Review

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Exercise in cirrhosis: Translating evidence and experience to practice

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Summary

Physical inactivity, sarcopenia, and frailty are highly prevalent, independent predictors of morbidity and mortality in patients with cirrhosis. Across a range of chronic diseases, exercise training is a key recommendation supported by guidelines and, for some conditions, even by governmental funding of exercise programmes. Consistent with the broader chronic disease literature, the evidence for a benefit of exercise in cirrhosis is promising. Several small trials have reported significant improvements in muscle health (mass, strength, functional capacity), quality of life, fatigue, and reductions in the hepatic venous pressure gradient, without adverse events. With strong emerging evidence surrounding the substantial risks of sarcopenia/frailty and our first-hand experiences with liver pre-transplant exercise programmes, we contend that routine patient care in cirrhosis should include an exercise prescription. Some clinicians may lack the resources and necessary background to translate the existing evidence into a practicable intervention. Our team, comprised of physiotherapists, exercise physiologists, hepatologists, transplant specialists, and knowledge translation experts from six North American centres, has distilled the essential background information, tools, and practices into a set of information ready for immediate implementation into clinics ranging from a family practice setting to specialty cirrhosis clinics. Augmenting the rationale and evidence are supplementary materials including video and downloadable materials for both patients and the physician. Supporting the exercising patient is a section regarding information about nutrition, providing practical tips suitable for all patients with cirrhosis.

Keywords: Physical activity; End-stage liver disease; Pre-transplant candidate; 6-min walk test; Pre-habilitation; Frailty; Sarcopenia; Nutrition.

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Introduction

In accordance with the American College of Sports Medicine (ACSM) guidelines for the management of people with chronic diseases and disabilities,[1–5] exercise training is a key recommendation for all patients with chronic disease. In its online teaching resource, the American Association for the Study of Liver Diseases recommends personalised exercise interventions for patients with cirrhosis.[6] The American Society for Transplantation has recommended a robust clinical research agenda for exercise interventions in patients in need of solid organ transplantation.[7] In certain chronic disease populations, accumulated evidence has led to governmental funding of exercise rehabilitation programmes. Despite recommendations in cirrhosis, the application of exercise training in this population lags well behind that for other chronic diseases.[2–5] This may in part be because of initial caution about acute rises in portal pressure with exercise,[8,9] however recent controlled trials have consistently demonstrated safety, improvements in physical fitness, muscle mass and health-related quality of life (HRQoL).[10–12]

Overall physical activity levels in cirrhosis are low, with 76% of waking hours spent in the sedentary state.[4,13–15] Multiple barriers to activity exist including the lack of available supervised or home-based exercise programmes, symptoms of fatigue and a lack of practical evidence-based tools for clinicians to translate the literature into a safe, effective exercise assessment and prescription.[15]

Ideally, every cirrhosis patient would have ready-access to a certified exercise professional to perform a detailed functional assessment and design a patient-specific exercise regimen that is modified at regular follow-up sessions. Unfortunately, this is not the reality. Even among the most highly resourced patients with cirrhosis (patients on the liver transplant waiting list), as an example, only one in seven Canadian centres offers regularly scheduled exercise programming.[16]

Consistent with the ACSM guidelines for chronic disease[1] and our collective experience from six North American centres, we support personalised exercise programming as an essential tool to empower patients to maintain independence in their daily life and optimise their fitness and health, especially while awaiting liver transplantation. The aim of this article is to summarise cirrhosis-specific exercise data and guideline-based exercise recommendations into a practical approach shaped by our clinical experience. The evidence was assimilated using a rapid structured review of the literature. Through the data-gathering and writing process, teleconferences were held to supplement the evidence with consensus-based suggestions of the authors' guidance on best practices.

We present a three-step process involving: i) screening to minimise exercise-related adverse events, ii) baseline physical capacity assessment, and iii) exercise programming with subsequent

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monitoring. Although this process is ideally carried out by a multidisciplinary group led by a CEP (certified exercise professional), if this is not available, clinicians wanting to provide their patients with an exercise prescription can mix and match the options provided in each step of this manuscript, based on consideration of staffing and resources at their clinic. It is essential that all suggestions provided are tailored for each patient and implemented conservatively using caution and common sense. The easy-to-use set of patient handouts included in the supplementary materials support prescribing and promoting cirrhosis-specific exercise by clinicians from all specialties (*e.g.*, family physicians to hepatologists). In patients where exercise safety or efficacy is unclear, or where a CEP, such as a licensed physiotherapist or certified personal trainer (*e.g.* from the Canadian Society for Exercise Physiology or the American College of Sports Medicine) is readily available, patients should be referred to the CEP as a first-line therapeutic option.

Rationale for exercise training

Sedentary time is one of the strongest known predictors of adverse outcomes including all-cause mortality, cardiovascular disease, malignancy, musculoskeletal disease and metabolic disorders.[17] In cirrhosis, a high prevalence of physical inactivity works in combination with multiple other factors including aging, malnutrition, decreased hepatic protein synthesis, hypermetabolism, an increase in inflammatory cytokines, hyperammonemia and low testosterone levels. Cardiac and skeletal muscle deconditioning result in reduced cardiovascular function and reserve, physical frailty, decreased skeletal muscle mass (sarcopenia), strength, and HRQoL.[18–22]

Key point

Physical inactivity, sarcopenia, and frailty are highly prevalent, independent predictors of morbidity and mortality in cirrhosis.

Key point

In cirrhosis, exercise studies have reported improvements in muscle health, quality of life, fatigue, and reductions in the hepatic venous portal gradient, without adverse events.

