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Exercise physiology in cirrhosis and the potential benefits of exercise interventions – a review

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Running head: Exercise physiology in cirrhosis

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Abstract

Reduction in muscle mass is a highly prevalent phenomenon in cirrhosis and is now well-documented to be associated with significant morbidity and mortality. Research into muscle loss in cirrhosis remains limited by an ongoing poor understanding of its relationship with muscle function, physical activity and aerobic capacity. Alterations in exercise physiology have been documented in studies of individuals with cirrhosis that provide important information on physical function that is not captured by simple quantification of muscle mass. Despite expert consensus recommending regular exercise in end-stage liver disease to maintain muscle mass and function, there is little evidence guiding clinicians as to which form of exercise or delivery mechanism is most effective. It also remains unproven whether any specific intervention can alter clinically relevant outcomes. This review article summaries the available literature regarding the changes in exercise physiology observed in cirrhosis, the associated impact on physical capacity and the results of existing trials that examine the potential benefits of exercise delivery in patients with cirrhosis, particularly pertaining to their impact on exercise physiology.

Keywords: cirrhosis, exercise, frailty, sarcopenia, muscle

Introduction

The adverse clinical impact of malnutrition and sarcopenia is well-established in cirrhotic liver disease, with reports of increased morbidity and mortality both pre- and post-liver transplant. (1) Their prevalence varies depending on the chosen definition and diagnostic method, but sarcopenia has been estimated to occur in up to 70% of patients with cirrhosis. (2) Despite strong recommendations from consensus groups regarding nutritional therapies for patients with cirrhosis, evidence remains weak, and although some promising nutraceuticals and pharmacological agents have been studied, there is still no intervention for sarcopenia that is supported by large multi-centre randomised trials. (3, 4)

Patients with cirrhosis similarly display very low levels of physical activity and have altered exercise physiology with impairment in aerobic capacity. (5) Although less extensively studied in cirrhosis than sarcopenia, these impairments in physical capacity can be measured objectively and have also been associated with adverse clinical outcomes. (6, 7) Physical function may in fact be a better measure of risk than muscle mass, as evidenced by general population data demonstrating quadriceps strength to be a more powerful predictor of mortality than muscle area. (8) Steps walked per day are also significantly associated with lower all-cause mortality, and measures of cardiorespiratory fitness and physical performance predict mortality. (9, 10)

In the general population, aerobic exercise improves cardiorespiratory fitness, which in turn lowers risk of all-cause mortality. (11) Physical exercise has been shown to improve muscle strength and functional ability in frail older adults, as well as increase functional capacity in chronic disease populations such as chronic kidney disease. (12, 13) Similar research in cirrhosis is at an early stage, with concerns regarding safety of exercise in patients with cirrhosis potentially impeding its progress in the past. This review summarises the current literature evaluating the alterations in physical capacity observed in cirrhosis and the potential benefits of exercise interventions.

Methods

Articles were retrieved via a search of Pubmed and MEDLINE via Ovid in April 2020. Databases were searched from inception to April 2020 using the MeSH terms ‘Liver Disease’, ‘Liver Transplantation’, ‘Exercise’, ‘Exercise Therapy’, ‘Physical Activity’, ‘Activities of Daily Living’,

'Muscular Atrophy', 'Frailty', 'Muscle Strength' or 'Muscle Mass'. Prominent authors in the field, other relevant journals and primary source reference lists were searched manually. All articles examining exercise interventions that included at least 3 patients with cirrhosis were included. Publications that included only patients with non-cirrhotic liver disease or exclusively post-liver transplant subjects were excluded. Controlled and observational studies were included however case reports were not.

Results

Alterations in exercise physiology in cirrhosis

Severe malnutrition is common in cirrhosis; reduced total energy intake combined with derangement of complex metabolic pathways results in substantial loss of skeletal muscle mass and function. (3) These metabolic derangements cause patients to derive a lower proportion of energy from carbohydrate, evidenced by low respiratory quotients in patients with cirrhosis as measured by Indirect Calorimetry (IC). (14) Reduced hepatic glycogen stores drive an inappropriate consumption of body fat and protein stores for gluconeogenesis, in a capacity that resembles a state of starvation. (15) Basal metabolic rate is also commonly elevated in patients with cirrhosis, which likely drives further consumption of body fat and protein stores. (16)

Patients with cirrhosis also exhibit an increased baseline cardiac output. Splanchnic vasodilatation occurs as a result of increased circulatory vasodilators, resulting in redistribution of blood volume, increased splanchnic blood flow, and central hypovolaemia. (17) This results in a hyperdynamic circulation, whereby baseline heart rate and cardiac output are increased while systemic vascular resistance and arterial blood pressure are decreased. (18) This elevated baseline cardiac output and associated cirrhotic cardiomyopathy with chronotropic incompetence is one of the contributors to impaired aerobic capacity in cirrhosis. Altered metabolic responses to exercise affecting glucose production and usage, reduced skeletal muscle mass and function, underlying anaemia and impairment in pulmonary gas exchange also play a role. (5, 19)

