



Review

The Role of Physical Activity and Nutrition in the Sarcopenia of Cirrhosis

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Abstract: The aim of this review is to understand how physical activity and nutrition are involved in the improvement of sarcopenia in patients affected by liver cirrhosis. The pathogenesis of sarcopenia in cirrhosis involves three major factors: inadequate dietary intake, metabolic disturbances, and malabsorption. Although in the early stages muscles appear to be spared, sarcopenia progressively leads to mobility limitations and its consequences, such as propensity to falls and drastically reducing life quality. Several studies confirm the important role played by physical activity and balanced nutrition in this chronic condition. Exercise and nutritional intervention should be recommended in these patients in order to improve quality of life.

Keywords: hepatic cirrhosis; sarcopenia; muscle loss; nutrition; physical activity

1. Introduction

Cirrhosis of the liver is responsible for 13.7%–14.7% of age-standardized death rates across the world. The onset of the condition results from chronic or long-lasting aetiological factors such as long-term excess alcohol consumption, infectious diseases like hepatitis B and C, and non-alcoholic fatty liver diseases (NAFLD), usually arising as a result of the metabolic syndrome [1]. Patients with end-stage liver disease show a higher prevalence of malnutrition, which is associated with increased morbidity and mortality [2]. Clinical complications are in part due to generalized tissue wasting, especially the loss of muscle mass [2]. Patients with more advanced cirrhosis are catabolic and are usually significantly affected by malnutrition and sarcopenia as a result.

Energy balance (EB) is composed of energy intake and energy expenditure. A correct EB is closely related to healthy weight maintenance. When food intake is less than energy expenditure (negative EB), the depletion of energy stores and consequent weight loss have a negative effect on patient outcome [2].

The liver plays an essential role in the supply, passage and metabolism of essential nutrients like proteins, fat and carbohydrates to all parts of the body. If this process is altered, all the functional properties of the liver are impaired and the effect is an increased protein catabolism, decreased hepatic and skeletal muscle glycogen synthesis and finally increased lipolysis [3]. Therefore, chronic liver disease undernutrition, due to dietary restriction, altered nutrient biosynthesis and modified intestinal absorption, is responsible for an enhanced protein loss and pro-inflammatory cytokine levels, resulting

in a catabolic state [3] with myopathies and general sarcopenia. Such sarcopenia is associated not only with the aggravation of other complications of cirrhosis such as ascites, hepatic encephalopathy, and portal hypertension, but also with NAFLD in individuals affected by metabolic syndrome [4,5]. Loss of muscle mass directly contributes to exercise intolerance and impaired activities of daily living, which makes it a strong determinant of quality of life and subsequent mortality [6]. Indeed, the survival rate in patients with sarcopenia is significantly lower than in patients without sarcopenia [5]. The aim of this narrative review is to explore the interrelationship between sarcopenia and liver disease and the possible beneficial role of nutrition and physical activity.

2. Sarcopenia

Sarcopenia is a syndrome characterised by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and, ultimately, death [7]. Although the primary cause of muscle depletion is aging, sarcopenia can also occur in patients with chronic disease, particularly in end-stage liver disease. The most typical symptom of sarcopenia is muscle wasting, defined as a progressive and generalized loss of muscle mass [8]. The first manifestation of sarcopenia is atrophy: the muscle progressively reduces its size, muscle fibres are replaced by fat and fibrous tissue, with increased oxidative stress, muscle metabolism changes, and neuromuscular junction degeneration arises, leading to progressive loss of muscle function and frailty [8,9]. For the diagnosis of sarcopenia, the European Working Group on Sarcopenia in Older People recommends using the presence of both low muscle mass and reduced muscle function (strength or performance). Several techniques can be used to quantify muscle mass, including three imaging techniques: computed tomography, magnetic resonance imaging and dual energy X-ray absorptiometry. However, there are fewer well-validated tools to assess muscle strength. Handgrip strength is widely used and correlates well with most relevant outcomes, although the lower limbs are more important than the upper limbs for gait and physical function. Furthermore, to assess physical performance, a wide range of tests are used, including the Short Physical Performance Battery, usual gait speed, 6-min walk test and the stair climb power test [7].

