Role of Exercise in the Management of Hepatic Encephalopathy: Experience From Animal and Human Studies

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Sarcopenia and malnutrition are common features in patients with hepatic encephalopathy. Ammonia, a factor implicated in the pathophysiology of hepatic encephalopathy, may be cleared by the muscle via the enzyme glutamine synthetase when the liver function is impaired. Hence, optimizing muscle mass in patients suffering from hepatic encephalopathy is a potential strategy to decrease ammonia levels. Exercise could be an efficient therapeutic approach to optimize muscle mass and therefore potentially reduce the risk of hepatic encephalopathy in patients with chronic liver disease. This review reports the current evidence regarding exercise and hepatic encephalopathy from animal and human studies. After defining concepts such as frailty, sarcopenia, and malnutrition, the present knowledge regarding exercise as potential therapy in cirrhotic patients with or without hepatic encephalopathy is discussed. Recommendations and future aspects are also considered. (J CLIN EXP HEPATOL 2019;9:131–136)

HEPATIC ENCEPHALOPATHY AND SKELETAL MUSCLE

Hepatic encephalopathy (HE) is a debilitating complication of liver disease and is characterized by a constellation of symptoms, including cognitive, psychiatric, and motor disturbances, and can progress to coma.¹ In this review, we only focus on HE caused by chronic liver disease. The pathophysiology of HE is multifactorial and is still incompletely understood. However, hyperammonemia is believed to play an important role.¹

Skeletal muscle may substitute the liver in clearing ammonia during cirrhosis because it contains the enzyme glutamine synthetase which removes ammonia via the amidation of glutamate to glutamine. Therefore, muscle mass depletion from malnutrition and increased catabolism may impair the removal of ammonia from the systemic circulation, increasing the risk of hyperammonemia in patients with cirrhosis. Supporting this, a study showed that HE occurs more often in patients with sarcopenia than in nonsarcopenic patients.² Conversely, hyper-

ammonemia itself may precipitate sarcopenia by an impaired protein synthesis and increased autophagy.³

FRAILITY, COGNITIVE DYSFUNCTION, SARCOPENIA, AND MALNUTRITION

Frailty is an independent predictor of mortality in cirrhosis and a condition characterized by low physiologic reserve, increased vulnerability, and decreased functional status. As much as 40% of patients with cirrhosis are functionally impaired, with 1 of 5 patients considered frail.⁴ The concept of frailty is a multidimensional construct; it is the manifestation of multiple processes including cognitive dysfunction, sarcopenia, and malnutrition, all of which share and reinforce the same pathophysiological processes (Figure 1).

Cognitive Dysfunction

Cognitive dysfunction is the loss of intellectual abilities used for perceptions, acquiring, understanding, and responding to information presented to a person. This can affect a person's thought, memories, and reasoning capabilities.

Sarcopenia

Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength or physical performance, and it is strictly correlated with physical disability, poor quality of life, and death. Although it is primarily a disease of the elderly, its development may be associated with conditions that are not

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Abbreviations: BCCA: Branched-Chain Amino Acids; HE: Hepatic Encephalopathy; HVP: Hepatic Portal Vein Pressure

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Figure 1 The concept of frailty as a multidimensional construct.

exclusively seen in older persons. Sarcopenia or muscle wasting from malnutrition and increased catabolism is a critical component of frailty. Specifically, in patients with cirrhosis, sarcopenia is of clinical importance as it can also affect their quality of life.⁵

Malnutrition

Malnutrition is the most frequent complication of chronic liver disease.⁶ Although there is no single generally agreed definition of malnutrition, this condition is commonly defined by the presence of nutrient imbalance as a result of the deficiency or excess in nutrition. In cirrhosis, malnutrition is identified as undernutrition. Patients with chronic liver disease are particularly vulnerable to developing malnutrition because of the key role played by the liver in regulating nutritional state and energy balance. The presence of chronic liver disease can also reduce the appetite and thus influence the nutrient intake.⁷ Therefore, the causes of malnutrition in this patient population are multifactorial in nature. HE contributes to frailty in 2 ways. First, each stage of the spectrum of HE from early deficits in executive functioning to coma is associated with decreased function. Second, HE is associated with sarcopenia or severe muscle wasting.