VO_{2peak} is the peak oxygen uptake achieved by a patient exercising to volitional exhaustion during cardiopulmonary exercise testing (CPET), and provides a global reflection of a patient's cardiorespiratory fitness. (20) Studies of patients with cirrhosis have demonstrated VO_{2peak} values

to be as low as 51.7% of predicted values. (21) A recent systematic review of Cardiopulmonary Exercise Testing (CPET) in 1107 liver transplant (LT) candidates found the weighted mean baseline VO_{2peak} to be 17.4 (1.9) mL/kg/min. (6) This corresponds to the level predicted in a sedentary female in her 70s, and falls below the 18mL/kg/min threshold considered necessary for full and independent living. (22, 23) The alterations in exercise physiology that occur in cirrhosis are summarised in Figure 1.

Physical capacity is reduced in cirrhosis

While reduced muscle mass has been estimated to occur in 40-70% of patients with cirrhosis depending on the method of assessment, the prevalence of frailty in patients awaiting LT ranges from 17-43%. (3, 24) Such frailty measures encompass gait speed, balance and physical strength. Physical capacity is a measure of a patient's function, assessing ability to perform tasks that are dependent on their musculoskeletal and aerobic capacity. (25) Impairment in the ability to perform activities of daily living (ADLs) have been reported in cirrhosis, with 31% of patients having difficulty with at least 1 ADL and 40% requiring assistance with ≥1 ADL. (26)

General activity levels are lower in patients with cirrhosis, and the advent of personal activity trackers has allowed objective measurement of this. A Japanese study comparing 74 patients with cirrhosis to 27 healthy volunteers found that when measured objectively via an accelerometer, patients with cirrhosis had significantly lower average steps per day, and lower exercise levels than healthy individuals. (27) A second study found that despite patients self-reporting near-normal levels of daily activity, average daily step count approximated that of patients with dialysis-dependent chronic renal failure and COPD, and found that patients with cirrhosis spent 75.9% of their time in sedentary behaviour compared to reference values of 62% for people aged 60-69. (28)

Other commonly quantified measures of physical function in cirrhosis include the 6-minute walk distance (6MWD) and handgrip strength (HGS). Reported values in patients with cirrhosis are well below that seen in healthy controls. A study comparing 45 healthy subjects with 98 liver cirrhosis patients found the average 6MWD of healthy controls was 115m longer than that of patients with cirrhosis (p=0.001). (29) Similarly, reduced HGS is common among patients with cirrhosis, with a

reported prevalence of up to 63% compared to 21.7% and 4.08% of control groups of hypertensive patients and patients with functional gastrointestinal disorders respectively. (30)

Clinical Impact of reduced physical capacity in cirrhosis

Impaired physical capacity has broad prognostic implications in cirrhosis, most importantly on mortality. Table 1 summarises the current evidence linking the various domains of impairment to mortality in patients with cirrhosis.

Morbidity is similarly impacted by reduced physical capacity. In a study of 587 patients with cirrhosis awaiting LT, the presence of frailty was independently associated with total hospitalisation days per year, with an incidence rate ratio of 1.21 when adjusted for MELD, albumin and sex (p=0.03). (31) A separate study in a cohort of 373 patients with cirrhosis evaluated for LT assessing physical function via gait speed found that each 0.1m/s decrease in gait speed was associated with 22% greater subsequent hospitalisation days (p<0.001). (32) This association remained significant when adjusted for liver disease severity. Physical capacity was assessed via the Short Physical Performance Battery (SPPB) test in an Egyptian study of inpatients with cirrhosis, which showed that patients who were subsequently readmitted to hospital within 90 days had a significantly lower mean frailty score than those who were not (4.88 $\pm$ 1.96 versus 7.56 $\pm$ 2.95; p<0.001). (33)

Importantly, reduced physical capacity may render a patient with cirrhosis untransplantable. In a study of 197 outpatients with cirrhosis waitlisted for LT, physical frailty was assessed via both handgrip strength and gait speed, with both assessments being associated with waitlist drop-out. Patients removed from the waiting list due to medical concerns had weaker handgrip strength at the time of listing than those who remained (46.14 lb vs 59.6 lb; p<0.005), and had slower gait speed during the 5-metre walk test (0.92m/s vs 1.03m/s; p<0.005). (34)

Poor cardiorespiratory fitness as assessed by ventilatory threshold (VT) is also a risk factor for infections in cirrhosis. VT is a submaximal marker of cardiorespiratory fitness, representing the onset of increased anaerobic metabolism at the point when aerobic capacity becomes insufficient

for exercise intensity. (35) In a cohort of 82 patients waitlisted for LT, patients who developed a septic episode had a significantly lower VT than those who did not (median [IQR] 9.5 [7.8-11.9] mL/kg/min versus 11.8 [10.5-13.8] ml/kg/min; p=0.003). (35) On multivariate logistic regression analysis, VT was independently associated with the development of sepsis (Odds ratio, 0.675; 95%CI 0.471-0.965; p=0.03). These findings are in keeping with data documented for the increased susceptibility of sarcopenic waitlisted patients to bacterial infections. For example, one study of 112 patients evaluated for LT found the frequency of sepsis-related deaths to be 22% in sarcopenic patients compared to 8% in non-sarcopenic patients (p=0.02). (36)

