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Review

Nutritional support in cirrhotic patients with sarcopenia

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SUMMARY

Sarcopenia has been linked to oncologic and chronic diseases such as liver cirrhosis. In fact, sarcopenia is present in 25–70% of patients with liver cirrhosis. Furthermore, sarcopenia is an independent predictor of poor prognosis in many diseases.

Currently cirrhotic patients are recommended to adopt a high protein diet (1.5 g/kg/day) with 30–40 kcal/kg/day and several meals throughout the day, being late evening snack intake with at least 50 g of carbohydrates of special importance. Despite the growing interest in the impact of sarcopenia in cirrhotic patients, there are still gaps in knowledge in the appropriate diagnostic criteria for this syndrome, the role of gut microbiota, as well as the most appropriate nutritional therapy.

1. Introduction

The term sarcopenia was first used by Rosenberg in 1988 and originates from Greek, meaning loss (*penia*) of flesh (*sarx*) [1]. In 2017 the *European Society for Clinical Nutrition and Metabolism* (ESPEN) defined sarcopenia as a syndrome characterized by the progressive and generalized loss of skeletal muscle mass, strength and function with a consequent risk of adverse outcomes [2]. It is often associated with the process of ageing (known as primary sarcopenia) and precedes the onset of frailty, which is a state of vulnerability and non-resilience with limited reserve capacity in major organ systems [2,3]. Additionally, secondary sarcopenia results from pathogenic mechanisms related to several diseases, lack of physical activity or nutritional deficits [2,3].

Sarcopenia has been linked to oncologic and chronic diseases such as liver cirrhosis (LC) and has arisen as an independent predictor of poor prognosis in several clinical illnesses [4]. In 2017, the most recent systematic review and meta-analysis on sarcopenia in LC, Kim et al. concluded that sarcopenia is consistently associated with a lower survival rate in individuals with LC regardless of age or liver failure (as assessed by *Model for End-Stage Liver Disease-MELD-score*) [4]. Furthermore it has been associated with an increased risk of infection and length of hospital stay [4]. According to same meta-analysis, sarcopenia prevalence in LC ranges from 25% to 70% [4]. Noteworthy, all studies included in that meta-analysis classified sarcopenia as the loss of skeletal muscle mass alone [4], rather than evaluating the loss of skeletal muscle mass along with the strength, as it is currently recommend by the *European Working Group on Sarcopenia in Older People* [5].

2. Muscle mass metabolism

Skeletal muscle mass is mainly regulated by two opposing growth factors, insulin-like growth factor 1 (IGF1) and myostatin (Fig. 1). IGF1 is regulated by physical exercise [6] and stimulates skeletal muscle growth through the activation of the protein kinase B (Pkb/Akt), which not only activates mammalian target of rapamycin (mTOR) but also inhibits forkhead transcription factor (FoXO) and glycogen synthase kinase 3β (GSK 3β) [7,8]. Pkb/Akt can also be upregulated by testosterone and leucine and has the ability

Abbreviations: BCAA, branched chain amino acids; CP, cirrhotic patients; EASL, European Association for the Study of the Liver; EN, enteral nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; FoXO, forkhead transcription factor; GSK 3β, glycogen synthase kinase 3β; IGF1, insulin-like growth factor 1; LC, liver cirrhosis; LES, late evening snack; mTOR, mammalian target of rapamycin; OS, oral supplements; Pkb/Akt, protein kinase B; SCFA, short-chain fatty acids; TNF-α, tumor necrosis factor-α.

