarcopenia in cirrhosis. Moreover, muscle biopsies have shown higher myostatin expression in patients with advanced liver disease compared with controls [10]. The cause of elevated myostatin levels is uncertain; one hypothesis is that ammonia levels are frequently higher in advanced liver diseases, stimulating myostatin expression [10,11]. IGF 1 enhances muscle growth and muscle protein synthesis through the activation of protein kinase B and is upregulated by physical exercise, testosterone and BCCA's (branch chain amino acids) – particularly leucine; these factors activating the recruitment of the satellite cells [12].

There are several causes of sarcopenia in patients with cirrhosis, such as a) malnutrition [13], b) altered metabolism due to abnormal use of protein as energy source [14], c) anorexia caused by higher level of leptin and tumor necrosis factor (TNF – α) [15], d) hormone deficiency [13] and e) low socioeconomic status and inadequate nutrition intake associated with alcoholism.

One observational study, which included a cohort of 50 patients, reported that the median caloric intake per patient with cirrhosis is much lower compared with non-cirrhotic patients

[13], leading to the conclusion that malnutrition plays a major role in sarcopenia. Other potential causes of reduced dietary intake in cirrhosis include appetite reduction due to higher levels of leptin and TNF – α [14], ascites and increased intra-abdominal pressure, dysgeusia and alcohol abuse.

Due to a state that mimics starvation, in cirrhosis there is a switch to the use of fat and protein as an energy source; this fact being not normal in physiologic conditions. The use of proteolysis and lipolysis is due to a reduction of glycogen stores, which results in the need to create glucoses from other sources [14]. This metabolic switch to the use of amino acids and fats, to create glucose, leads to increased ketogenesis [16] and low levels of BCAA, the essential compounds preferred by muscle tissue [17].

Diagnosis of sarcopenia

Anthropometry indices, such as body mass index, can be a poor indicator of nutritional state in cirrhotic patients, as it cannot differentiate muscle mass from fat mass [18].

Hand grip strength is a basic functional measure of musculoskeletal function of the hand and forearm and is independently correlated in a large population study of >140 000 with all-cause mortality ($p < 0.0001$) [19].

Magnetic resonance imaging (MRI) can distinguish between adipose tissue and fat-free mass and can create accurate high-resolution body structure and composition with no radiation exposure, making it adequate for long-term follow up [20]. A special MRI technique, magnetic resonance spectroscopy, can evaluate the molecular composition of tissue and furthermore, can differentiate between intra-myocellular and extra-myocellular fat [20]. However, these techniques have high prices and limited access.

Computer tomography (CT) techniques are able to evaluate and differentiate all body tissues and have been considered the gold

standard for investigating changes in muscles and fat [21]. Cross-sectional measures at the third (L3) and/ or fourth (L4) lumbar vertebrae positively correlate with total body muscle mass [21]. The most commonly used method for the diagnosis of sarcopenia in cirrhosis is L3 skeletal muscle index, with more accuracy than anthropometric indices, functional measures and Dual-energy X-ray absorptiometry (DEXA) scanning [22]. The use of CT techniques is limited by high costs and radiation exposure.

DEXA measures the absorption of multiple low-dose X-rays that can show the amount of fat and lean tissue in the whole body. A commonly used index that correlates well with total muscle body mass is appendicular lean mass (APLM). A major limitation of DEXA is that the lean mass readings cannot differentiate water from muscles, raising errors in cirrhotic patients with ascites and peripheral edema. Although the radiation exposure is minimal, the costs and access make it difficult to use in some parts of the world.