Frailty and sarcopenia are also implicated in the pathogenesis of hepatic encephalopathy. In the absence of normal liver function, skeletal muscle plays a compensatory role in the metabolism of ammonia, reducing levels via the enzyme glutamine synthetase. (37) Consequently, the reduction in skeletal muscle mass and function seen in sarcopenia and physical frailty further decreases the body's capacity to metabolise ammonia, leading to increased risk of hyperammonaemia and the development of hepatic encephalopathy. (38, 39) Impaired physical function also has implications for quality of life, and frailty has been associated with poorer health-related quality of life as measured by tools such as the 36-Item Short-Form Health Survey (SF-36). (40)

Clinical Trials of Exercise Interventions in Cirrhosis

Seventeen studies investigating the impact of exercise were identified in patients with cirrhosis and are summarised in Table 2.

Eight randomized control trials (RCT), 1 non-randomised control trial (NRCT), and 8 observational cohort studies were reviewed, ranging from 6 to 50 subjects in size. Duration of intervention varied from 6 weeks to 12 months, and frequency of exercise sessions ranged from 1 to 3-times weekly, discounting those with daily step count targets.

Exclusion criteria varied between studies although there were observed similarities. Nine studies excluded patients based on presence of cardiovascular comorbidity, 10 studies excluded patients with any physical or musculoskeletal limitations to exercise, 10 studies excluded patients due to

presence of hepatocellular carcinoma, and 8 studies precluded participation based on recent hepatic decompensation.

Ten studies were comprised of a purely aerobic exercise intervention, 6 had both an aerobic and resistance exercise component, and 1 study was purely a resistance exercise intervention. In regard to the aerobic interventions, 3 studies used a combination of cycle ergometry and walking exercise, 5 used solely cycle ergometry and 6 used solely walking exercise. One study implemented a gym-based aerobic intervention and 1 study used bench step exercises. Of the 7 studies that included a resistance exercise component, 5 used either weights, resistance bands or gym machines, 1 used body weight exercises only, and 1 used kinesiotherapy.

Eight of the 17 studies used directly supervised interventions, and a further 2 studies used partially supervised programs whereby patients would be supervised intermittently. Sixteen studies showed significant positive results while 1 study demonstrated no significant benefits of exercise therapy.

Impact of Exercise on Aerobic Capacity

All 17 of the reviewed studies investigated the effect of exercise on aerobic capacity. Nine studies used CPET to measure aerobic outcomes, with 5 studies reporting significant improvements in VO_{2peak} following the exercise intervention (41-45) and 4 showing no benefit. Improvements ranged from 1.7mL/kg/min to 5.3mL/kg/min, and resulted from a minimum regimen of 6-8 weeks of 3-times-weekly aerobic exercise. The negative studies were relatively small in size and tended to assess aerobic capacity as a secondary outcome, focusing on outcomes such as the safety of exercise programs and the effect of exercise on hepatic venous pressure gradient. (46-49)

When analysed, compliance influenced efficacy of exercise interventions. Kruger et al. reported an absolute increase of 1.7mL/kg/min in VO_{2peak} in 20 outpatients with cirrhosis using cycle ergometers ($p=0.03$). (41) This improvement increased to 2.9mL/kg/min when stratified for patient adherence, defined as attendance at $\geq$80% of sessions ($p=0.01$).

VO_{2peak} tended to decrease over time in subjects following usual care practices in studies with control arms. Two studies showed trends in their usual care groups toward a decreased VO_{2peak} while Morkane et al. reported a significant 1.9mL/kg/min decrease in VO_{2peak} (p=0.03). (44, 45, 49) In the one study that assessed durability of response to exercise, follow-up CPET 6 weeks after program cessation showed that VO_{2peak} increase declined from 2.3 to 1.2ml/kg/min above baseline, and the improvement was no longer significant. (45)

Six studies reported significant improvements in the 6MWD following an exercise intervention. (41, 43, 44, 49-51) In 4 of these studies, the increases in 6MWD resulted from 2 to 3-times weekly cycle ergometry sessions at 60-80% of maximal intensity for between 8 and 12 weeks, and resulting improvements were 80m, 33.7m, 40m and 41.4m (p=0.01, p=0.02, p<0.02 and p=0.02 respectively). When stratified for adherence, the 6MWD recorded by Kruger et al. improved from an increase of 33.7m to 46.4m compared to the usual care group (p=0.009). (41)