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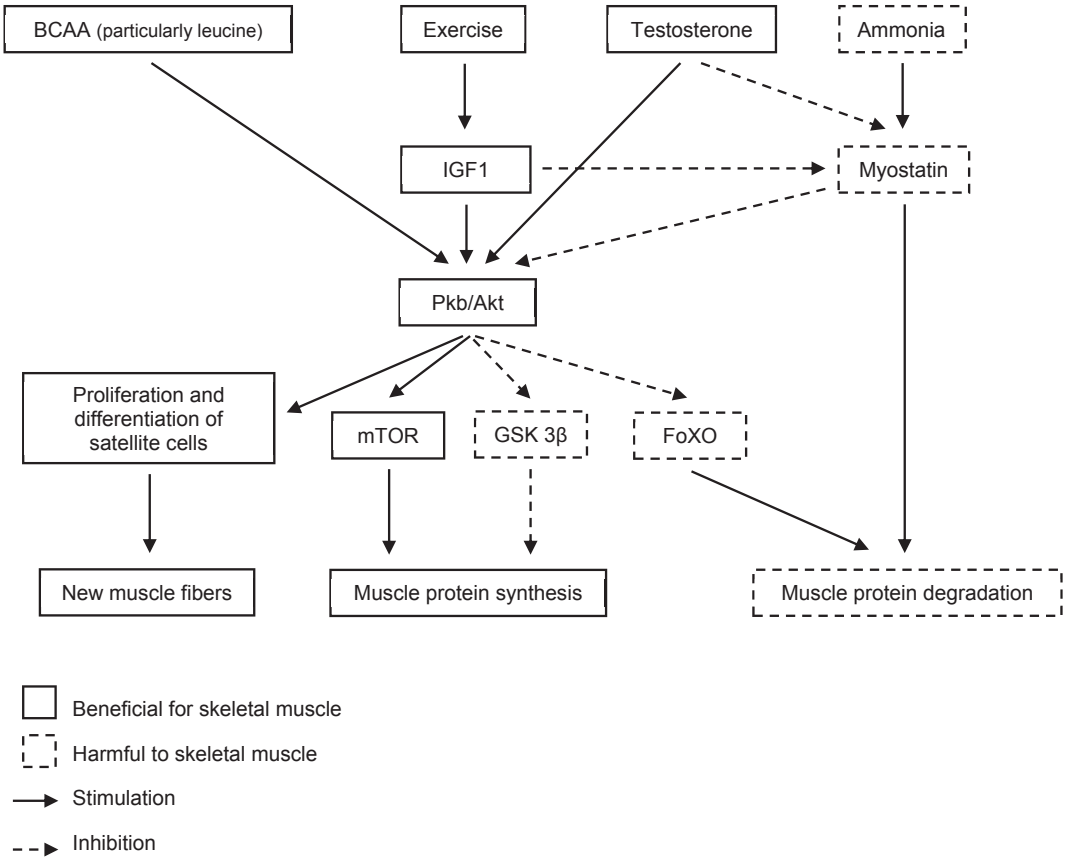

Fig. 1. Regulation of muscle growth.

to activate satellite cells, precursors of new muscle fibers [6]. In opposition, myostatin which is upregulated by testosterone and ammonia levels [6], has an inhibitory effect on muscle growth through the suppression of Pkb/Akt [9] and a catabolic effect on skeletal muscle [8]. The main pathways for its proteolysis are the ubiquitin-proteasome pathway and the autophagy process [6].

2.1. Causes and potential therapeutic targets

There are several factors that predispose cirrhotic patients (CP) to sarcopenia, such as: i) nausea and early satiety caused by ascites, enteropathy and delayed gastric emptying [10], ii) anorexia caused by increased levels of leptin and tumor necrosis factor (TNF-α) [10], iii) alteration of palate due to zinc deficiency [10], iv) physical inactivity or obesity [10], v) hypermetabolism caused by systemic inflammation [10], vi) inadequate nutrition intake and low socioeconomic status associated with alcoholism [10], vii) low dietetic intake caused by inappropriate counseling or self-imposed restrictions [10], viii) small intestinal bacterial overgrowth [10], ix) early gluconeogenesis after short periods without nutritional intake [11]. The treatment of sarcopenia in LC that has been suggested is focused on hormone replacement, antibiotics and gut microbiota manipulation, ammonia reduction, myostatin antagonists, nutritional supplementation, such as branched chain amino acids (BCAA) supplements [6,12,13]. Finally, treatment of portal hypertension [6] and liver transplantation also significantly improve sarcopenia [12,13].