Sarcopenia

Sarcopenia is present in 22–62%[23–26] of patients with cirrhosis, is most common in those with advanced disease[26,27] and is independently associated with both waiting list and post-liver transplant morbidity (infection rates and length of hospital and intensive care unit stay[24–26,28–31]) and mortality.[26] The addition of sarcopenia to scoring systems has improved their predictive utility,[32–34] with the greatest benefit of the combined model for end-stage liver disease (MELD)-sarcopenia score observed in patients with a low MELD score (MELD ≤15), who are traditionally deemed to have a low risk of death.[33] A recent article put a price tag on sarcopenia, stating that their hospital costs (median estimated) were nearly double those of patients without sarcopenia.[35]

Reduced cardiorespiratory fitness

Oxygen uptake during peak aerobic exercise is the gold standard measure of aerobic power (peak VO_2) while the distance covered during a 6-min walk test (6MWT) is a measure of aerobic endurance. A reduction in each of these measures correlates with increased mortality[36–39] and may be a more sensitive predictor of mortality than sarcopenia.[40] In a systematic review of 1,107 cirrhotic patients who underwent liver transplant (LT) evaluation, the mean VO_{2peak} was 17.4 ml/kg/min, a value falling below the minimum level required for full and independent living (<18 ml/kg/min) and corresponding to the VO_2 expected of a sedentary female in the eighth decade of life.[39,41] A lower aerobic endurance for activity (as measured by the 6MWT) has also been linked to poor prognosis. Specifically, after adjusting for age and native MELD score, patients with a 6MWT <250 m had a twofold increase in mortality for every 100 m decrease in walking distance.[38]

Exercise improves health outcomes in cirrhosis

Exercise is associated with a wide range of health-related benefits (Fig. 1). Few published clinical trials have been exclusively dedicated to exercise in patients with cirrhosis (Table 1).[10–12] Programmes ranging from 8–14 weeks of supervised aerobic exercise training have been associated with consistent improvements in peak VO_2, aerobic endurance, muscle mass and strength, HRQoL and reductions in the hepatic venous pressure gradient (HVPG). It remains unclear whether the reduction in the HVPG seen after 12–16 weeks of exercise is related exclusively to exercise[42] or to weight loss and concurrent decreases in hepatic steatosis/resistance,[43] but it is promising that exercise could reduce the risk of clinical decompensation in cirrhosis. The impact on post-transplant outcomes remains an area requiring evaluation, as does the use of home-based programming, which has been evaluated in two studies.[44,45]

Is my patient safe to start an exercise programme?

As presented (Table 2), the pre-exercise safety screen can be divided into three major categories: disease-related safety issues, screening for cardiopulmonary safety, and assessing the impact of other comorbidities. As discussed in Exercise training principles and components, as a key safety feature, the programme should be personalised by asking each patient to maintain activity at a rate of perceived exertion (RPE) no more than 5–6/10 on a Borg 0–10 scale,[46] an intensity that is "somewhat hard" but still allows them to talk.[1]

Exclusion criteria in published cirrhosis exercise trials vary between studies (Table 1). Although the trials universally excluded patients without adequate primary or secondary prophylaxis for varices, others excluded patients with hepatocellular carcinoma, cardiopulmonary disease (identified by various screening techniques – Table 1), alcohol consumption within the past three months, haemoglobin level <110 g/L, mental

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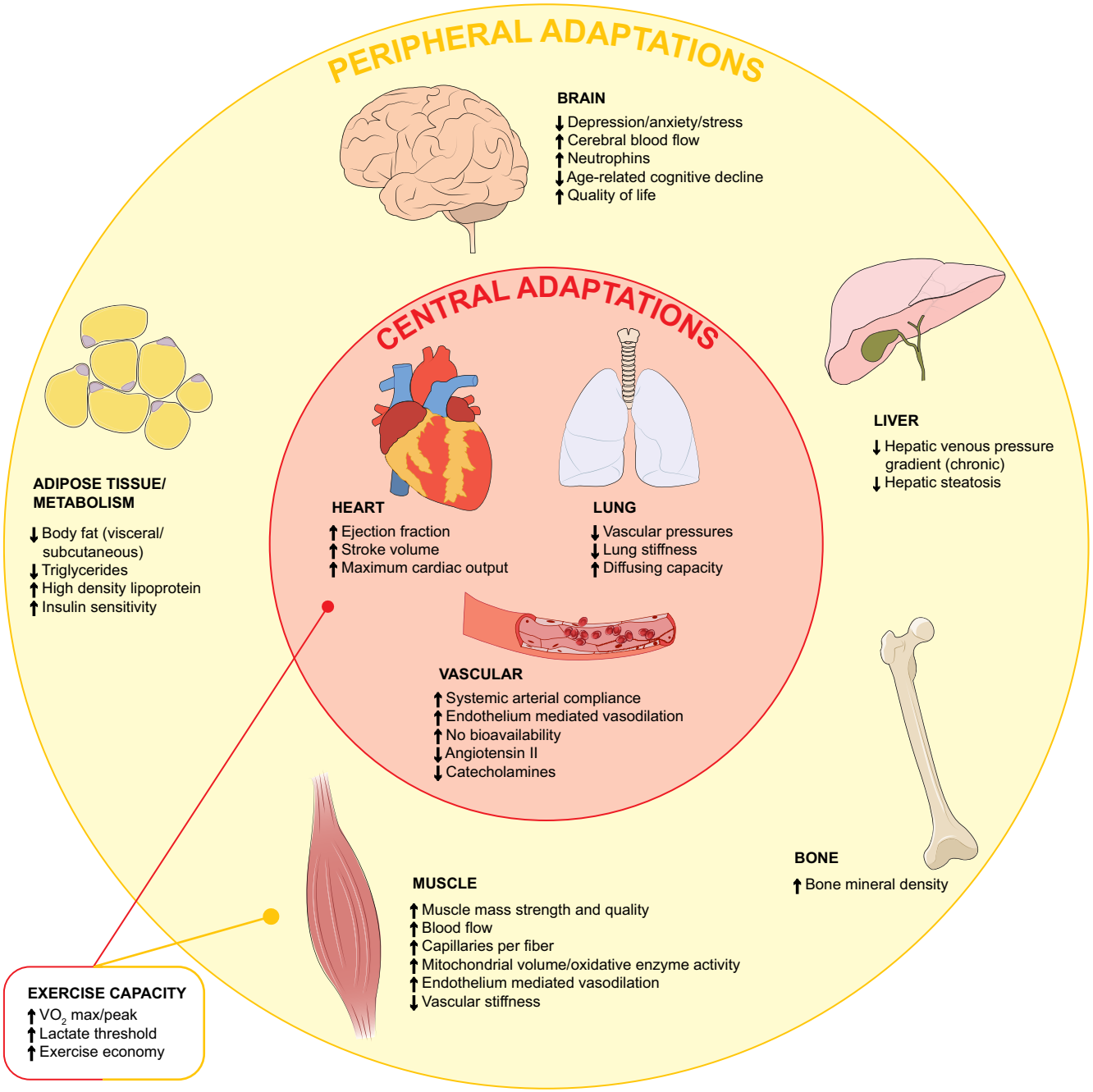

Fig. 1. Benefits of exercise for the patient with cirrhosis. Exercise has multiple benefits, resulting from both central (cardiovascular and pulmonary) adaptations and peripheral adaptations. A simplified version of this Figure is provided in the supplementary materials – patient package.

or physical disabilities preventing exercise, or other significant comorbidities.

