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Interventions to improve physical function and prevent adverse events in cirrhosis

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Abstract

Cirrhosis is associated with debilitating complications that significantly impact on a patient’s physical function and reduce quality of life. Owing to highly prevalent sarcopenia, malnutrition and hepatic encephalopathy, functional impairment or frailty is a common complication of cirrhosis. Frailty in turn increases the patient’s risk of hospitalization, accidental falls and fractures, and death. The management of frailty and its associated adverse effects is imperative in improving the overall prognosis of patients with advanced liver disease. The cornerstone of therapy revolves around optimizing physical function with appropriate nutrition and exercise. Nutritional therapy with protein supplementation has shown significant benefit, while studies on exercise have been controversial. However, newly emerging studies trend towards a beneficial effect of physical exercise with improvement in quality of life. The implementation of technology in liver disease management shows future promise. Fitbits and other wearable devices can be used to help monitor a patient’s personal progress in physical exercise and nutritional optimization. Additionally, the progressive development of new smartphone applications to help aid in the diagnosis and monitoring of complications of cirrhosis provides a sophisticated avenue for improving care of patients with cirrhosis.

Key words: Hepatic encephalopathy; frailty; sarcopenia; malnutrition; liver disease

Introduction

Cirrhosis is associated with a multitude of complications that directly impact quality of life and lead to significant morbidity and mortality. A major complication of cirrhosis is frailty—a condition characterized by low physiologic reserve and decreased functional status. Forty percent of patients with cirrhosis are functionally impaired, with one out of five patients considered frail [1]. 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. The impact of frailty, readily apparent in everyday clinical practice, includes falls, fractures, hospitalization, limited recovery from insults and death [1–3]. To prevent such harms, a timely diagnosis of frailty is imperative. Herein, we review the interventions indicated to forestall and possibly reverse frailty.

The concept of frailty

Frailty is a functional assessment that concisely reflects many adverse processes (Figure 1). Patients with severe muscle depletion are often frail because they have lost function. Muscle function relies on muscle strength and bulk, which are reduced in
patients with cirrhosis resulting in weakness. Yet, the function of muscle also involves coordination, executive functioning and balance. Cognitive impairment and neuropathy, such as those observed in hepatic encephalopathy (HE) or ongoing alcohol use, further precipitate frailty by interfering with these processes. At the same time, muscle plays an essential role in the clearance of ammonia in patients with portal hypertension. Further, ammonia metabolism is itself a catabolic process. Even as sarcopenia can lead to hyperammonemia, elevated ammonia levels can, in the setting of malnutrition, precipitate sarcopenia [4]. Malnutrition, common in patients with cirrhosis, is critical to frailty [5]. It is characterized by both inadequate macronutrients and consequential deficiencies in a host of vitamins (e.g. vitamin D deficiency is associated with infections and falls) and

**Figure 1.** A schematic diagram illustrating the complications of cirrhosis that reduce physical functionality and their associated interventions.

*Appropriate nutrition and exercise should be implemented to prevent this cascade of complications in cirrhosis. Exercise should be moderate in intensity and patients should be informed of potential adverse events. Exercise and nutrition can be monitored using wearable devices, fitbits and smartphone applications.

*In a patient who may have cognitive dysfunction, the diagnosis of covert hepatic encephalopathy can be made with the help of EncephalApp. Rifaxmin with lactulose should be administered once covert hepatic encephalopathy is diagnosed.
minerals (e.g. zinc deficiency is associated with HE). Portal hypertension worsens all processes, causing the shifted and increased metabolic demands and triggering hepatic decompensations, such as ascites.

Performing a frailty assessment

The assessment of frailty is challenging in the clinical setting. Complicating the challenges—namely the time and resources required—frailty suffers from a lack of standard definition. In general, frailty assessments vary from the subjective—e.g. activities of daily living (ADL) or Karnofsky performance status (KPS)—to the objective—e.g. hand grip, chair stands, six-minute walk. Objective tests, although more reliable and with less inter-rater reliability, are costly and may require special training. Beyond these factors, the literature appears to have conflated several concepts into one. Specifically, there is benefit in separating dysfunction, disability and sarcopenia. Hereafter, we will refer to disability (generally a subjective assessment) and frailty (a functional assessment that is informed in part by sarcopenia).