The pathogenesis of sarcopenia in cirrhosis has three major contributory causes: inadequate dietary intake, metabolic disturbance and malabsorption. There are several factors responsible for an altered dietary intake in patients with cirrhosis. Some report nausea, early satiety and loss of appetite. This commonly depends on the presence of ascites, upregulation of leptin and tumor necrosis factor- α [10] and zinc deficiency, which is usually responsible for altered taste sensation [11]. Altered visceral motility, and the overgrowth of small intestinal bacteria are also very common [12]. Sodium restriction, decreased protein intake and iatrogenic fasting during hospitalization contribute to aggravating poor oral intake (Figure 1).

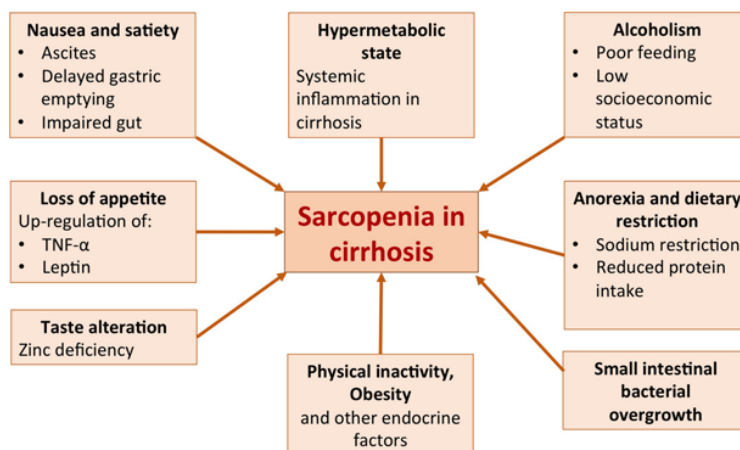


Figure 1. The pathogenesis of sarcopenia in patients with cirrhosis.

As previously described, the liver plays a critical role in the body's metabolic homeostasis and especially in the synthesis and storage of glycogen. The cirrhotic liver tissue loses the capacity for this physiological function with increasing decompensation, resulting in the breakdown of fat and muscle and finally in the promotion of gluconeogenesis from non-carbohydrate sources [13]. This process leads to muscle wasting. Malabsorption of nutrients in patients with cirrhosis may also be a consequence of chronic pancreatitis, as a result of alcohol abuse, or intraluminal bile acid deficiency, because of its decreased production, and overgrowth of bacteria in the intestine [14]. Paradoxically, sarcopenia may also be related to obesity, particularly in the context of NAFLD cirrhosis. Indeed, there are frequent citations in the current literature describing this co-morbidity condition. The prevalence of this condition, also known as sarcopenic obesity is more frequent in women than in men, with a reported a range from 4% to 84% in men and from 4% to 94% in women [15]. Moreover obesity is known to be closely related to hepatic steatosis [4]. Several recent studies showed a relation between low skeletal muscle mass and fatty liver [4]. Insulin resistance is linked both with excess fat tissue and sarcopenia, given that skeletal muscle is one of the major target tissues of insulin action [4]. However, insulin resistance is not the only factor involved in the development of hepatic steatosis and other hormones have effects on body composition, lipid and glucose homeostasis. Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) may be involved and this could explain the interrelationship between liver steatosis and sarcopenia [4]. Several studies showed how GH secretion is blunted in obese subjects, with GH and IGF-1 linked to fatty infiltration of the liver [4]. Moreover, ectopic fat deposition has proven to be associated with reduced GH levels. Impairment in GH production occurring with aging is one of the factors causing the changes in body fat and muscle compartments leading to both excess adiposity and sarcopenia [4].