Cirrhosis-related safety considerations

The 2015 Baveno VI Consensus recommends screening for varices in all cirrhosis patients with a Fibroscan score ≥20 kPa or platelet count ≤150,000/μl.[47] If high-risk varices are seen or if the patient has had a previous variceal bleed, primary or secondary variceal prophylaxis must be in place before exercise is prescribed.[48] For other cirrhosis-related considerations, none are absolute contraindications to low-intensity activity, however large volume ascites, pedal oedema, and hepatic encephalopathy (HE) can impact the efficacy of the exercise prescription as well as adherence and tolerability,[12] thereby necessitating some exercise programme modifications (Table 2). In patients with transient or overt HE, readiness to engage, understand, and safely follow-through with exercise directions should be considered, however we do not routinely carry out testing for covert HE before prescribing exercise. The one caveat in these patients is that a caregiver must be present during exercise sessions. Studies in patients with acute brain injury, dementia,

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Table 1. Clinical trials of exercise in patients with cirrhosis. *Additional exclusion criteria for studies not detailed here included: varices, alcohol consumption, etc. 6MWT, 6-min walk test; BCAA, branched chain amino acids; BIA, bioelectrical impedance analysis; CHF, chronic heart failure; CP, cardiopulmonary; CPE, cardiopulmonary endurance; CTP, Child-Turcotte-Pugh; Ctrl, control study group; HR, heart rate; HRQoL, health-related quality of life; HVPG, hepatic venous pressure gradient; Int, intervention study group; LVEF, left ventricular ejection fraction; MELD, model for end-stage liver disease; NSD, no significant difference; RCT, randomised controlled trial.

1st Author, year, study design, duration	Characteristics, CP, exclusion criteria*	Study group(s)	Outcomes
Roman 2014[123], RCT, 12 weeks	MELD 7–13, CP-A 82% n = 17, "Marked symptomatic comorbidities"	*Int:* supervised moderate exercise (n = 8). *Ctrl:* (n = 9) All pts received leucine (10 g/d)	Within group comparison relative to baseline measures: *Int:* 6MWT (365 *vs.* 445 m, $p = 0.01$) and 2-min step test ($p = 0.02$); thigh muscle mass (41 *vs.* 46 cm, $p = 0.02$); SF-36: general health, vitality & social function significantly improved. *Ctrl:* NSD
Zenith 2014[89], RCT, 8 weeks	MELD 10, CP-A 84%, n = 20, LVEF < 60%, history of CAD, positive exercise stress test	*Int:* supervised aerobic exercise + 250–300 kcal on exercise days (n = 9). *Ctrl:* usual care (n = 10)	Between group comparison, with *Int* better than *Ctrl* for: Peak VO_2 being 5.3 ml/kg/min higher ($p = 0.01$); thigh muscle mass ($p = 0.01$); thigh circumference ($p = 0.001$); EQ-VAS self–perceived health ($p = 0.01$); less fatigue ($p = 0.01$)
Debette-Gratien 2015[124], cohort, 12 weeks	MELD 13–21, CP-A 63% n = 13, LVEF <45%, positive stress test; all completed max exercise threshold & pulmonary function testing	Supervised exercise	Improvements seen relative to baseline measures: Peak VO_2 being 1.7 ml/kg/min higher ($p < 0.008$); maximum power ($p = 0.02$); 6MWT ($p < 0.02$); knee extensor muscle ($p = 0.008$); ventilatory threshold power ($p = 0.02$) [Study dropouts, n = 6]
Macias–Rodriguez 2016[42], RCT, 14 weeks	MELD 7–14, CP-A 64% n = 22, "Cardiopulmonary disease"	*Int:* Supervised exercise + 30% calories on exercise days (n = 11). *Ctrl:* (n = 11) All received nutrition therapy according to HBE	Between group comparison, with *Int* better than *Ctrl* for: HVPG being 6.5 mmHg lower ($p = 0.009$); within group comparison relative to baseline showed *Int* had significant improvements in ventilatory efficiency ($p = 0.033$). *Ctrl:* NSD
Roman 2016[64], RCT, 12 weeks	MELD 8 ± 0.4, CP-A 5.4 ± 0.2 n = 23, "Contraindication to exercise"	*Int:* supervised exercise (n = 14). *Ctrl:* relaxation programme (n = 9)	Within group comparison relative to baseline showed *Int* had: Muscle mass increase ($p < 0.01$); fat body mass decrease ($p = 0.003$); lean body mass increase ($p \leq 0.03$); fall risk decrease ($p = 0.02$) *Ctrl:* NSD
Berzigotti 2017[43], cohort, 16 weeks	MELD 9 ± 3, CP-A 92% n = 60, BMI 26 kg/m^2, "History of CAD"	Supervised/gym exercise + 500–1,000 kcal/d reduction in diet	Within group comparison relative to baseline showed improvements in: Body mass decrease by 5 kg ($p < 0.0001$); HVPG decreased by 1.6 mmHg ($p < 0.001$) [Study dropouts, n = 10]
Kruger 2018[44], RCT, 8 weeks	CP-A 70% (n = 40), history of LVEF <60% or CAD, or positive outcome on exercise stress test	*Int:* home-based exercise + 250–350 kcal on exercise days (n = 20). *Ctrl:* usual care (n = 20) All pts received guideline-based nutrition counselling	Between group comparison, with *Int* better than *Ctrl* for: 6MWT increase by 33.7 m ($p = 0.02$). Between group comparison for *Int adherents* (≥80% training sessions) better than *Ctrls* for: 6MWT increase by 46.4 m ($p = 0.009$); peak VO_2 increase by 2.8 ml/kg/min ($p = 0.02$) [Study dropouts, n = 3]
Hiraoka, 2017[45], cohort, 12 weeks	CP-A 91% (n = 33), patients with "other organ disease" – CHF, chronic respiratory disease	Home-based exercise + 210 kcal snack and 13.5 g BCAA at night (n = 33)	Increases seen relative to baseline measures: Average daily steps ($p = 0.02$); muscle volume, leg and handgrip strength ($p < 0.01$ for each); BCAA/tyrosine ratio ($p = 0.001$) [Study dropouts, n = 2]