Several options for frailty assessment exist, each with its own limitations. Subjective assessments are frequently performed. Two commonly used subjective tests include ADL and KPS [6,7]. These tests are relatively simple to perform, but have poor inter-rater reliability, similar to other subjective tests. The ADL assessment is a measure of disability where patients report their ability to care for themselves and predicts mortality (odds ratio for the effect of an ADL score below 12 out of 15 on mortality is 1.83 with 95% confidence interval [CI]: 1.05–3.20) [6]. The KPS is a simple scale that expresses physical function as a percentage from 0% (dead) to 100% (normal physical function) or trichotomized as A-B-C where A denotes ability to work, B denotes ability to care for self and C denotes neither [7].

Several recent studies—one from the United Network for Organ Sharing database and the other from a multicenter study of patients hospitalized with acutely decompensated cirrhosis—have established that KPS is associated with pre-transplant mortality [7,8]. Subjective measures are simple and valid but likely more sensitive for disability than frailty.

Objective measures of frailty are more likely to discriminate risk in non-disabled (i.e. Karnofsky A-B) patients. There are many options. These include 6-minute walk, hand grip and 30-second chair-stands tests [8,9]. Using objective measures to evaluate the physical function of 309 transplant-waitlisted patients (median MELD 15, 83% Child class B or C), Lai et al. found that declining physical function was associated with waitlist mortality and delisting [10]. The average reduction in physical function every 3 months while on the waiting list was as follows: -0.38 kg in grip strength, -0.05 meters/second in gait, 0.03 seconds in chair stands and -0.16 Short Physical Performance Battery points (range 12 to 0). Adjusting for MELD-Na, albumin, hepatocellular carcinoma and baseline physical function, the change in each functional measure was significantly associated with waitlist mortality: grip (hazard ratio [HR] = 0.89, 95% CI: 0.83–0.95), gait (HR = 0.72, 95% CI: 0.62–0.84), chair stands (HR = 1.17, 95% CI: 1.05–1.25) and Short Physical Performance Battery of less than 10 points (HR = 1.45, 95% CI: 1.15–2.20).

Targets for frailty interventions in cirrhosis

Sarcopenia

Sarcopenia, or muscle wasting from malnutrition and increased catabolism, is a critical component of frailty. Sarcopenia affects 65–90% of patients with end-stage liver disease [4,11] and predisposes to associated adverse effects. Sarcopenia, in conjunction with the liver’s reduced ability to metabolize ammonia, results in cognitive dysfunction and HE. It reduces quality of life, prolongs hospitalizations, increases infectious complications, worsens liver transplant outcomes and is an independent prognostic factor for survival in patients with cirrhosis [12]. In a study done in the USA involving 163 liver transplant recipients (MELD of 19.3 ± 7.6), the presence of pre-transplant sarcopenia strongly correlated with mortality after transplantation (HR = 3.7 per 1000 mm² decrease in psosas area, p < 0.0001) [13].

HE

HE contributes to frailty in two ways. First, each stage of the spectrum of HE from early deficits in executive functioning to coma is associated with decreased function. Even the earliest stage, minimal hepatic encephalopathy (MHE), increases the patient’s risk for overt hepatic encephalopathy (OHE), multiple hospitalizations and death [14–16]. MHE dramatically reduces patient-reported outcomes, specifically by impairing daily function, driving, work productivity and increasing caregiver burden [17]. HE is a state of uncertainty and disability [18].

Second, HE is associated with saropenia. The pathophysiology of HE involves, at a minimum, a complex interaction with systemic inflammation and endotoxemia with hyperammonemia. Hyperammonemia is precipitated in cirrhosis due to a decrease in intrinsic hepatic function and increased portosystemic shunting, which leads to the inability to process ammonia and gut-derived bacterial products from the systemic and portal circulations [4]. The liver’s reduced capacity to remove ammonia leads to a significant dependence on the skeletal muscle for ammonia detoxification. However, muscle-mass depletion from malnutrition and increased catabolism impairs the removal of ammonia from the systemic circulation, precipitating its accumulation. The combination of these processes results in systemic accumulation of ammonia and precipitates HE [19].

Accidental falls

Patients with cirrhosis have a reduced functional capacity, an increased risk of falls and increased morbidity [10]. The risk of falls is more common in patients with cognitive dysfunction, as seen in HE [20,21]. Individuals with covert hepatic encephalopathy (CHE) are more prone to traffic accidents and accidental falls, which lead to hospitalization and increased health-care burden [20–23].