The largest reported increase in 6MWD was 151m, shown by Chen et al. following their pedometer guided intervention (p=0.03). (49) Aamann et al. reported a 32m increase in 6MWD within their exercising group following their program of resistance exercise only (p<0.01). (51) The one study which reported no significant improvement in 6MWD was an 8-week cycle ergometry study which was primarily focused on assessing the safety and feasibility of exercise training in patients awaiting LT. (47)

One study assessed aerobic capacity by determining patients' anaerobic threshold via blood samples analysed with a portable blood lactate measuring device. (52) Anaerobic threshold was measured in Metabolic equivalents of task (Mets), a measure of the ratio of energy expended compared to the energy used when completely at rest, which is defined as 1 Met. (52) Following a 12-month program of bench-step exercises performed at anaerobic threshold for 140 minutes per week, patients demonstrated an increase in median anaerobic threshold of 1.5 Mets, equivalent to a 39% increase (p=0.03).

Impact of Exercise on Body Composition

Fourteen studies investigated the impact of exercise on body composition in cirrhosis. (41, 42, 44-46, 48-56) These studies used a variety of methods to measure muscle mass, including Dual-energy X-ray Absorptiometry (DXA), thigh circumference and thickness by ultrasound, cross-sectional area of the quadriceps muscle via MRI, cross-sectional muscle area using CT scan, and bioelectrical impedance (BIA). Eight of these 14 studies demonstrated increases in muscle mass, with improvements resulting from a minimum of 8-12 weeks of 3-times-weekly exercise. (41, 44, 46, 48-51, 53) Cumulatively across the 8 positive studies, significant improvements in muscle mass were demonstrated as assessed by each of the imaging modalities.

Fat mass was also reduced with exercise interventions, with Pattullo et al. also demonstrating an 11cm loss in the median waist circumference of patients following their 24-week pedometer-guided step count intervention ($p<0.001$). (56) A BIA study was able to demonstrate a 5kg decrease in body weight associated with a significant decrease in fat mass but no change in lean mass ($p<0.0001$), (42) similar to Konishi et al who reported a 2.2kg decrease in median fat weight following a 6-month pedometer-guided intervention ($p=0.008$). (55) Konishi et al. also used Computed Tomography to specifically measure areas of subcutaneous fat (SFA) and visceral fat (VFA), and found median SFA decreased by 34.6cm^2 ($p=0.001$) and median VFA decreased by 11.4cm^2 ($p=0.041$).

Impact of Exercise on Muscle Strength and Function

Seven studies assessed changes in muscle strength and function brought about by exercise, with 5 reporting positive findings. (43, 45, 51, 53, 57) Hiraoka et al. demonstrated a significant improvement in handgrip strength (HGS), reporting a 5.6% increase following their 12-week walking exercise program with daily step count targets ($p<0.01$). (53) An 11% increase in their patients' leg strength was also demonstrated, as measured on a cycle ergometer following the 12-week program ($p<0.01$). This is in keeping with other studies examining leg strength as an outcome. (43, 51) Williams et al. investigated the effect of exercise on functional capacity as measured by the Short Physical Performance Battery (SPPB). (57) They found an increase of 2.5

points in the SPPB score following their 12-week home-based exercise program of daily step targets and biweekly whole-body functional resistance exercises (p=0.02).

Impact of Exercise on Quality of Life

Thirteen studies investigated the effect of exercise on health-related quality of life (HRQoL) (41-44, 47-52, 55-57) using a variety of different techniques with 8 returning positive findings (42-44, 49-51, 56, 57). Three studies demonstrated an improvement in the SF-36 questionnaire post-intervention, including improvements in the general health, vitality, mental health, and social function domains of the SF-36. (43, 50, 51) The Chronic Liver Disease Questionnaire (CLDQ) was used by 5 studies however only 2 showed significant improvement. (42, 44) Improvement was particularly evident in patients who achieved a clinically relevant degree of weight loss. Williams et al. showed a 17.5% improvement in HRQoL as measured by the EQ-5D-5L (p=0.04) (57) and Pattullo et al. demonstrated a 26.5-point decrease in the Fatigue Impact Scale (p=0.006) and 4-point improvement in the Montgomery-Asberg Depression Rating Scale (p<0.001). (56)

Impact of Exercise on Portal Hypertension

Two studies to date have focused on the direct effects of exercise interventions on chronic portal hypertension. (42, 48) Berzigotti et al. investigated a leptin and weight-loss mediated effect on hepatic venous pressure gradient (HVPG) and demonstrated a 1.6mmHg reduction following 16 weeks of a once-weekly gym-based exercise session (p<0.0001). (42) A reduction of ≥10% in HVPG was deemed clinically-relevant and was seen in 42% of the population, with a ≥10% loss of bodyweight being associated with a greater decrease in HVPG (p=0.024).

A decrease in HVPG of 2.5mmHg in exercising subjects was demonstrated by Macias-Rodriguez et al. following 14-weeks of moderate-intensity cycle ergometry and kinesiotherapy three times a week (p=0.05). (48) The control group in the study, who received nutritional therapy only, showed a 4mmHg increase in HVPG over the same time period (p=0.039), leading to a significant between-group difference at completion of the study (p=0.009).