and serious mental illness support the efficacy and feasibility of exercise despite cognitive issues.[49–51] Although thrombocytopenia is not considered a contraindication to exercise, in keeping with data in stem cell transplant patients,[52] exercises with high risk of injury or falling should be avoided, especially if platelets are <20,000/μl.

Cardiopulmonary safety screening

Recognising the high prevalence of cardiovascular risk factors in the population and their low correlation with events, guidelines have shifted to no longer require mandatory cardiac testing for individuals with ≥2 traditional cardiac risk factors (*e.g.*, male age >45 y, female age >55 y, hyperlipidemia, hypertension, tobacco use, family history of early coronary artery disease [first-degree relative male <55 y, female <65 y]).[53,54] More recent recommendations like the ACSM guidelines,[54] recommend "medical clearance" for those who are starting a moderate intensity programme AND have signs, symptoms, or a history of cardiovascular (*i.e.*, cardiac, peripheral artery, cerebrovascular), metabolic (*i.e.*, type 1 or 2 diabetes mellitus) or renal disease. The exact procedure for medical clearance is left at the discretion of the clinician. Notably, the ACSM defines moderate intensity as 40–59% heart rate reserve, a VO_2 reserve of 3.0–5.9 metabolic equivalents (METs), or an RPE of 12–13 on a 6–20 Borg scale (or 5–6 on a 0–10 scale), an intensity that causes noticeable increases in HR and breathing. How can we practically apply this information? As summarised by another recent review in the area, asymptomatic patients wanting to pursue low-moderate activity should adhere to the tenant to "start low and go slow"[11]. Most associations agree that non-vigorous physical activity (not exceeding

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Table 2. Pre-screening to establish exercise safety and intensity. **For all patients, exercise should be guided by the rate of perceived exertion and start at the introductory level unless otherwise specified. CEP, certified exercise professional; MELD, model for end-stage liver disease.

Topic	Exercise prescription modification
Part I Cirrhosis-related screening	
MELD >20?	Case-by-case assessment to determine if CEP referral is needed for the patient to progress beyond Introductory exercises
High-risk varices?	Ensure adequate primary or secondary variceal prophylaxis is in place prior to programme
Hepatic encephalopathy?	Medical optimisation of hepatic encephalopathy prior to exercising; programming supervised by caregivers or if not possible, requires CEP supervision
Ascites?	Optimise medical management; progress beyond introductory exercise on days where ascites accumulation is insignificant and/or does not affect balance; caregiver supervision is ideal
Platelets <20,000/μl or Hb <8.0 g/dl	Exercise limited to Introductory level to avoid falls and/or injury
Diabetes mellitus?	Blood glucose checks completed before and after exercising (hypoglycaemia unawareness)[55]
Diuretic therapy?	At-risk of volume depletion and hypotension with exercise. Prescribe a home blood pressure monitor for use after exercising[125]
Part II Cardiopulmonary safety concerns	
"Medical clearance" required if any of the following are present	
Signs and Symptoms	Chest discomfort with exertion; unreasonable breathlessness; dizziness, fainting, blackouts; heart palpitations; lower limb claudication; known heart murmur
Past or current medical conditions	Heart attack; heart surgery, cardiac catheterisation, or coronary angioplasty; pacemaker/implantable cardiac defibrillator/rhythm disturbance; heart valve disease; heart failure; heart transplantation; congenital heart disease; diabetes; renal disease; ***The method of "Medical Assessment" is left at the discretion of the physician[54]
Part III Overall physiological competence	
Heart rate >100 or <50; systolic blood pressure >160 mmHg or <85; diastolic blood pressure >110 mmHg or <50 mmHg; oxygen saturation <92%	Raises concerns about patient's physiological competence to complete unsupervised exercises Patient requires "medical clearance" before receiving an exercise prescription. Will likely require CEP supervised programming
Specific musculoskeletal (MSK) limitations: history of arthritis, joint swelling, or MSK conditions that limit ambulation or daily activities	Referral to physiotherapy for pre-exercise counselling and therapy May require CEP to perform assessment and specialised programming if MSK issues are unresolved
Fall risk: history of ≥3 falls within the last year; Hb <8.0 g/dl; hepatic encephalopathy; instability or unsteadiness observed during baseline testing	Exercise in supported positions to avoid falls/injury (Intro level) Progression beyond Introductory exercises requires CEP consultation and supervision

the demand of a brisk walk) does not require pre-participation cardiac clearance.[55]

Selected comorbidities

All patients should be asked whether they get exertional symptoms that limit their activities of daily living (ADL). This question may help to identify additional diagnoses (*e.g.*, muscle cramping, claudication, joint pain/limited range of motion) that may require programme modification or physiotherapy intervention prior to the initiation of an exercise programme.[1] Fall risk should be specifically assessed, although no screening tool has been validated in patients with cirrhosis. Falls in cirrhotic patients are strongly associated with especially high risk of morbidity and death.[56] Knowing that many factors can increase the risk of falls (*e.g.*, covert HE, psychoactive drugs, and muscle weakness),[57] observations made during baseline patient assessment (*e.g.*, unsteadiness, tremors, use of chair or wall for support) are indicators of fall risk. So too is a history of three or more falls in the past year, routine use of a cane or walker, and self-reported fear of falling.[58–60] Patients suspected to be at high risk for falls require supported activity (*i.e.*, exercises performed while seated; or if standing, using a support such as a grab bar or handrail to hold on to) and, ideally, should be supervised by a caregiver. Multimodal exercise programmes have reduced fall risk in the elderly[61–63] and in patients with cirrhosis.[64] The safety implications of additional comorbidities, including concurrent end-stage renal disease and pulmonary disease requiring oxygen, are beyond the scope of this review, but have been covered in detail in disease specific guidelines and in the recent ACSM guidelines.[1] For patients at risk of falling, programming beyond the introductory level of supported activity provided in this guide is best advanced after consultation with a CEP.