MUSCLE MASS AND FUNCTION OPTIMIZATION STRATEGIES

As mentioned previously, muscle mass may contribute to the removal of plasma ammonia and, in turn, hyperammonemia may impair skeletal muscle synthesis, contributing to worsening of sarcopenia; further loss of muscle mass may play a role in precipitating/worsening HE.⁸ However, the amount and quality of muscle mass may dictate its efficiency in removing ammonia. Therefore, optimizing

muscle mass and function may become an important strategy in attenuating cirrhosis-related complications, including HE. One interesting, simple and low-cost approach that may impact muscle mass in HE is exercise training; targeting the muscle with exercise could be an efficient therapeutic strategy in reducing the risk of HE in patients with chronic liver disease.⁸

Exercise

Investigations regarding the effects of exercise on chronic liver disease and its complications are relatively recent and scarce.^{9,10} There is an important association between inactivity and losses of muscle mass and strength. Regular physical activity favorably impacts the risk for disease onset and progression of several chronic diseases. Also, there are other potential benefits related to physical exercise including increased bone mineral density, insulin sensitivity, quality of life, decreased risk of cancer, cardiovascular, and metabolic diseases such as type 2 diabetes and dyslipidemia.¹¹ Exercise activates protein synthesis, stimulates muscle satellite cell proliferation, both in healthy animal models and in humans, and has been shown to significantly enhance lean mass and strength.¹² This suggests that physical activity may be a protective factor not only in the prevention but also in the management of frailty, sarcopenia, and thus HE. It has been shown that a lack of physical activity exacerbates muscle wasting in cirrhotic patients.⁵

Exercise and Cirrhosis

Patients with cirrhosis show a reduced tolerance to exercise and may disrupt exercise training because of symptoms before reaching their predicted maximal cardiac frequency. Complications from cirrhosis, such as malnutrition, fluid overload, ascites, and fatigue greatly limit physical exercise in this group of patients. However, 4 randomized trials evaluating the role of supervised or home-based exercise in cirrhosis Child-Pugh A/B showed that moderate aerobic exercise is well tolerated and improves skeletal muscle mass in the exercising groups quantified by ultrasound-measured quadriceps thickness, dual-energy X-ray (DXA) leg/appendicular lean mass, and/or thigh circumference.¹³⁻¹⁶ Thus, an improved exercise capacity may reduce the risk of HE through an increased ability to be physically active and thereby increase skeletal muscle mass; however, studies including HE patients should be conducted. The current knowledge on resistance training and muscle mass in cirrhosis and HE is still at an early stage. Preliminary data from an unpublished trial indicate that 12 weeks of supervised progressive resistance training increases muscle strength and muscle size in cirrhosis Child-Pugh A and B patients compared with control subjects and improves physical function and emotional health in exercisers. The increased muscle

mass in the exercisers did not show a change in ammonia metabolism tested by the Oral Glutamine Challenge.¹⁷

Interestingly, exercise-induced hyperammonemia was less evident after a 14-week combined aerobic/resistance exercise program that improved ventilatory efficiency in exercisers. Of supporting nutrition-related outcomes, only phase angle by bioelectrical impedance analysis was reported and improved.¹⁸ Also, one trial investigated the effect of a 12-week aerobic program on the Psychometric Hepatic Encephalopathy Score and Critical Flicker Frequency but showed no effect despite increased thigh circumference; however, HE was not an inclusion criterion, and ammonia levels were normal.¹³

In these small trials testing patients with compensated liver cirrhosis, moderate physical exercise has been reported as safe. A general concern is that exercise may acutely increase hepatic portal vein pressure (HVPG).^{9,19} The latter is a measure of portal hypertension; increased HVPG would be linked to the subsequent higher risk for variceal bleeding.¹⁹ Interestingly, a small trial and an observational study reported that HVPG decreased significantly in patients allocated to 14 weeks of aerobic exercise and kinesiotherapy compared with control subjects, despite the fact that both groups were treated with nonselective beta-blockers¹⁸ and that lifestyle intervention including diet and exercise in overweight patients with cirrhosis lowered HVPG.²⁰ As portal hypertension represents the underlying cause for most of the cirrhosis-related complications and mortality, any intervention capable of lowering the HVPG could translate into positive clinical outcomes in cirrhosis. Despite encouraging results, the long-term effect of physical exercise, particularly on mortality in cirrhosis and HE, are still unknown. Experience from clinical randomized trials is still limited. Studies with larger sample sizes including patients with HE are required for further confirmation.