Impact of Exercise Training on Clinical Outcomes in Cirrhosis

Only one study to date has investigated the effect of an exercise program on clinical outcomes in patients with cirrhosis undergoing LT and interpretation of results is limited by its retrospective observational nature. (58) Al-Judaibi et al. reviewed 458 consecutive LT patients, comparing outcomes in those who were transplanted before and after the implementation of a physiotherapist-led exercise program. Patients who were deemed to require exercise conditioning by the multidisciplinary transplant team underwent the program until baseline functional target values of 6MWD >250m, HGS >30kg for men and >14kg for women, and Duke Activity Status Index score >4 were met. Patients in the exercise group had a significantly lower median length of intensive care unit stay prior to LT compared to the non-exercise group, (2 vs 3 days, p=0.0001). (58)

Safety of Exercise in Cirrhosis

Pre-commencement health screens took place before inclusion in each of the 17 trials that were reviewed. The American College of Sports Medicine recommends that any patient history or symptoms suggestive of cardiovascular, metabolic or renal disease should prompt medical referral and clearance prior to commencement of the exercise program. (59) Baseline assessment of exercise capacity identified health concerns in 1 study (48), where baseline CPET identified silent ischaemia in 3 prospective patients who were subsequently excluded from the intervention. Appropriate primary or secondary prophylaxis for variceal rupture was a criterion of inclusion for each trial that was included in the review.

Although regular exercise can reduce chronic portal hypertension, in the acute setting exercise has been shown to induce increases in portal pressure, even at intensities of 30-50% of maximal exertion levels. (60) This pressure increase has been shown to be blunted by the use of non-selective beta-blockers, with this blockade being demonstrated to induce a decrease in the HVPG during exercise in patients with cirrhosis. (61). Despite this increase there have been no reported incidences of complications arising from increased portal pressures in any of the studies reviewed.

Few side effects of exercise interventions have been reported in the existing literature, and include one patient withdrawing from an exercise program due to the development of hepatorenal syndrome that was likely unrelated to intervention (43), and one patient experiencing a minor knee injury which did not preclude continued exercise training (47). Marcias-Rodriguez et al. reported one episode of a hypertensive crisis relating to pre-existing cardiac disease during CPET. Two other reported complications included one episode of upper GI bleeding secondary to a duodenal ulcer induced by self-prescribing NSAIDs, and the development of a perianal abscess in a patient who was subsequently terminated from the study. (48)

Chen et al. reported one patient in the exercising group being admitted to hospital on two occasions for overt hepatic encephalopathy, along with an acute kidney injury in one of the admissions. (49) MELD-sodium score was unchanged throughout the study for both controls and exercising patients however. Aamann et al. reported two hospitalisations in exercising patients for paracentesis of ascites, and one patient leaving the program after 9 sessions due to pain from Scheuermann's disease. (51) There were numerous hospital admissions and two patient mortalities in the non-exercising control group, with both mortalities resulting from acute on chronic liver failure. Pattullo et al. reported one patient with cirrhosis developing clinical ascites associated with infectious diarrhoea, however this responded to diuretics and the patient continued the study. (56)

Nutrition Modification During Exercise

Fourteen of the 17 studies incorporated some form of specific nutrition intervention alongside the exercise program. Seven studies included dietician-prescribed daily calorie targets, all of which accounted for increased physical activity and were calculated using either patient weight, patient BMI or resting energy expenditure. (41, 42, 44, 45, 48, 55, 56) Two of these 7 studies intentionally prescribed a caloric deficit, however both included a reduction in bodyweight as a study endpoint and ensured an adequate protein intake was maintained. (42, 56) Ten studies in total included daily protein targets, all of which prescribed a minimum daily protein intake of either ≥1.2g/kg bodyweight or ≥20% of total dietary energy intake. (41, 42, 44, 45, 48, 49, 51, 55-57) Three studies prescribed patients branched-chain amino acid (BCAA) supplements, ranging from

10g/day up to 13.5g/day, (50, 52, 53) and one study prescribed 1000mg/day L-carnitine supplementation. (54)

Discussion

The prevalence of sarcopenia and frailty have been well established across multiple studies, and this study summarises the existing literature that shows that cirrhosis also has significant negative impacts on physical capacity. The adverse clinical implications of functional impairment in cirrhosis are similar to those previously reported for sarcopenia, with an increase in both pre-and post-transplant morbidity and mortality. Although a number of studies have examined exercise interventions to specifically address these impairments they are markedly heterogeneous, have significant limitations and it remains unknown how best to address reduced physical capacity in cirrhosis.