Assessing baseline physical performance

Studies have confirmed the robust prognostic value of a range of performance tools in cirrhosis, including composite measures such as the short physical performance battery (SPPB) and single components, such as gait speed.[65–68]

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The evaluation of baseline physical performance serves two important purposes. It overlaps with the safety pre-screen as an evaluation of cardiopulmonary endurance and capacity to exercise. It also establishes an objective baseline against which progress can be measured. We present a toolkit of our selected measures for use in clinical practice. The specific details for performing each measure are available in the supplementary materials – Physician Resource Package. If only one test can be done, we suggest the 4 m gait speed, with the SPPB or liver frailty index (LFI) of three tests (<3 min) as more comprehensive second choices. Further information on the tools available, including those described below, is available at Can-Restore (https://www.cntrp.ca/cr—healthcare-professionals), while rehabmeasures.org provides information regarding psychometric properties, normative data, instrument description and equipment, and minimally important differences.

Key point

Both composite measures of physical performance and single components have been shown to have robust prognostic value in cirrhosis.

Activities of daily living – duration ~1 min

The Katz Activities of Daily Living Scale assesses a patient's self-reported independence, a low score was associated with an almost twofold risk of 90-day mortality.[69] Screening for ADLs identifies very deconditioned patients. Under caregiver supervision, and at the discretion of the practitioner, even this group may be able to carry out supported introductory level activities.

Duke Activity Status Index – duration ~2 min

The Duke Activity Status Index (DASI) is a 12-item questionnaire that measures perceived functional capacity, has been validated against the VO_{2peak}, is an accepted component in the pre-cardiac surgery risk stratification algorithm,[70] and has been used successfully in multiple chronic disease populations.[71–74] Moreover, it is sensitive to change with an intervention, two or more units considered to be clinically meaningful.[75] The score (www.mdcalc.com) can be converted into an approximate daily MET and an estimate of VO_2 peak (in ml/kg = 0.43 × DASI + 9.6). The ranges for interpretation of functional capacity include excellent (>10 METs), good (7 to 10 METs), moderate (4 to 6 METs) and poor (<4 METs). Despite the potential for over-reporting of activities[13] and the lack of cirrhosis-specific research in this area, in our experience the DASI is quick to administer, can help determine if a patient requires a lower training level, and is useful for monitoring progression over time.

Composite batteries – short physical performance battery[67,76] OR liver frailty index[62,72,73] – duration ~3–5 min

Both composite batteries share two of three tests: i) time to do five unassisted chair stands (arms folded across chest), and ii) seconds holding balance in three positions. The third test in each of the batteries is: gender-adjusted grip strength for the LFI and gait speed for the SPPB. Both composite tools predict transplant waiting list mortality and hospitalisation risk, and are supported by online calculators https://liverfrailtyindex.ucsf.edu/ and http://www.geriatricmobility.com/sppb-calculator/ respectively. Notably, specific to exercise testing, some concern has been raised in the ACSM guidelines regarding the lack of correlation between grip strength and overall physical performance or the performance of ADLs.[1]

4-m gait speed – duration <1 min

Included in the SPPB, this test is one of the best predictors of disability, morbidity, mortality, and fall risk across a range of chronic diseases and in the elderly.[77,78] It is recommended by the ACSM guidelines as a basic test of function prior to exercise initiation.[1] In 373 patients with cirrhosis, gait speed was independently associated with the rate of hospitalisation after adjusting for covariates such as MELD and Child-Pugh score.[79] Mean gait speed was 0.95 m/s with every 0.1 m/s decrease in gait speed associated with a 22% increase of hospital day stay with significant projected cost implications. Gait speeds of <0.6 to <0.8 m/s have been associated with poor outcomes in older adults.[80]

The 6 Minute Walk Test (6MWT) – duration ~15 min

The lengthiest of the suggested performance measures, the 6MWT is highly recommended but left optional for the clinician to judge whether it can be practically incorporated into the pre-exercise screen. Beyond mortality prediction,[34,35] the 6MWT is an excellent opportunity to observe the patient's aerobic capacity, risk of adverse events (*e.g.*, does the patient have any symptom limitations, chest pain, dyspnoea as they walk, fall risk), readiness and motivation to exercise, muscle function, mobility, and balance. Repeated measures over time demonstrate responsiveness to change with an exercise intervention. Moreover, it offers a long enough period of activity to be an opportunity for the health care practitioner to educate the patient about how to measure their exercise intensity based on the RPE Borg 0–10 scale[46] (Exercise training principles and components).

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) is routinely utilised at some European centres for pre-transplant evaluation. A recent systematic literature review including patients awaiting liver transplantation confirmed the use of CPET testing as independent predictors of pre-transplant and post-transplant mortality.[39] As this technique takes at least 30 min and requires dedicated equipment and trained personnel, although extremely objective and very helpful for exercise prescription, it is not routinely carried out at many centres.

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Sarcopenia assessment as defined by low muscle mass

There are a range of muscle mass measures that are robust predictors of adverse clinical outcomes in the cirrhosis population.[81] Given that muscle strength/performance measures likely have a higher sensitivity than muscle mass,[40,82,83] our team variably performs muscle mass measurements before prescribing exercise. From the literature, it is clear that cross-sectional imaging offers the most accurate assessment of body composition,[26] particularly relevant in the setting of sarcopenic obesity.[84] If this modality can overcome the practical limitations of repeatability, cost, and safety and is incorporated into standard of care radiology reporting, it would be a very valuable metric to follow alongside an exercise intervention.