Although sarcopenia is important as a prognostic factor in the clinical setting of liver disease, current prognostic clinical scores do not include sarcopenia and are not completely satisfying. A recent study indicates that sarcopenia is present in almost one half of patients with cirrhosis evaluated for liver transplantation [16] and that it is independently associated with a twofold risk of mortality. Thus, several authorities have proposed the modification of MELD (Mayo End stage Liver Disease) to include sarcopenia (MELD-sarcopenia), given that its inclusion is associated with improvement in the prediction of mortality in patients with cirrhosis [17].

3. Physical Activity

Exercise training has to be planned according to strength and resistance, flexibility and balance/gait training of the body [18]. Given that exercise capacity in patients with cirrhosis is reduced, regimens must be tailored for gradual exercise increments [19]. One of the main concerns with respect to physical activity in patients with cirrhosis is the risk of causing complications of the underlying liver disease [16].

Nevertheless, it is clear that muscle wasting increases fatigue, reducing the possibility of practising physical exercise and finally leading to the worsening of sarcopenia through inactivity (Figure 2).

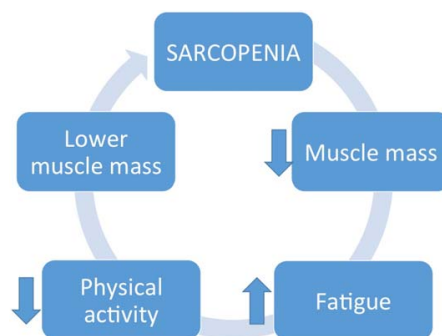


Figure 2. The vicious cycle of sarcopenia. “↑”: increase; “↓” decrease.

As previously stated, the mechanisms responsible for these changes are related to protein synthesis and metabolic alteration, leading to sarcopenia and cardiomyopathy. To this end, patients with cirrhosis demonstrate a decreased cardiac response to exercise [19]. Moreover, the severity of liver disease appears to be related to the extent and severity of sarcopenia and cardiomyopathy and finally to a consequent reduction in exercise capacity [19]. Despite this evidence and the decreased exercise capacity and muscle strength in patients with cirrhosis of the liver, it also seems that the only single useful intervention in the treatment of muscle wasting in sarcopenia is physical activity. No other therapeutic interventions are known. Exercise training attenuates or even reverses the process of muscle wasting, thanks to anti-inflammatory and anti-oxidative effects able to oppose the pathways associated with protein degradation [6]. Exercise training programs have been performed in patients with autoimmune hepatitis in clinical remission while receiving immunosuppressive therapy. The physical training was well tolerated, since the clinical condition did not worsen, and physical performance capacity improved [20]. In a recent study, patients with cirrhosis underwent a moderate intensity exercise program, although this uncovered previous complications of cirrhosis in those who were otherwise compensated at the time of the study. Other studies reported that in patients with portal hypertension not undergoing beta-blockers therapy, exercise could lead to an increased risk of variceal bleeding through an increase in portal pressure [21]. However, subjects with previous variceal bleeding or with large esophageal varices on secondary or primary bleeding prophylaxis with β -blockers and/or variceal ligation did not present adverse effects from the exercise programme [16]. Patients undertook a 12-week exercise program of treadmill walking and cycle ergometry, consisting of 1-h sessions, three days a week, similar to programs used in other studies on patients affected by chronic heart or respiratory disease [16]. The moderate exercise programme associated with leucine supplementation improved exercise capacity, leg muscle mass and quality of life. Basal exercise capacity was significantly impaired due to decreased muscle strength, deconditioning, fatigue, neuropsychiatric factors and cardiorespiratory impairment secondary to hepatopulmonary syndrome or hepatic cardiomyopathy.