Potential therapeutic targets in sarcopenia

The main therapeutic interventions for sarcopenia in LC are diet and exercise. High energy and high protein diet (1-1.5g of protein per kg of body weight per day) improves nitrogen balance (4.3 ± 3.2 g of nitrogen per day compared to 2.2 ± 1.9 g of nitrogen when fasting) [23]. Late evening snacks consisting in complex carbohydrates and proteins have been shown to enhance nitrogen balance by minimizing muscle breakdown during sleep in patients with low hepatic glycogen deposits [24]. At the same time, mild physical activity may prevent muscle loss and sarcopenia. When tolerated, 30 minutes of walking 4 times per week together with resistance training 2-3 times per week as tolerated are strongly recommended [12].

Drug therapies for sarcopenia in LC are not well defined, but there are several agents that can be used. BCAA supplements may lead to a

decrease in myostatin through detoxification of ammonia, protecting the muscle mass [25,26]. Also, BCAA supplementation can enhance carbohydrate metabolism by lowering gluconeogenesis and protein catabolism [27]. Recent studies concluded that BCAA supplements may improve muscle strength, but there is no effect on mortality, quality of life and nutritional parameters [28]. Rifaximin may decrease myostatin levels by improving serum ammonia, releasing BCAAs that can be used for muscle mass, but further studies are needed to validate the use of rifaximin for the treatment of sarcopenia in LC.

Testosterone therapy (intramuscular testosterone or topical testosterone gel) may enhance muscle mass by activating androgen receptors which inhibit myostatin and activate muscle protein synthesis [12]. Testosterone levels were found to be lower in sarcopenic cirrhotic patients compared to the non-sarcopenic ones [29]. It has been demonstrated that insulin-like growth factor 1 (IGF-1) has a favorable effect on nitrogen metabolism in cirrhotic rats by increasing muscle mass [30]. However, further studies on human subjects are needed to validate these findings.

Conclusions

Sarcopenia is a common complication and a frequently encountered feature in LC. Also, it is a strong prognosis factor and a predictor of mortality in patients with advanced liver disease [5]. The old evidence that this condition responds to physical exercise and a high-protein dietary intake does not take into account the altered metabolism that leads to muscle waste in patients with LC. Despite the clear benefit of diagnosing sarcopenia using different diagnostic methods, there are no standardized and validated protocols for the existing tests. Further research with randomized controlled trials is clearly required to develop specific therapeutic methods that target the underlying nutritional derangements in cirrhosis.

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Conflict of Interest statements

Authors state no conflict of interest.

References

1. Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr.* 1997; 127:990S. <https://doi.org/10.1093/jn/127.5.990S>.
2. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr.* 2017; 36:49e64. <https://doi.org/10.1016/j.clnu.2016.09.004>.
3. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F et al. Sarcopenia: European consensus on definition and diagnosis. *Age Ageing.* 2010; 39:412e23. <https://doi.org/10.1093/ageing/afq034>.
4. Kim G, Kang SH, Kim MY, Baik SK. Prognostic value of sarcopenia in patients with liver cirrhosis: a systematic review and meta-analysis. *PLoS One.* 2017; 12:e0186990. <https://doi.org/10.1371/journal.pone.0186990>.
5. 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.
6. Bhanji RA, Moctezuma-Velazquez C, Duarte-Rojo A et al. Myosteatosis and sarcopenia are associated with hepatic encephalopathy in patients with cirrhosis. *Hep Intl.* 2018; 12:377-86.
7. van Vugt JLA, Buettner S, Alferink LJM et al. Low skeletal muscle mass is associated with increased hospital costs in patients with cirrhosis listed for liver transplantation-a retrospective study. *Transpl Int.* 2018; 31:165-74.
8. Ha Y, Kim D, Han S et al. Sarcopenia Predicts prognosis in patients with newly diagnosed hepatocellular carcinoma, independent of tumor stage and liver function. *Cancer Res Treat.* 2018; 50:843-51.
9. Montano-Loza AJ. Skeletal muscle abnormalities and outcomes after liver transplantation. *Liver Transpl.* 2014; 20:1293-5.
10. Tsien C, Davuluri G, Singh D et al. Metabolic and molecular responses to leucine-enriched branched chain amino acid supplementation in the skeletal muscle of alcoholic cirrhosis. *Hepatology.* 2015; 61:2018-29.
11. 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 USA.* 2013; 110:18162-7.
12. Sinclair M, Gow PJ, Grossmann M, Angus PW. Review article: sarcopenia in cirrhosis - aetiology, implications and potential therapeutic interventions. *Aliment Pharmacol Ther.* 2016; 43:765e77. <https://doi.org/10.1111/apt.13333>.