Malnutrition assessment

Assessment of malnutrition involves evaluation of dietary intake and the factors that may compromise intake, including taste fatigue, poor palatability of sodium restricted diets, ascites, early satiety, and socioeconomic factors.[81] Ideally, the malnutrition assessment should be performed by a registered dietitian. Even in the absence of an assessment, basic nutrition education should be provided to all patients, highlighting the patient's daily protein and calorie targets (the nutrition prescription for exercising patients section and supplementary materials – Patient Resource Package).

Identify and treat muscle-specific metabolic issues

Patients should have baseline testing and aggressive management of muscle-wasting metabolic disorders, such as diabetes, thyroid disorders, vitamin D deficiency, and especially ammonia excess, the primary metabolic driver of cirrhotic sarcopenia.[85]

Assessing exercise readiness and overcoming barriers to exercise

Fatigue and sedentary behaviour are ubiquitous in cirrhosis. Additional barriers to exercise include: i) a paucity of multidisciplinary teams or prehabilitation programmes despite improvements in clinical outcomes and cost-savings;[13,65] ii) inactivity due to unplanned hospital stays (average of six days each year[13,67]) which may trigger or accelerate physical decline; iii) cost and accessibility issues associated with supervised nutrition/exercise programming;[43] iv) mental health issues counter-active to exercise, such as depression, anxiety, and fear of falling due to kinesiophobia – the psychological inhibition of activity;[86,87] and, v) lack of awareness of the benefits of exercise regarding morbidity and mortality, transplant delisting, quality of life and symptom management.

Recognising that this article is a stepping stone on the path to universal exercise prescription in cirrhosis, well-known barriers can be addressed with the information herein and changes to the way we practice. i) Each patient can be provided with customised exercise and nutrition instructions and supporting information. ii) Although hospitalisation is a period of high risk for physical decline[88] it can be utilised as a valuable opportunity to connect the patient with an exercise professional and dietitian. Patients should ideally be followed by these practitioners in hospital and educated about a home exercise regimen at the time of discharge. iii) Patients can be encouraged to access our online supplementary videos to support their home-based activities and to co-exercise with family or friends, thereby converting exercise into a social activity.[43,89] iv) Mental health issues, such as depression and anxiety, should be identified and treated. v) Educational material provided with the clinician's endorsement will help to highlight the importance of exercise and nutrition in the medical care of cirrhosis.

Knowing that patients and clinicians underestimate the sedentary lifestyle of LT candidates,[13] if available to them, we encourage patients to access wearable activity monitors offering real-time awareness of steps per day, calories expended per day, and percent sedentary-moderate physical activity. This is an objective approach to assessing activity and provides a benchmark for improvement.

Motivational interviewing can also be incorporated into clinical interactions. This is an empathetic, non-confrontational approach to changing behaviour where the patient is an equal partner. This effective technique uses open-ended questions to collaboratively explore a patient's readiness, motivation, and confidence to change and to resolve ambivalence, emphasise autonomy, and provide patient self-efficacy.[90] We provide sample questions that are used in our practices and have been well received (Table 3).

Table 3. Motivational interviewing questions to elicit behaviour change in cirrhosis. Adapted from.[126]

Assessing ambivalence/motivation for exercise & nutritional changes
How is your loss of muscle strength and sedentary lifestyle affecting you right now?
What have you done in the past to increase muscle strength or mobility?
What are your hopes for the future if you can become stronger and improve your symptoms?
Assessing exercise readiness
How would you like your health to be different?
How ready are you to change your activity and eating patterns to improve your strength and mobility?
Some people do not wish to discuss their weakness, tiredness, or challenges with doing things they were previously able to do, while others do not mind talking about these things. How do you feel about this?
The importance of change
What do you think would happen if you continue to become weaker?
If you were to regain strength and mobility, what would that be like?
Building confidence
What would make you more confident about making these changes?
If you decided to change, what are your options to achieve this?
Identifying possible barriers
What may interfere with you from being more physically active or eating better?
Do you have any concerns or fears about your ability to participate in exercise?

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Exercise training principles and components

Exercise training principles

The most important advice for any exercise programme in a patient with chronic disease is to "start low, progress slowly, and be alert for symptoms"[1]. Exercise is differentiated from physical activity as it is planned and performed on a repeated basis over an extended period of time for the purpose of improving fitness, performance, and health.[91]

The exercise training prescription provided to each patient follows the FITT principles: **F**requency, **I**ntensity, **T**ime, **T**ype of exercise. The FITT table for exercise principles in cirrhosis is presented in Table 4 and in the supplementary materials – Patient Resource Package, modified to be printed as a set of instructions that can be personalised for each patient.[1]

Key point

The benefits of exercise lead us to recommend that all patients with cirrhosis should be encouraged and supported to engage in exercise appropriate for their physical abilities.

Exercise programming details

Encourage non-exercise activity thermogenesis

Non-exercise activity thermogenesis (NEAT) involves continuous and vital low-intensity movements. It encourages patients to take advantage of opportunities for physical activity within their day-to-day routine and thereby can complement exercise, resulting in a more sustainable increase in activity levels.[1,11] Examples of NEAT activities may include choices such as parking 10 min away from a store when shopping, stepping in place while watching TV, washing dishes instead of putting them in the dishwasher, and climbing stairs instead of taking the elevator.[92] A detailed list of calories burned using NEAT activities is found in a recent review on the topic.[92] The capacity of a cirrhosis patient to partake in these additional activity opportunities will depend upon their baseline level of function.

Scheduled exercise programming

For individuals living with chronic disease, scheduled exercise programmes are generally structured to include a warm-up (5–10 min), an exercise phase with aerobic and resistance exercise components (20–60 min; for severely deconditioned patients, this can be performed with rest breaks, as their fitness improves, it can become continuous), and a cool-down phase including flexibility and balance training (5–10 min).[1,93] We have developed instructional exercise videos for the resistance, flexibility, and balance training components. The descriptions are provided (Table 5) and are available at www.wellnesstoolbox.ca. We have provided a detailed set of steps to formulate an exercise prescription and included this in the supplementary materials – Physician Resource Package. This includes details on baseline exercise instructions and the how to's of prescribing exercise programme progression and reassessment.