The optimal exercise program regarding type, variation, and frequency in cirrhosis is still unexamined. In healthy elderly, aerobic exercise especially benefits the cardiopulmonary system, resistance training induces skeletal muscle hypertrophy and increased strength, flexibility exercises maintain range of motion, and balance activities reduce risk of falls. Overall, present evidence has shown that trials of moderate intensity aerobic exercise lasting 8–14 weeks, either supervised or home based, are well tolerated in cirrhosis Child-Pugh A/B with a positive effect on exercise capacity (peak VO₂ and 6-minute walk test), and quality of life.^{13–16,18} The accumulating results on skeletal muscle mass from both resistance and aerobic exercises indicate that the loss in muscle mass seen in cirrhosis may be reversed. No randomized trials have yet investigated the effects of exercise in people with decompensated cirrhosis and HE. A small observational study tested a program of both aerobic and anaerobic exercise on patients awaiting liver transplantation including few participants with cirrhosis Child-Pugh C, and they did not report any

adverse events.²¹ Further investigations are needed to fully understand the mechanisms of exercise in cirrhosis, including effects of exercise on HE and cirrhosis Child-Pugh C.¹⁰ Regarding the setting, home-based programs may reach a larger number of patients. But group exercise may counteract the social isolation and diminished quality of life described in patients with former HE episodes.²²

Exercise and Microbiota

There is increasing evidence that the pathogenesis of HE may be linked to a dysbiotic gut microbiota and to harmful by-products, such as ammonia, indoles, oxindoles, and endotoxins.²³ It has been reported that patients with HE show a different microbiota composition in many regions of the alimentary tract. For example, some specific microbiota composition in the sigmoid colonic mucosa was correlated with good cognition and decreased inflammatory markers, while others were associated with poor cognitive performance.²⁴ Interestingly, exercise has been shown to modulate gut microbiota²⁵ by, among other mechanisms, reducing bacterial translocation in cirrhosis. Exercise might also influence gut microbiota diversity.²⁵ The association between the microbiota, cognition, and inflammatory cytokines in patients with HE show the critical need to study in depth the gut mucosa metabolites because several important processes in the pathogenesis of HE occur at the mucosal interface rather than in the lumen, such as translocation and interactions between the gut microbiota and the immune system. The effect of exercise on the gut microbiota composition in relation with HE should be further investigated.

Nutritional Strategies

An interesting strategy to optimize muscle mass and function is nutrition. It is important to emphasize that exercising under insufficient nutrient and protein intake could be risky in patients with cirrhosis and HE, given that it could promote further protein catabolism and loss of muscle mass. Hence, it is imperative to ensure that the cirrhotic patient is receiving correct and sufficient nutrition. Therefore, a proper nutritional assessment is indicated before initiating physical training in this population. Accordingly, evidence has demonstrated that patients with cirrhosis and HE benefit from nutritional supplementation and high-protein diets.²⁶ It has also been suggested that branched-chain amino acids (BCAAs) supplementation may be beneficial in cirrhosis.²⁷ BCAAs (valine, leucine and isoleucine) are essential amino acids, which, unlike others, are not metabolized by the liver but by the skeletal muscle. BCAAs are mainly responsible for stimulating muscle protein synthesis and inhibiting protein breakdown. Interestingly, it has been speculated that the beneficial effect of BCAA intake on HE demonstrated in clinical studies may be related to an improved muscle mass and

nutritional status rather than to ammonia-lowering effect of BCAA themselves.²⁷ In a Cochrane review, it was also emphasized that BCAA has beneficial effect on HE.²⁸ However, exercise studies did not find any benefit from protein/amino acid supplementation in control groups not exposed to physical training.^{13,18} In line with these results, the effects of leucine (BCAA) alone or in combination with exercise training were tested in a rat model of cirrhosis (6-week bile-duct ligated rat). The bile-duct ligated rat was reported as a relevant model to investigate muscle mass metabolism in cirrhosis and HE.²⁹ Leucine-treated cirrhotic rats showed an improvement in brain edema, muscle mass, and metabolic activity, further ameliorated by exercise. In addition, cirrhotic rats treated by leucine and exercise showed an improved cognitive and psychomotor function, suggesting decreased HE (unpublished data). Interestingly, BCAA supplementation and walking exercise were found to be effective and easily implemented for improving muscle volume and strength in Child-Pugh A/B cirrhotic patients.³⁰ Furthermore, in experimental model of nonalcoholic fatty liver disease, it has been suggested that exercise has effects superior to those of dietary modifications regarding glucose homeostasis and hepatic mitochondrial function. However, effects in relation to HE in this particular etiology of cirrhosis have not been investigated. Overall, in humans, combined exercise and nutritional/BCAA studies with regards to cirrhosis (especially Child-Pugh C) and HE are warranted.