It is likely that physical exercise interventions confer benefit in cirrhosis, and this is supported by the overall findings of the studies reviewed here. Five studies out of the 9 which assessed patients via CPET demonstrated a significant improvement in VO_{2peak}, while 6 of 7 studies assessing 6MWD found significant increases in distance walked. Four studies reported significant increases in muscle strength and function, with one study showing improvement in HGS following a walking exercise with no specific upper body exercises, demonstrating the full-body benefits of aerobic exercise. (53) In addition, although heterogeneous in outcome measures, several studies reported increases in lean muscle mass. Measures of HRQoL also improved in 8 out of 13 studies in which they were assessed. The benefits that exercise has shown in cirrhosis along with the postulated mechanisms through which these occur are summarised in Figure 2.

Despite the encouraging findings, the studies included in this review have numerous limitations. All trials included predominantly male patients with well-compensated cirrhosis and relatively low MELD scores. There was a high degree of heterogeneity in both intervention types and outcome measures, particularly relating to muscle strength and muscle mass, which limits the generalisability of the results. Exclusion criteria also varied between trials, particularly in regard to comorbid illness and presence of hepatocellular carcinoma. Studies were generally small and of

short duration, however it is encouraging that despite this they were able to produce statistically significant results in certain domains, which raises the possibility that they may underestimate the potential benefits of a more sustained intervention, as progressive gains in function may occur with longer duration. While it is reassuring that there were no major complications directly attributable to the exercise interventions in the reported studies (in an appropriately screened cohort), a larger population size is clearly required to identify rare adverse effects, particularly those of high consequence such as variceal haemorrhage.

The relationship between outcome and exercise type, intensity and duration remains poorly understood. Small study sizes and variation in intervention type is undoubtedly a contributing factor to the variation in outcomes, though there is also the potential for patient factors, such as comorbidities, liver disease severity, intervention adherence and alterations in health behaviour outside the study, to be contributing. Few studies have actively monitored or measured patient activity levels outside of the prescribed intervention. Accounting for general changes in health behaviour resulting from being in an exercise-oriented study in future studies may help to quantify the contribution being made by external exercise activity to outcome measures.

It is also unknown what constitutes a clinically significant change in physical capacity in patients with cirrhosis. For example, improvements in VO_{2peak} that are considered clinically significant are derived from data determined in cardiac populations, which may not translate directly into patients with cirrhosis. (62) Similarly, an increase of 30.5meteres during the 6-minute walk is the minimal improvement required to confer a clinical benefit in patients with all-cause pathology, but this has not been validated in patients with cirrhosis. (63) It may be the case that absolute level is a more important intervention target than relative increase, and absolute thresholds for measures like VO_{2peak} should be sought rather than minimum clinically-relevant improvements. A recent systematic review was unable to establish a CPET-derived mortality threshold for pre-transplant mortality or post-transplant mortality due to heterogeneity in CPET parameters and CPET cut-off values used by different studies. (6) An absolute 6MWD of 250m has been associated with significantly higher mortality in several studies of patients with cirrhosis however, and may present a general threshold at which interventions can be aimed. (29, 64)

Exercise delivery can be either hospital-based exercise and home-based exercise. The majority of studies of exercise in cirrhosis to date have prescribed hospital-based exercise interventions that allow direct supervision of patients by clinicians as well as the provision of coaching and support. The formal commitment and group training environment that a hospital-based program constitutes also provides a degree of comradery and formalised discipline for patients. (41) Drawbacks are the requirement to attend the training site multiple times a week, leading to issues with health, transportation, distance, parking availability, costs, hospital resources as well as interference with domestic and work obligations for patients. (41, 57) This may preclude their use in many clinical environments for real-world use outside a clinical trial. Home-based exercise programs are more cost-effective, flexible in regard to timing and are inherently more accessible to all patients and thus have more potential for long-term use. (41, 57) Whether home-based exercise interventions can confer the same level of benefit remains unknown and requires future study.

Regardless of delivery method, adherence to exercise is vital to efficacy, as demonstrated by bigger improvements in VO_{2peak} and 6MWD when stratified for ≥80% exercise session attendance. (41) Despite weekly phone calls and biweekly attempts to visit patients in-home to supervise exercise sessions, total adherence to a home-based intervention was only 55%. (41) A second study reported good exercise adherence for the first six weeks of the exercise intervention when patients were receiving weekly phone calls, though this dropped sharply following cessation of phone calls. (57) Remote exercise monitoring and Telehealth offers a potential solution to adherence problems arising from home-based exercise programs, as demonstrated in multiple other populations. (65, 66) Such issues would need to be resolved prior to widespread uptake of an exercise intervention.

Given the known association between reduced physical capacity and adverse outcomes, it is feasible to postulate that exercise interventions can improve clinical outcomes for patients with cirrhosis. Although there are clear benefits in improving health-related quality of life and physical function for both the patient and their care-givers, data pertaining to hospitalisation, infection risk and mortality both pre- and post-LT is required to guide clinician decision-making. Existing studies however were primarily powered to assess the safety and feasibility of exercise interventions in cirrhosis, consequently lacking the power to detect clinical outcomes. Although retrospective data

suggests that improving muscle mass may reduce mortality in patients with cirrhosis, (67) no adequately powered randomised study has been performed for exercise or any other nutritional or pharmacological intervention to assess for clinical outcomes.