The nutrition prescription for exercising patients

We include an excerpt of "The Nutrition in Cirrhosis Guide", the full version available at www.wellnesstoolbox.ca and the Canadian Liver Foundation's website[94] (supplementary materials – Patient Resource Package). Patients should ideally be assessed by a dietitian and given four main targets for their routine daily intake.

Target caloric intake

Patients are informed of their caloric intake target (ranging from 20–40 kcal/kg/day) stratified by their dry weight body mass index.[95] Barriers to intake are explored and solutions provided, including: when and which liquid food

Table 4. FITT (Frequency, Intensity, Type, Time) recommendations for exercise in cirrhosis (adapted from reference[1]).

Characteristic	Aerobic	Resistance	Flexibility & Balance
Frequency	Start with 4 days/week; aim to do every day	2 or more days/week on non-consecutive days if using external resistance	2 or more days/week
Intensity	Moderate intensity 5–6 on a 10-point Borg Scale. The exerciser should pass the talk test = be able to speak comfortably during exercise to ensure they are not overexerting themselves	Ensure good form for the exercises to work the correct muscles and have the desired effect. Perform with a weight or exercise resistance band that a rest is needed after 10–15 repetitions (a "set"). When 3 sets of 10–15 repetitions can be completed easily, increase the stiffness of the resistance band or the weight to make the 10–15 repetitions difficult again	Stretch until there is a feeling of tightness or slight discomfort
Time	The very deconditioned may need to start with walk 1-min, rest 1-min then repeat for a total time of 5 min. Gradually increase walking time and decrease resting time. Build to 40 min in each session. **Aim:** 150 min each week	Videos are divided into 7 major muscle groups. Start with 3–4 exercises per session, doing 1 set of 10–15 repetitions. **Aim:** Increase to all 7 exercises per day, doing 3 sets of 10–15 repetitions	1 set of 3 repetitions. Stretches can be held for 30–60 s. **Aim:** 1 set of 3 repetitions (5–10 min)
Type	Walking (indoors or outdoors) to improve overall functionality. Other activities can be selected by the patient (*e.g.*, cycling, elliptical)	Progressive weight training activities or functional strengthening exercises, such as stair climbing	Stretches and balance exercises targeting the large muscles of the upper and lower body

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Table 5. Programming levels and link to associated videos (www.wellnesstoolbox.ca).

Muscle strengthening & resistance activities – start with 1 set of 10–15 repetitions		
Shoulders:	Intro	Lateral arm raises
	P1	Lateral arm raises with banding
	P2	Lateral arm raises with free weights
	P3	Lateral arm raises with free weights and single leg
Biceps:	Intro	Arm curls with light or no weights
	P1	Arm curls with banding
	P2	Arm curls with free weights
	P3	Arm curls/single leg
Triceps:	Intro	Seated triceps extension with banding
	P1	Over-head triceps extension with banding
	P2	Over-head triceps extension with free weights
	P3	Triceps dip
Quadriceps:	Intro	Seated leg extensions
	P1	Seated leg extension held for a longer time
	P2	Seated leg extensions with banding
	P3	Seated leg extensions with banding (higher resistances)
Hamstring:	Intro	Standing leg curls
	P1	Standing hamstring curl with towel on wall
	P2	Standing leg curls with banding
	P3	Standing leg curls with banding (higher resistances)
Lower Leg:	Intro	Seated calf raises
	P1	Standing calf raises
	P2	Standing calf raises with banding
	P3	Single leg calf raises with or without banding
Multi-joint:	Intro	Chair sit to stand
	P1	Wall squat
	P2	Squat with banding or hand held free weights
	P3	Increase resistances or weights
Flexibility – 1 set of 3 repetitions		
	Intro	Simple range of motions for shoulders, elbows, lower back, and knees to Static stretches that can be performed seated in a chair (*e.g.*, chair sit and reach, lateral side bends, chest stretch)
	P1	Standing static stretches (*e.g.*, toe touch, calf stretch, shoulder stretch, triceps stretch, chest stretch)
	P2	Floor and standing stretches (*e.g.*, hurdler's stretch, calf stretch, wrist stretch, shoulder and chest stretch)
	P3	Floor and standing stretches (*e.g.*, hurdler's stretch, calf stretch, wrist stretch, shoulder and chest stretch)
Balance – 1 set of 3 repetitions		
	Intro	Single leg raises with assistance of a chair
	P1	Single leg raises with assistance of a chair and eyes are closed
	P2	Dynamic balance: walking in a straight line with a narrow gait
	P3	Dynamic balance: walk heel to toe

supplements to consume; eat a meal or snack every 3 to 4 h; avoid low calorie liquids (*e.g.*, tea, coffee) before meal-times as they may reduce appetite.[94]

Target protein intake

Dietary protein is an essential macronutrient in exercising adults, providing both the required amino acids and the anabolic stimulus necessary for muscle protein synthesis.[96] There is retrospective evidence linking low protein intake with mortality in cirrhosis[97] and observational evidence linking low protein intake to muscle mass and strength loss in the elderly.[98,99] Branched chain amino acid (BCAA) supplementation has been associated with improvements in liver function, HRQoL, muscle mass, and reductions in HE, but their expense and poor taste minimises frequent use.[100–102] Patients are provided with their guideline-based daily protein intake target (1.2–1.5 g/kg/day) in g/day[95,103] and information about high protein and BCAA-rich foods. It remains unclear whether animal- or vegetable-based protein is of greater benefit in patients with cirrhosis.[95]

Late evening snack

Patients are advised that cirrhosis impairs glycogen storage. This creates an accelerated state of starvation leading to a rapid breakdown of fat and muscle after just a 10-h fast.[104] They are advised to eat a snack containing 20–40 g of protein and 50 g of complex carbohydrates either shortly before bedtime or during night-time hours, an intervention proven to increase muscle mass.[105,106]

Adjusting intake for exercise

Evidence-based recommendations are available guiding nutrient intake in healthy, exercising