RECOMMENDATIONS, FUTURE RESEARCH, AND CONCLUSION

It is important to emphasize that the knowledge about exercise in cirrhosis and HE is still limited and at an early stage. Several limits from animal and human studies must be considered. For example, one cannot simply translate results from trials including patients with Child-Pugh A/B to patients with HE who are more frequently Child-Pugh B/C. Also, most of the studies were of short duration with a relatively small number of mostly compensated patients and different exercise protocols. Importantly, HE was frequently excluded from protocols. Animal studies testing exercise and chronic liver disease are still very limited, and data are unpublished. The current knowledge on ammonia effect on muscle in cirrhosis still mainly derives from animal studies.

Nevertheless, considering the results to date as well as the limits, several recommendations may carefully be suggested. In HE, frailty and sarcopenia must be managed using a multimodal approach that addresses malnutrition and intensifies therapy for HE. In clinically stable patients, a moderate physical activity level may be encouraged. An exercise program in combination with the optimal nutrition may help to maintain and even increase muscle

mass and thereby prevent sarcopenia and frailty in HE. In people with cirrhosis Child-Pugh A/B, it is reasonable to recommend 3 days per week of moderate physical activity. Trials have tested treadmill walking and ergometry bicycling; this could be transferred to, e.g., outdoor walking or cycling 30–60 min. For example, reaching 5000 steps or more each day is an easy way of increasing physical activity; to this end, a pedometer is a useful approach to track the activity level. Also, an exercise specialist or a physiotherapist in collaboration with the physician can help design an appropriate exercise program consisting of moderate aerobic exercise and resistance training. Nutritional management of patients with HE regarding energy, protein, meal pattern, fibers, micronutrients, and sodium is based on current evidence and consensus opinion²⁶ and is summarized in Table 1. A registered dietitian is the nutrition specialist that can help patients with HE to optimize their nutritional status.

Future research in HE and exercise should aim to investigate the effect of exercise on short- and long-term effects in known patients with HE Child-Pugh A/B and also test a supervised program of nonstrenuous exercise in stable patients with cirrhosis Child-Pugh C. Comparison of different types of exercises, e.g., aerobic and resistance training and settings, should also be addressed to ensure a well-designed, well-tolerated program ideally improving the ability to perform daily living activities and health in patients with HE. The design of intervention studies should include nutritional supplementation and a relatively large sample size. Also, as the gut–liver–brain axis reveals a microbial challenge in HE, studies implicating exercise and nutrition as microbiota modulators should be conducted. Finally, animal studies should be included to provide mechanistic insight into the effects of exercise on skeletal muscle in cirrhosis.

A moderate-exercise regimen along with nutritional optimization may help prevent or attenuate cirrhosis

Table 1 Nutritional Management of Patients With HE.

Nutrient/pattern	Recommendation
Daily energy (kcal/kg)	30–40 ^a
Daily protein (g/kg)	1.2–1.5 ^a
Meal patterns	Small frequent meals throughout the waking hours
Late-evening snacks	Encourage ingestion of 50 g of complex carbohydrate
Daily fibers	Encourage ingestion of diets containing 25–45 g
Micronutrients	Encourage multivitamin ingestion
Sodium (when ascites)	Less than 2000 mg a day $\approx$ 5 g of salt

HE, Hepatic Encephalopathy.

^aDepending on the body mass index and nutritional status and adjusted when obese [see the study by Amodio et al.²⁶ (2013)].

complications including HE. The goal of these therapeutic approaches is to improve sarcopenia and frailty, reduce HE, increase independency, minimize hospitalizations, and improve quality of life and mortality in patients with cirrhosis, but further trials are needed to accumulate knowledge and strengthen recommendations.

CONFLICTS OF INTEREST

The authors have none to declare.

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