- org/10.1111/apt.13549.
13. Thapaliya S, Runkana A, McMullen MR et al. Alcohol-induced autophagy contributes to loss in skeletal muscle mass. *Autophagy*. 2014; 10:677-90.
14. Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. *J Gastroenterol Hepatol*. 2012; 27:430-41.
15. Trovato F, Aiello F, Larocca L, Taylor-Robinson S. The role of physical activity and nutrition in the sarcopenia of cirrhosis. *J Funct Morphol Kinesiol*. 2016; 1:118e25. <https://doi.org/10.3390/jfmk1010118>.
16. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol*. 2016; 65:1232e44. <https://doi.org/10.1016/j.jhep.2016.07.040>.
17. Dam G, Sorensen M, Buhl M et al. Muscle metabolism, and whole blood amino acid profile in patients with liver disease. *Scand J Clin Lab Invest*. 2015; 75:674-80.
18. Loguercio C, Sava E, Marmo R, del Vecchio Blanco C, Coltorti M. Malnutrition in cirrhotic patients: anthropometric measurements as a method of assessing nutritional status. *Brit J Clin Pract*. 1990; 44:98-101.
19. Leong D, Teo K, Rangarajan S. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet*. 2015; 386:266-73.
20. Erlandson MC, Lorbergs AL, Mathur S, Cheung AM. Muscle analysis using pQCT, DXA and MRI. *Eur J Radiol*. 2016; 85:1505-1511.
21. Sergi G, Trevisan C, Veronese N, Lucato P, Manzato E. Imaging of sarcopenia. *Eur J Radiol*. 2016; 85:1519-1524.
22. Giusto M, Lattanzi B, 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 Gastro Hepatol*. 2015; 27:328-34.
23. Dichi JB, Dichi I, Maio R et al. Wholebody protein turnover in malnourished patients with child class B and C cirrhosis on diets low to high in protein energy. *Nutrition*. 2001; 17:239-42.
24. Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. *J Gastroenterol Hepatol*. 2012; 27:430-41.
25. Dasarathy S. Etiology and management of muscle wasting in chronic liver disease. *Curr Opin Gastroenterol*. 2016; 32:159e65. <https://doi.org/10.1016/j.coviro.2015.09.001> [Human].
26. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol*. 2016; 65:1232e44. <https://doi.org/10.1016/j.jhep.2016.07.040>.
27. Kawaguchi T, Taniguchi E, Sata M. Effects of oral branched-chain amino acids on hepatic encephalopathy and outcome in patients with liver cirrhosis. *Nutr Clin Pract*. 2013; 28:580e8. <https://doi.org/10.1177/>.
28. Gluud LL, Dam G, Les I, Cordoba J, Marchesini G, Borre M et al. Branched-chain amino acids for people with hepatic encephalopathy. *Cochrane Database Syst Rev*. 2017. <https://doi.org/10.1002/14651858.CD001939>.
29. Moctezuma-Velazquez C, Low G, Mourtzakis M et al. Association between low testosterone levels and sarcopenia in cirrhosis: a cross-sectional study. *Ann Hepatol*. 2018; 17:615-23.
30. Lang CH, Frost RA, Svanberg E, Vary TC. IGF-I/IGFBP-3 ameliorates alterations in protein synthesis, eIF4E availability, and myostatin in alcohol fed rats. *Am J Physiol Endocrinol Metab*. 2004; 286:E916-26.