Another interesting and recent survey performed in a Japanese cohort showed how walking 5000 or more steps per day and maintaining a total energy intake of approximately 30 kcal/ideal bodyweight may be a goal sufficiently great to prevent sarcopenia in compensated cirrhosis patients. The study showed that both of these targets have to be reached in order to secure an energy intake sufficient for synthesis of body protein. Moreover, this standard of physical activity is necessary to maintain and increase skeletal muscle mass [22]. Nevertheless, it should be highlighted that performing physical activity with insufficient nutrients and proteins intake could be detrimental in patients with decompensated cirrhosis, since it could promote further protein catabolism and loss of muscle mass. Thus, a proper nutritional assessment and supplementation are necessary before initiating exercise programs in such patients. It should be noted, however, that patients with ascites and marked stimulation of vasoconstrictor systems (renin-aldosterone and sympathetic nervous systems), could have an impairment of renal function after exercise. Nevertheless, a tailored, adapted physical activity program (cycloergometry + muscle strengthening according to ventilatory threshold) for 12 weeks seems feasible and sufficiently safe in patients awaiting liver transplant [21].

4. Nutrition

Food intake is commonly decreased in patients with advanced liver disease due to the presence of nausea, early satiety, anorexia, vomiting and drug use [2]. Malnutrition is a frequent complication in patients with cirrhosis of the liver and is also an important prognostic factor [2].

The assessment of nutritional status is also necessary for the treatment of patients with end-stage liver disease [5]. In such patients, undernutrition is caused by poor dietary intake, malabsorption, impaired protein synthesis, and acceleration of protein breakdown, which lead to the development of sarcopenia. Negative EB is highly prevalent among patients on the waiting list for liver transplants, and is also associated with the severity of liver disease. A recent research study demonstrated that low food intake is the principal factor responsible of this negative EB [2].

People with chronic liver disease show alterations in energy metabolism, resulting in amino acid oxidation and protein deficiency [3]. Moreover end-stage liver disease patients exhibit early onset of gluconeogenesis after short-term fasting, due to the decreased ability to store glycogen as a consequence of reduced liver function. This accelerates the metabolic reaction to starvation and explains the increased protein requirements and muscle depletion of those with established cirrhosis [23]. Additionally, fat-soluble vitamin deficiencies and diminished reserves are related to cirrhosis of the liver, and this results in an increased severity of both end-stage liver disease and sarcopenia [3,24,25].

Both anorexia and obesity worsen sarcopenia. Anorexia and a reduced dietary intake decrease the nutritional components which are essential for movement, while obesity contributes to worsening sedentary life. Nevertheless, a fatty and rich diet associated to physical inactivity lead to the formation of fat deposits, which are also able to produce proinflammatory adipokines, and inflammatory consequences, such as a catabolic effect on muscle mass [26–29]. Both anorexia and obesity finally lead to the loss of metabolically active components accompanied by an impaired body energy balance (Figure 3).

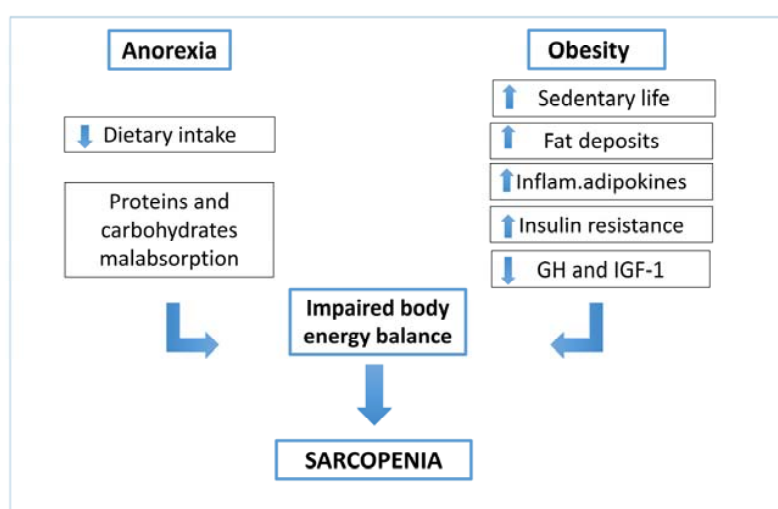


Figure 3. The effects on body energy balance of impaired dietary intake. GH: Growth hormone; IGF-1: insulin-like growth factor 1, “↑”: increase; “↓” decrease.