Bone disease and fractures

Bone disease, including osteopenia, osteoporosis and osteomalacia, is more common in individuals with advanced liver disease.Bone disease in cirrhosis, or hepatic osteodystrophy, is associated with significant morbidity, quality-of-life impairment and impacts survival. Hepatic osteodystrophy, in conjunction with the added risk of falls, increases a cirrhotic patient’s risk of fractures. The prevalence of fractures in patients with chronic liver disease ranges from 3 to 22% [24–26]. Initial studies of fracture risk in this cohort of patients were limited in power [20,21,24,25]. A nationwide population-based study from Taiwan evaluated the rate of fractures in patients with cirrhosis with and without HE [26]. During the 18-month follow-up period, the rate of fractures was increased but comparable in the cirrhotic patients with and without HE (7.09% in the group with HE, 7.72% in the group without HE, p < 0.05), while the
control group had a lower rate of 4.05% (log-rank $p < 0.001$). Interestingly, the group with cirrhosis and HE had a higher rate of skull fractures compared to the cirrhosis group without HE (incidence rate ratio [IRR] = 2.61, 95% CI: 1.04–6.57). This evidence highlights the importance of preserving bone health in individuals with cirrhosis.

**Reviewing the interventions**

Managing the complications of cirrhosis is challenging, but imperative in optimizing a patient’s quality of life, reducing mortality and decreasing caregiver burden. Table 1 reviews the different trials evaluating these interventions.

**The role of nutritional therapy**

Protein-energy malnutrition is associated with reduced survival in patients with cirrhosis [27,28]. Optimizing the nutritional status is imperative in the management of patients with advanced liver disease. Patients with malnutrition in cirrhosis have increased morbidity and impaired quality of life due to the development of associated adverse effects. One randomized controlled trial from New Delhi, India, assigned patients with cirrhosis and MHE into a group that received nutritional support (30–35 kcal/kg/day, 1.0–1.5 g/kg/day of vegetable protein) and a group that did not for 6 months [29]. Both groups had a mean MELD of 16. The former group had reversal of their MHE (71.1% vs 22.8%, $p = 0.001$) and an increased health-related quality of life (HRQOL) ($p = 0.001$) compared to the latter group. Ten percent of patients in the nutritional therapy group progressed to OHE compared to 21.7% in the group without nutritional therapy ($p = 0.04$).

Adequate protein supplementation is fundamental during nutritional optimization of patients with cirrhosis. Evidence has demonstrated that patients with cirrhosis and HE benefit from nutritional supplementation and high-protein diets [30,31]. In fact, protein restriction can lead to sarcopenia and worsen clinical status. The European Society for Parenteral and Enteral Nutrition (ESPEN) recommends an intake of 35–40 kcal/kg/day and 1.2–1.5 g/kg/day of protein in patients with liver disease [32,33]. Additionally, the supplementation of branched-chain amino acids, such as leucine-enriched amino acids, can reduce the progression of liver disease, improve survival, enhance neuropsychological function and improve HRQOL in patients with liver disease [34,37].

The timing of nutritional administration seems to influence overall nourishment in cirrhosis. It is postulated that overnight fasting in patients with cirrhosis leads to increased fatty acid oxidation and enhanced gluconeogenesis, which leads to an abnormal fuel metabolic state that causes a decline in their overall nutritional status [36,37]. In a 12-month randomized controlled trial from New Zealand, 103 patients (50% Childs A, 30% Childs B, 20% Childs C) were randomized to receive either daytime or nighttime supplementary nutrition (710 kcal/day) [37]. The total body protein was similar in both groups at baseline, while the group receiving nighttime nutrition had significant increases at 3 (0.38 ± 0.10 kg, $p = 0.0004$), 6 (0.48 ± 0.13 kg, $p = 0.0007$) and 12 months (0.53 ± 0.17 kg, $p = 0.003$) compared to baseline. There were no significant changes in total body

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HE, hepatic encephalopathy; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; HRQOL, health-related quality of life; SIP, sickness impact profile (HRQOL tool); PHES, Psychometric Hepatic Encephalopathy Score; TBP, total body protein; HVPG, hepatic venous pressure gradient; SF-36, Short Form-36 (HRQOL questionnaire); CPET, cardiopulmonary exercise test.
protein seen in the group receiving daytime nutritional therapy. Nighttime nutritional supplementation in patients with cirrhosis can potentially halt their catabolic state and increase their body protein composition, leading to development of more lean muscle tissue.

**Optimizing the management of HE**

HE is central to the development and progression of frailty. However, preventing episodes of overt HE can be challenging. First, the treatment of CHE can forestall overt HE and potentially reduce the risk of falls and the other sequelae associated with untreated hyperammonemia (e.g. sarcopenia). Treatment is not frequently provided given limited access to proven testing modalities such as neuropsychology consultation. Second, secondary prophylaxis of HE is confounded by a number of factors. The combination of rifaximin with lactulose prevents HE, and is superior to lactulose alone for the prevention of subsequent episodes [38,39]. However, insurance coverage for rifaximin can be limited. Additionally, patients with cirrhosis are frequently prescribed psychoactive medications. Agents that reduce gut motility, such as opioids, facilitate ammonia absorption and can precipitate or worsen HE [11,40]. Benzodiazepines and gabapentinoids are also commonly prescribed and may precipitate HE by enhancing gabanergic tone, the dominant neurologic aberration of HE [4].