3. Nutritional support in LC

Regarding nutritional guidelines in LC, the American Association for the Study of Liver Diseases recommend an energy intake of 35–40 kcal/kg/day [14], while European Association for the Study of the Liver (EASL) recommends at least 35 kcal/kg/day in non-obese CP [15]. In most recent guidelines, ESPEN recommends 30–35 kcal/kg/day in patients with muscle depletion [16]. As for protein intake, the three societies are consensual in the 1.2–1.5 g/kg/day [14–16], although ESPEN advises specifically to provide 1.5 g/kg/day in patients with muscle depletion [16]. Concerning the protein origin, one third should come from dairy products, a third from sources of vegetable origin, and a third from non-dairy animal origin [17].

In the case of inadequate oral food intake, ESPEN recommends oral supplements (OS) or enteral nutrition (EN) [18], although EASL only recommends EN in malnourished CP with inadequate oral diet [15]. EN is recommended despite the presence of esophageal varices, improving not only nutritional status [18], but also liver function and disease's prognosis [16,18]. Notwithstanding most awake patients reject tube placement so EN should be reserved for obtunded or comatose patients. The EN formulation indicated for CP is polymeric formula, however in the presence of ascites it should be of high energy density in order to reduce fluid intake and in the case of hepatic encephalopathy the formula should be enriched in BCAA [18,19].

In advanced cases of LC, severely malnourished patients benefit from supplementation with EN in addition to oral feeding [18] and the use of BCAA-enriched formulas have shown improvements in survival [16]. However, in cases of less severe LC the best nutritional intervention seems to be the promotion of oral feeding along with customized nutritional advice [18]. Nevertheless, according to the review launched by Cochrane in 2012 there is no evidence for the regular use of parenteral nutrition, EN and OS in patients with liver disease [20].

According to ESPEN guidelines, long-term oral BCAA supplementation improves event-free survival and quality of life in advanced LC [16]. BCAA have been used in these patients to restore muscle mass and enhance hepatic encephalopathy, although there is no strong evidence supporting significant improvement in nitrogen balance [21]. There is a suggestion that this supplementation may be initiated in all patients with a BCAA/tyrosine ratio <4, even in compensated LC [22]. However, the ideal timing for this supplementation remains unclear [22]. In Japan the treatment of LC due to hepatitis C virus infection includes the use of BCAA supplementation in maintenance of liver function and prevention of hepatocellular carcinoma [23]. The ratio usually used is 1.2:2:1 of the amino acids valine, leucine and isoleucine, respectively [23–25]. In the new EASL guidelines on nutrition, BCAA supplementation is only recommended in decompensated CP when oral diet is insufficient to achieve adequate nitrogen intake [15].

LC is characterized by a change in the normal substrate usage, due to a preference for lipid and protein oxidation and a decrease in glucose oxidation [26–28]. CP should maintain a large number of small meals (nibbling pattern) rather than a small number of large meals (gorging pattern), as they tend to develop a metabolic state similar to starvation after short periods without food intake [22,28].

In fact, after just an overnight fast these patients have a metabolic status similar to healthy subjects on 2–3 days of fasting [29]. In LC there is a preference for lipid substrate usage instead of carbohydrates and this preference can be improved through nocturnal caloric supplementation [22,27], therefore highlighting the importance of meal timing in this disease [22]. Thus, late evening snack (LES) appears to be very important in CP [15,29–32], not only because it is associated with an increase in lean mass but also because it inhibits the increase of blood glucose levels, enhances nitrogen balance, increases respiratory quotient [29], and improves glucose [29,32] and fat oxidation [32]. Besides, LES seems to show greater benefits than daytime supplementation in CP [11]. In most studies, LES was consumed between 21 and 23 h and, when compared to isolated energetic supplementation it seemed to promote greater benefits regarding nitrogen retention and substrates utilization [29]. Regarding composition of this meal, it seems to be more effective when enriched with BCAA, although an ideal proportion of these amino acids is yet to be defined [29]. LES with high energy density, as well as an amount of at least 50 g of carbohydrates, will have clinically significant enhancements in body composition and prognosis [29,31].

Even though scientific evidence concerning LES in clinical outcomes is scarce, it is the only nutritional intervention that is easily accessible, “without side effects” and with clinical potential to reverse sarcopenia in CP. LES represent an unique opportunity to promote the anabolic process [29].