This process is also worsened with aging where lean muscle mass changes [27]. In patients with cirrhosis, obesity is closely linked to fatty liver and insulin resistance, and can accelerate hepatic decompensation, enhance hepatocarcinogenesis, and result in poor patient survival. Thus, nutrition management is imperative for obese patients with cirrhosis [24]. As previously stated, sarcopenia is more frequent in women than in men due to reduced muscle mass in women and lower muscle strength compared to men, and finally a major predisposition to accumulate body fat [15].

In cirrhosis, the nutritional status must be accurately assessed in the individual patient in order to tailor the nutritional intervention, prevent complications and improve survival and quality of life. Amodio *et al.* recently published some nutritional recommendations [30]. According to these recommendations, hepatotoxic agents, such as alcohol, should be avoided and the correct daily energy intake should be approximately about 35–40 kcal/kg body weight, distributed in 4–6 meals per day, enough to restore and maintain nutritional status and help liver regeneration. Protein intake should be about 1.2–1.5 g/kg body weight, according to the severity of undernutrition. Since cirrhotic patients are predisposed to entering a starvation state after a relatively short fasting period, small and frequent meals (“nibbling” pattern), rather than a small number of large meals (“gorging” pattern), is considered preferable to maintain optimal energy metabolism [23]. Indeed, this pattern of meals throughout the day and a late-night snack of complex carbohydrates can help in minimizing gluconeogenesis from

protein utilization [31,32]. Moreover, a randomized controlled trial in cirrhosis patients suggested that nocturnal energy supplementation may be superior to daytime energy supplementation for protein accretion [33]. A lack of branched chain amino acids (BCAAs) in cirrhotic patients can worsen muscular protein catabolism, decrease the synthesis of albumin, and is associated with hepatic encephalopathy [23]. The oxidative use of glucose by skeletal muscle is regulated by BCAAs through the stimulation of glucose recycling via the glucose-alanine cycle [23]. In particular, leucine seems to play a crucial role in carbohydrate metabolism [34]. Skeletal muscle tissue is also crucial for the removal of plasma ammonia and, in turn, hyperammonemia impairs skeletal muscle synthesis, contributing to worsening of sarcopenia and hepatic encephalopathy. In a recent study, the effects of leucine alone or in combination with physical activity (15 min at 10 cm/s) every other day for five weeks were tested in a rat model of cirrhosis. Leucine treated rats showed an improvement in muscle mass and metabolic activity, further ameliorated by exercise, beyond an improved cognitive and psychomotor function [21]. Minerals also have a great importance in a correct diet and zinc, magnesium and selenium in particular [30]. Reduced levels of sodium have a detrimental effect on brain function, contributing to hepatic encephalopathy. Moreover dietary sodium restriction is usually prescribed to patients with ascites, although the poor evidence for this recommendation. Sodium intake should not be less than 60 mmol/day, because otherwise the diet becomes unpalatable, compromising total energy and protein intakes. Hyponatremia is more likely to occur when the intake of sodium is low, while the intake of water is maintained or increased. Thus, careful monitoring of sodium and water balance is required [30].

5. Conclusion

Sarcopenia is a common complication in people afflicted by cirrhosis of the liver, owing to a great number of mechanisms that contribute to muscle wasting. Among these, a reduced nutrient intake is associated with decreased taste sensation and appetite, nausea and early satiety, but also dietary restrictions in sodium and water in order to prevent fluid accumulation. Undernutrition and physical inactivity worsen the clinical course of patients with cirrhosis, leading to sarcopenia. Several studies confirm the important role played by physical activity and balanced nutrition in chronic liver disease. Tailored exercise and nutritional intervention should be strongly recommended in these patients in order to improve people's quality of life.

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Abbreviation

BCAA	Branched Chain Amino Acids
EB	Energy Balance
MELD	Mayo End stage Liver Disease
NAFLD	Non-alcoholic Fatty Liver Disease

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