**The emerging role of exercise**

Recent evidence suggests beneficial effects from exercise in cirrhosis. In fact, a reduced exercise tolerance in patients with cirrhosis is an independent prognostic factor of pre- and post-liver transplantation morbidity and mortality [41–43]. The increased muscle mass from exercise can facilitate the removal of ammonia from the muscle and reduce the development of HE [44–46]. One study from Spain evaluated a 12-week moderate-exercise regimen with the supplementation of a branched-chain amino acid (BCAA), leucine, in patients with cirrhosis, where 17 patients were randomized to either a supervised exercise group (n = 8, mean MELD of 9.5) or control group (n = 9, mean MELD of 9) [47]. In the exercise group, there was an increase in exercise capacity measured by a 6-minute walk test (from 365 to 445 meters, p = 0.01) and 2-minute step test (p = 0.02), an increase in lower thigh circumference (from 41 to 46 centimeters, p = 0.02) and enhanced HRQOL (p = 0.03) as well as social function (p = 0.04). There were no significant changes observed in the control group and there were no complications of cirrhosis in either group during the study period.

Cirrhosis appears to alter oxygen hemodynamics associated with exercise. A decreased exercise tolerance in patients with cirrhosis is associated with a reduced peak exercise oxygen uptake (peak VO2) [41,42,48,49] and is in fact 40% lower in individuals with even early stages of cirrhosis compared to healthy controls [48,50]. This is likely secondary to the associated cardiovascular and skeletal muscle dysfunction that results in decreased oxygen delivery to and impaired oxygen extraction by muscles [48]. In patient cohorts without liver disease, peak VO2 improves with aerobic exercise training [51]. Exercise-mediated increase in peak VO2 is associated with reduced morbidity and mortality, as well as an improvement in fatigue, depression and quality of life [52–54]. A prospective randomized pilot study from Canada evaluated the effect of aerobic exercise and peak VO2 in patients with Childs class A or B cirrhosis (mean MELD 10 ± 2.2) [49]. A supervised exercise regimen was performed 3 days per week for 8 weeks at 60–80% of baseline peak VO2 in the exercise group (n = 9), where the peak VO2 increased by 5.3 ml/kg/min at week 8 compared to the control group (n = 10, 95% CI: 2.9–7.8, p = 0.001). The exercise group also exhibited an improvement in the fatigue scores, compared to controls (p = 0.01). No adverse events were noted in this trial. Despite the encouraging evidence in this study, existing trials studying the effects of exercise on peak VO2 in cirrhotic patients are limited by low statistical power.

Exercise therapy may have a role in treating cirrhosis-induced frailty and preventing falls. Exercise prevents falls in elderly patients overall [55], but has not been extensively studied in patients with cirrhosis. However, another recent randomized controlled trial from Spain studied the effects of moderate exercise on functional capacity, body composition and risk of falls in patients with cirrhosis, where 23 patients were randomized to either an exercise group (n = 14, MELD 8.2 ± 0.4) or relaxation group (n = 9, MELD 9.1 ± 0.4) [56]. Functional capacity was measured by the cardiopulmonary exercise test, which showed an increase in total effort time (p < 0.001) and ventilator anaerobic threshold (p = 0.009) in the exercise group. The exercise group also exhibited an increase in lean body mass (1.05 kg, 95% CI: 0.27–1.82, p = 0.01) and a decrease in the Timed Up & Go Test (p = 0.02) at the end of the study compared to baseline, whereas there were no significant changes observed in the relaxation group. This evidence suggests that moderate exercise can potentially improve functional capacity, improve lean muscle mass and reduce the risk of falls; however, studies with larger sample sizes are required for further confirmation.

Data of exercise in patients with cirrhosis are scarce and controversial, particularly in individuals with portal hypertension. In a Spanish study of eight patients with cirrhosis and portal hypertension (mean Childs Pugh score of 6.9 ± 0.7), moderate levels of exercise, equivalent to 30% of peak workload, led to a significant increase in hepatic venous pressure gradients (HVPG) (from 16.7 ± 1.5 to 19.2 ± 1.6 mmHg, p < 0.01) and a significant reduction in hepatic blood flow (from 1291 ± 216 to 1034 ± 152 ml/min, p < 0.05) [57]. This increase appears clinically relevant, raising concern for the risk of variceal hemorrhage. Indeed, a similar degree of HVPG change with non-selective beta-blockers is associated with a reduced rate of variceal bleeding [58,59]. Other studies consistent with adverse effects are small and nonrandomized [44,57,60,61].