3.1. BCAA

BCAA are essential amino acids metabolized by skeletal muscle, and in LC, their serum values are decreased [6,13]. These amino acids, through detoxification of ammonia [33], may promote a decrease in myostatin, which is beneficial for the protection of muscle mass [6,12,13]. It is also suggested that BCAA can improve carbohydrates metabolism [33], leading to a lower gluconeogenesis rate, and per se, a lower protein catabolism. In the first decade of this century benefits from BCAA supplementation in prognostic markers of LC have been showed [25,34] and recent studies confirm these findings [35,36]. In 2015, Tsien et al. found that BCAA supplementation benefits protein synthesis in CP [37] while in 2017, Uojima et al. showed that BCAA supplementation increases CP muscle strength [38]. Hiraoka et al. showed that BCAA supplementation together with an increase of 2000 steps/day, leads to an increase of muscle mass and strength of CP [39]. On the other hand, Kitajima et al., in 2018 suggested that BCAA supplementation does not influence CP muscle mass, but improves hypoalbuminemia, which relates with decreased intramuscular fat, maintenance of muscle mass and increased glucose sensitivity, all of which are factors that increase CP survival [36].

In 2017, a systematic review from Cochrane, analyzing the effect of BCAA in patients with hepatic encephalopathy showed benefits in reversing this specific condition. However, it failed to demonstrate an effect on mortality, quality of life or nutritional parameters [19]. Notwithstanding, in the most recent systematic review regarding BCAA in LC, Ooi et al. concluded that BCAA supplementation may improve muscle strength but did not find a clear association with other measures of lean body mass [40]. The same authors found positive effects of BCAA supplementation on free fat mass in infants and children [40]. Table 1 summarizes the evidence concerning BCAA supplementation on nutritional parameters in LC.

3.2. Glutamine

Two decades ago an effect of glutamine supplementation in CP was hypothesized, mainly because it stimulates skeletal muscle protein synthesis and is indirectly involved in the reduction of intestinal permeability and endotoxemia [41]. In 2011, an in vitro study on murine muscle cells revealed a potential interest in

Table 1
BCAA supplementation in LC.

Authors	Year	Study type	Sample size	Follow-up	Conclusions
Tsien et al. [37]	2015	Clinical trial	14	Not applicable	BCAA supplementation acutely reversed the impaired mTOR signaling and increased autophagy.
Gluud et al. [19]	2017	Systematic review	827	Not applicable	BCAA supplementation had no effect on nutritional parameters.
Park et al. [35]	2017	Retrospective cohort	307	2 years	Long-term oral BCAA supplementation had beneficial effects in patients with advanced LC.
Uojima et al. [38]	2017	Clinical trial	82	24 weeks	BCAA supplementation improved low muscle strength in patients with chronic liver disease but did not increase muscle mass during the treatment period.
Hiraoka et al. [39]	2017	Clinical trial	31	3 months	BCAA supplementation and walking exercise were effective in improving muscle volume and strength in CP.
Kitajima et al. [36]	2018	Clinical trial	21	48 weeks	Amelioration of hypoalbuminemia associated with BCAA supplementation correlated with decreased fat accumulation in skeletal muscle, maintenance of skeletal muscle.
Ooi et al. [40]	2018	Systematic review	3241	Not applicable	BCAA supplementation may be beneficial in improving muscle strength but no effect was found in other measures of lean body mass. Positive effects on free fat mass in infants and children with end-stage liver disease were also observed.

Table 2
Glutamine in LC.

Authors	Year	Study type	Sample size	Conclusions
Oppong et al. [43]	1997	Observational study	17	Oral glutamine challenge impaired more subtle tests of central nervous system function.
Rees et al. [44]	2000	Randomized control trial	15	Oral glutamine challenge increased ammonia blood levels.
Ditisheim et al. [45]	2011	Observational study	57	Oral glutamine challenge increased cases of minimal hepatic encephalopathy.
Irimia et al. [46]	2013	Prospective study	54	Oral glutamine challenge increased cases of minimal hepatic encephalopathy.

supplementing glutamine as a strategy to increase muscle mass. Glutamine not only prevented TNFα-induced loss of skeletal muscle protein, but also normalized myostatin levels, whose presence is associated with overexpression of ubiquitin ligase atrogin-1 and increased activity of the Ca^{2+}-dependent proteolytic system [42].