Given these data, our transplant unit strongly recommends patients undertake a combination of aerobic and resistance exercise tailored to the individual's clinical status. We believe that exercise recommendations are most effective when they are specific, personalised prescriptions designed by a physiotherapist with expertise in managing patients with liver disease. This can provide a safe intervention in the context of potential comorbid states such as severe frailty, hepatic encephalopathy, balance impairment or portal hypertension, while also maximising the likelihood of exercise adherence and efficacy through the reduction of patient-specific barriers to exercise.

In conclusion, this review demonstrates that reduced physical capacity is common in cirrhosis and clearly associated with adverse outcomes. A small number of interventional studies have explored the feasibility of exercise interventions and found numerous promising results in regard to the impact on quality of life, physical function and physical capacity. The design limitations and heterogeneity of these studies mean that we are unable to make strong recommendations in regard to the best delivery of an exercise intervention, but it is clear that some form of exercise should be recommended to patients with cirrhosis after appropriate safety screening. To aid consensus, future studies should aim to formalise safety screening prior to exercise. As with any intervention, exercise delivery is dependent on patient adherence, and future studies should attempt to elucidate not just what form exercise program is most effective but how it should be provided, and larger scale studies are required to assess the potential impact on clinically meaningful outcomes.

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Table 1: Impact of Reduced Physical Capacity on Mortality in Patients with Cirrhosis

Study	No. Pts	Measure of Physical Capacity	Definition of reduced physical capacity	Prevalence of reduced capacity as per definition	Impact on Mortality
Carey et al., 2017 **(68)**	396	Sarcopenia	L3 SMI by CT, $\leq 39 cm^2/m^2$ for women, $\leq 50 cm^2/m^2$ for men	33% in women, 50% in Men	HR 0.95 for waitlist mortality on multivariate analysis for each unit increase in SMI (p<0.001)
Montano-Loza et al., 2012 **(36)**	112	Sarcopenia	L3 SMI by CT, $\leq 38.5 cm^2/m^2$ for women, $\leq 52.4 cm^2/m^2$ for men	40%	HR 2.21 for waitlist mortality on multivariate analysis if sarcopenia present (p=0.008)
Lai et al., 2019 **(7)**	1044	Frailty	Liver Frailty Index ≥4.5	25%	HR 1.82 for 1-year waitlist mortality on multivariate analysis if frailty present (p<0.001)
Hanai et al., 2019 **(69)**	563 (375 men)	Frailty	HGS <30kg for men, <15kg for women	59% 30%	HR 2.09 for mortality on multivariate analysis if low HGS present in men (p<0.001), HR 2.14 for mortality on multivariate analysis if low HGS present in women (p=0.02)
McNally et al., 2018 **(70)**	278	Impaired Aerobic Capacity	6MWD	NA	Mean 6MWD was 266.1m in patients who died versus 331.8m in those who did not (p=0.05)
Yadav et al., 2015 **(71)**	213	Impaired Aerobic Capacity	6MWD < 250m	12%	HR 6.2 for waitlist mortality on univariate analysis if impaired aerobic capacity present (p<0.001)
Faustini Pereira et al., 2016 **(72)**	86	Impaired Aerobic Capacity	6MWD < 410m VO_{2peak} < 17mL/kg	NA NA	97% survival rate for patients with 6MWD >410m compared to 55% survival rate for patients with 6MWD <410m (p=0.0001) 94% survival rate for patients with VO_{2peak} >17mL/kg compared to 55% survival rate for patients with VO_{2peak}<17mL/kg (p=0.0001)

Bernal et al., 2014 **(73)**	176	Impaired Aerobic Capacity	Anaerobic Threshold VO_{2peak}	NA	10% reduction in mortality for each 1mL/kg/min increase in AT independent of MELD (p=0.02). Patients who died within 12 months had lower median VO_{2peak} values than those who did not (13.8 vs 17.4mL/kg/min, p<0.001).
Ow et al., 2014 **(74)**	164	Impaired Aerobic Capacity	VO_{2peak}	NA	OR 0.75 for 90-day waitlist mortality for each 1mL/min/Kg increase in VO_{2peak} independent of MELD (p=0.02)
Carey et al., 2010 **(64)**	121	Impaired Aerobic Capacity	6MWD < 250m	NA	HR 0.48 for waitlist mortality for each 100m increase in 6MWD on multivariate analysis (p=0.0001)
Dharancy et al., 2008 **(75)**	135	Impaired Aerobic Capacity	VO_{2peak} < 60% Predicted	54%	Patients with VO_{2peak} ≥60% predicted had 96.4% waitlist survival at 12 months, versus 64.7% in those with VO_{2peak} <60% (p=0.0003)