Conversely, a study by Berzigotti et al. showed a beneficial effect of exercise on HVPG measurements [62]. The trial was a prospective, uncontrolled, multicenter study, which evaluated the effects of an intensive 12-week lifestyle intervention program in patients with compensated cirrhosis, portal hypertension and obesity (n = 50, age: 56 ± 8 years, 62% male, 24% with nonalcoholic steatohepatitis, BMI: 33 ± 3.2kg/m², 92% Child’s A cirrhosis, 72% HVPG ≥ 10 mmHg). The lifestyle intervention included a personalized diet with 60 minutes per week of supervised physical activity tailored by a trainer to achieve a rating of 4-5/10 on a visual analog scale of exertion. After 6 months of intervention, there were significant decreases in body weight (average, −5.0 ± 4 kg, p < 0.0001) and HVPG (from 13.9 ± 5.6 to 12.3 ± 5.2 mmHg, p < 0.0001). Patients with ≥10% bodyweight loss observed an even greater reduction in HVPG (−23.7 ± 19.9% vs −8.2 ± 16.6%, p = 0.024). Though the physical activity component was of low intensity and infrequent, there were no events of clinical decompensation associated with exercise.
The promising role of technology

The use of fitness trackers such as the Fitbit and smartphone applications provides an avenue to screen for conditions and monitor an individual’s progress in physical function and nutritional status. The implementation of these technologies to manage patients with advanced liver disease can be challenging. Ongoing research of their efficacy in patients with cirrhosis is emerging. Examples instructive of the potential power of these tools have been recently published by the Bajaj group.

Smartphone applications have been developed to deliver diagnostic tools for CHE at the point of care. In a multicenter study with more than 800 subjects and 300 controls, a smartphone application, called EncephalaApp, was evaluated against the more difficult-to-implement gold-standard tests, the Psychometric Hepatic Encephalopathy Score and the inhibitory control test (ICT), and was able to reliably predict the development of OHE within 6 months independently of MELD score and prior OHE status [15,63–65].

Extending this tool in a proof-of-concept trial, the Patient Buddy App was used to engage and educate recently discharged cirrhotic patients (admission MELD of 19.5 ± 6). EncephalaApp performance and performance in the Timed Up & Go Test frailty assessment. In this trial, eight potential HE-related readmissions were prevented by the smartphone application with the app-generated alert system and subsequent administration of early outpatient intervention.

Novel interventions modeled after the Patient Buddy App are warranted, including the use of fitbits and other wearable devices. Although smartphone applications and wearable devices can be implemented in the management of patients with cirrhosis, further research on whether their use translates to improved outcomes (or unintended harms) is still warranted. Treatments such as unsupervised exercise have unknown risk and may precipitate falls necessitating the proper monitoring of patients during such interventions.

Conclusions

Patients with cirrhosis have a reduced quality of life with increased morbidity and mortality. The identification, prevention and treatment of frailty are crucial to the improvement of their outcomes. Though the diagnosis of frailty can be challenging, it is essential. We recommend a two-tiered approach when evaluating for frailty in the clinic: use subjective tools to characterize disability and objective tools to provide risk-discrimination in able patients (i.e. those with ADL-independence or KPS-A). We use simple objective measures (grip strength and 30-second chair stands) to rapidly help identify frailty and to monitor their performance longitudinally.

Frailty must be managed using a multimodal approach that addresses malnutrition, intensifies therapy for HE and increases physical activity. The emerging data on the beneficial effects of optimal nutrition and exercise therapy are sufficient to recommend these interventions to patients with cirrhosis. Nutritional optimization, as recommended in the ESPEN guidelines, in conjunction with a moderate-exercise regimen, can help circumvent the secondary complications of cirrhosis as well as serve an important role in their overall management. The goal of this therapeutic approach is to improve sarcopenia, reduce HE, decrease accidental falls and fractures, optimize bone health, minimize hospitalizations and improve morbidity and mortality in patients with cirrhosis.

The advent of new technologies provides an avenue for patients and their physicians. Smartphone applications and wearable devices have the ability to diagnose complications of cirrhosis and monitor an individual’s personal progress in optimizing their physical health. The progressive integration of these technologies into clinical practice gives rise to an exciting era with a bright future ahead for the management of liver disease.

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