Nevertheless it is important to state that Oppong et al. revealed that oral glutamine load compromised reaction time and mean electroencephalography amplitude, significantly impairing more subtle tests of central nervous system function [43]. Additionally Rees et al. showed that oral glutamine load in CP promoted an increase in ammonia blood levels [44]. More recently, Ditisheim et al. and Irimia et al. found an increase in the diagnostic of minimal hepatic encephalopathy after an oral glutamine load [45,46]. Table 2 summarizes the few evidence regarding an oral glutamine load in LC.

3.3. Gut microbiota

Gut microbiota plays an important role in producing short-chain fatty acids (SCFA), whose absorption seems to be crucial for the release of IGF1 [47], an essential molecule in the anabolic process [7,8]. Besides the important role in producing SCFA, whose production is essential for improving insulin sensitivity, mitochondrial biogenesis, energy production, and modulation of inflammation, has also the capacity to produce folate, vitamin B_2, B_{12}, glycine betaine, tryptophan and urolithins, molecules with possible interest at muscular level [48]. Folate influences amino acid biosynthesis and DNA synthesis, methylation and repair [48]. Vitamin B_2 is involved in the enhancement of oxidation-reduction reactions, energy production and fatigue resistance [48]. Vitamin B_{12} is critical in preserving muscle strength, while glycine betaine and tryptophan through IGF1 synthesis, promote anabolism and cell proliferation [48]. Finally, urolithins promotes skeletal muscle cell preservation, mitochondrial activity and biogenesis, and muscle growth [48].

Literature on gut microbiota composition impacting muscle is scarce [48]. However, Buigues et al. found an improvement in muscle exhaustion and handgrip strength when a prebiotic (mixture of inulin + fructooligosaccharides) was ingested, compared to a placebo (maltodextrin) over a period of 13 weeks in a nursing home population [49].

It should also be noted that LC is a disease regularly associated with the use of antibiotics [50–52] and this practice has some risks regarding the diversity, composition and functionality of the microbiota [52]. Although there is not strong evidence that changes in microbiota results in muscle loss, it has been suggested that muscle adiposity can be regulated by this gut microorganisms [53]. Thus, knowing that intramuscular fat adversely affects muscle strength [54–56] and gait independence [55] (parameters evaluated in the diagnosis of sarcopenia), it could be possible to presume that the use of antibiotics may interfere with the pathophysiology of sarcopenia.

3.4. Alcohol

The effect of alcohol consumption on sarcopenia in CP remains sparsely studied. Alcohol has an opposite effect on the pathways that stimulate mTOR and is also a promoter of the skeletal muscle autophagy process, leading to increased muscle loss [17,57]. In a recent meta-analysis published by Steffl et al., including studies with non-cirrhotic elderly individuals, the effect of alcohol consumption on the development of sarcopenia was not proven [58]. However, alcoholic cessation is essential not only in maintaining compensated LC but also in increasing these patients' survival [59].

4. Conclusion

Sarcopenia is an important complication of LC, and should be considered along with hepatic encephalopathy, ascites and esophageal varices. Therefore, it is of the utmost importance to direct nutritional support to this prevalent problem. The current state-of-art recommendation for treatment of this complication, consists on a high protein diet (1.5 g/kg/day) with 30–40 kcal/kg/day and several meals throughout the day, being LES intake with at least 50 g of carbohydrates of special importance. Currently, the research focus is on supplementation that may be useful in CP, not only from a direct nutritional point of view, but also aiming at microbiota optimization, thus leading to a better nutritional status and muscle function [60,61].

Despite the growing interest in the impact of sarcopenia in CP, standardization of diagnostic criteria for this syndrome, the role of gut microbiota, as well as the most appropriate nutritional therapy (BCAA and glutamine) are expected to deserve more attention from the scientific community in the near future.

Further research with randomized controlled trials design regarding BCAA and glutamine supplementation are needed. The main outcomes should be related with nutritional status, specifically, muscle mass, strength and performance.

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JV participated in conceptualization and investigation. JV and MP wrote the original draft. CSG, JS and HCP reviewed and edited. JV, CSG, JS and HCP participated in visualization.

Competing interests

The authors declare no competing interests.

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