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adults[107,108] with protein intake every 3–4 hours resulting in improved tissue repair and augmented muscle protein synthesis. Although not directly transferable, these basic principles can be applied to patients with cirrhosis. Glycogen stores are easily depleted by high volume exercise. As in two of our published trials, on exercise days, it is our practice to recommend an additional 250–300 kcal of carbohydrate-based caloric intake pre- or post-exercise.[44,89] The only other exercise trial in cirrhosis which provided additional calories for exercising patients did so by increasing the daily caloric intake, estimated by the Harris-Benedict equation, by 30%.[42]

Future directions

To make exercise widely available in cirrhosis, we need to generate new models of delivery, by overcoming barriers of affordability and availability. Home-based exercise is the most attractive intervention, as it eliminates transportation needs, and emphasises ADLs. A recent trial of home-based therapy showed benefit in patients with compensated cirrhosis who adhered to the treatment regimen.[44] Technology, such as wearable activity monitors, video streaming, smartphones, and virtual reality should be exploited to create home-based telehealth or virtual interventions that can be remotely monitored by a specialised team. Objective activity monitoring is especially important to guide therapy for cirrhotic patients because of their strong tendency to grossly overestimate their self-assessed activity levels.[13]

The main aim of cognitive behavioural therapy sessions is to motivate and empower patients to be their own instrument of change, facilitating adherence and allowing more permanent lifestyle modifications.[109,110] Socialisation and gamification of exercise activities with the use of social media could further enhance interventions by providing peer support, modelling, and incentivising participation. Motivational interviewing (Table 3) is an efficient and effective method[90] that requires further exploration in cirrhosis.

Among nutritional interventions, BCAA are known for their beneficial effect on HE and lowering of circulating ammonia levels.[111] As shown (Fig. 2), hyperammonemia has a pivotal role in the aetiology and perpetuation of sarcopenia in cirrhosis, and evidence from both experimental and human studies shows BCAA, especially L-leucine supplementation, can support skeletal muscle anabolism. However, one of the side effects of BCAA is that, by depleting the Krebs (tricarboxylic) acid cycle, it can be detrimental to energy generation, and therefore, combining BCAA with an alpha-ketoacid donor (*e.g.*, L-ornithine-L-aspartate) has been proposed as a solution.[112] This requires further evaluation in cirrhosis.

The drug discovery pipeline for sarcopenia and disorders of physical function has been rather slow to produce therapeutics. Follistatin is a negative regulator of the muscle growth inhibitor myostatin (Fig. 2). It is secreted by hepatocytes in response to exercise, but secretion is impaired in cirrhosis.[113] Experimental data show that follistatin can reverse the impairment in skeletal muscle protein synthesis in animals with portosystemic shunting,[114] and patients with inclusion cell myositis treated with follistatin show increased performance in the 6MWT.[115] There is data from a randomised controlled trial supporting the effects of testosterone treatment on muscle mass in hypogonadal males with cirrhosis,[116] but theoretical safety concerns have precluded its widespread acceptance. Larger trials with longer follow-up times are required. Future studies evaluating the impact of HE therapies on muscle mass and function are awaited. With exciting advances in gut microbiota, there may be strategies to modify the microbiome to benefit skeletal muscle function in patients with cirrhosis.[117] Lastly, as has been done in other chronic disease populations, there is a justifiable need for educational initiatives and formal exercise guidelines through national hepatology and transplantation organisations. It is essential that health practitioners feel supported to make exercise and nutrition prescriptions a routine part of every clinic visit.

As has been demonstrated across a range of chronic diseases, including frailty management[118,119] and prevention,[120] lung disease,[121]

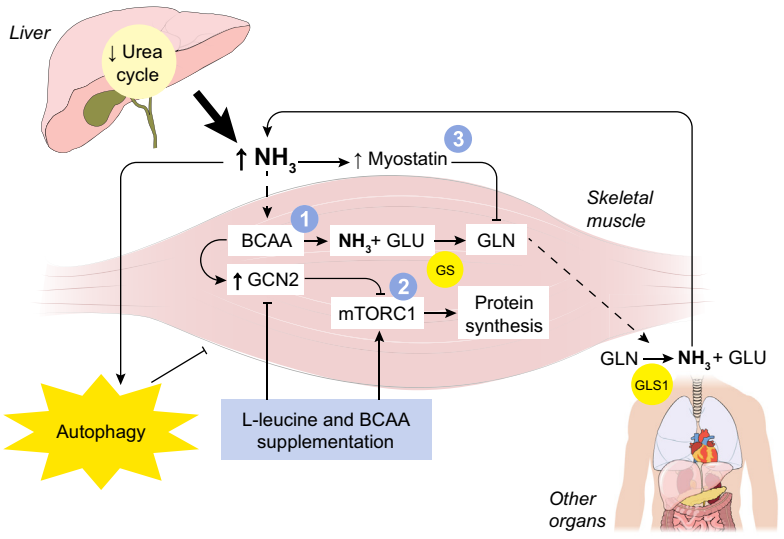

Fig. 2. Elevated ammonia as a cause for sarcopenia in cirrhosis. Hyperammonemia from impaired hepatic detoxification affects skeletal muscle by 1) causing intracellular amino acid depletion in association with production and export of glutamine (what is metabolised back to ammonia in extra-muscular tissues, thus perpetuating damage); 2) blocking of mammalian target of rapamycin complex 1 and affecting protein anabolism; and 3) increasing myostatin expression and favoring skeletal muscle catabolism. Experimental data also substantiates a role for hyperammonemia in promoting skeletal muscle autophagy. BCAA, branch-chain amino acids; GCN2, general control non-depressible 2 (amino acid deficiency sensor); GLN, glutamine; GLU, glutamate; GLS1, glutaminase; GS, glutamine synthetase; mTORC1, mammalian target of rapamycin complex 1; NH_3, ammonia.

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and colorectal cancer,[122] we believe that the routine integration of exercise and nutrition regimens will reduce health care costs/utilisation while improving muscle health, functionality, and HRQoL for our patients with cirrhosis.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

All authors contributed to the concept, design, recommendations, and manuscript preparation.

Supplementary data

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