Legend: TPTI, Transversal Psoas Thickness Index; HR, Hazard Ratio; L3-SMI, L3-Skeletal Muscle Index; CT, Computed Tomography; HGS, Handgrip Strength; WLM, waitlist mortality; NWLM, Non-waitlist mortality; MELD, Model for end-stage liver disease; SPPB, short physical performance battery; 6MWD, 6-minute walk distance; 6MWD, 6-minute walk distance; VO_{2peak}, Peak VO_2; AT, anaerobic threshold; OR, Odds ratio; LT, Liver Transplantation

Table 2: Exercise Interventions in Cirrhosis

***denotes p value <0.05**

Study	Design	Population (No., MELD, %CPA, %M)	Exclusion Criteria	Intervention ± Comparator	Duration, Exercise Intensity	Location, Supervision, Adherence	Outcome Measures	Key findings
Kruger et al., 2018 (41)	RCT	n=40 Outpatients with cirrhosis Mean MELD 9.4±2.9 70% CPA 58% M	Comorbid illness precluding participation – cardiac, HCC, dialysis, inability to use exercise bike	Int: Home-Exercise Therapy (HET) consisting of 3 x 30-60-minute exercise sessions/week. Aerobic exercise via cycle ergometer, delivered and set up at patient home by exercise specialist. Nutritional counselling. (n=20) Participants contacted by phone weekly and attempts made to visit biweekly for exercise session supervision. Con: Usual care and usual activity including nutritional counselling (n=20)	8 Weeks, Moderate (60-80% of maximum heart rate)	Home-based, Unsupervised, 55% of patients fulfilled adherence criteria	Aerobic: CPET, 6MWD Body Composition: USS (quadriceps muscle thickness) HRQoL: EQ-VAS, CLDQ	Aerobic: VO_{2peak} increased by 1.7mL/kg/min* within the HET group with no change seen in UC (p=0.03) 6MWD increased by 33.7m* in the HET group compared to the UC group (p=0.02) Body Composition: Increased thigh circumference by 1.8cm*in HET group, no change in UC group (p=0.024) HRQoL: No significant within or between group differences identified Safety: No adverse events occurred during exercise testing or training
Aamann et al. 2020 (51)	RCT	n=39 Outpatients with cirrhosis Mean MELD	Child-Pugh stage C cirrhosis, neoplasia, any degree of HE,	Int: 1 hour supervised exercise sessions 3 times per week. Resistance	12 Weeks, Moderate intensity:	Hospital-based, Supervised,	Aerobic: 6MWD Muscle Strength:	Aerobic: 32m* (6%) increase in 6MWD within exercise group (p<0.01),

		10.8±2.8 51% CPA 77% M	neurological or psychiatric disorders, atypical diet, physical disability prohibiting a moderate exercise program, already exercising regularly	training via gym machines - 7 exercises incorporating the whole body: 3 exercises for legs, 2 for arms and chest, 1 for lower back muscles and 1 for abdominal muscles. Gradual progression of training intensity occurred (n= 20) Con: Instructed not to change their daily activity level during the intervention (n= 19) Oral protein supplements were given to all patients who reported protein intake <1.2g/kg/day at baseline	last 2-3 repetitions in each set challenging	Median attendance per exerciser was 82% of exercise sessions (range, 25-100%)	Peak Isokinetic knee extension torque Body Composition: MRI (quadriceps CSA – measured at two distinct points relative to distal femur, termed CSA50% and CSA60%), BIA, Anthropometry HRQoL: SF-36	no significant between group difference Muscle Strength: Peak knee extension torque increased by 13%* within the exercise group (p<0.001). The exercisers showed an 11Nm* greater gain in muscle strength compared to the control subjects (p=0.05). Body Composition: 4.4cm^2* increase in CSA60% compared to control subjects (p<0.01) 4.0cm^2* increase in CSA50% (p=0.02) 3%* Increase in whole body lean mass (p<0.01) 3%* increase in dry lean mass (p=0.02) HRQoL: Significant improvement in mental component summary (p<0.01) and vitality (p<0.01) and mental health components (p=0.03) of SF-36 Safety: No mortality in exercising

								group. 2 hospitalisations for paracentesis of ascites, 1 episode of back pain. 2 mortalities in control group, both from acute on chronic liver failure.
Macias-Rodríguez et al., 2016 (48)	RCT	n=25 Outpatients with cirrhosis Median (IQR) MELD 9 (8-12) 64% CPA	Renal failure, TIPS, hepatic venous outflow obstruction, high risk oesophageal varices, previous LT, cardiopulmonary disease, history of stroke, musculoskeletal disease impairing exercise, ongoing alcohol intake or smoking, pregnancy	Int: 3 supervised exercise sessions a week. 40 minutes of aerobic exercise via cycle ergometry, and 30 minutes of kinesiotherapy aimed at improving muscle strength and balance each session. Patients also received nutritional therapy, with extra calories given to the exercise group to account for the physical activity. (n=13) Con: Nutritional therapy only (n=12) All patients were receiving a non-selective beta-blocker by the time of recruitment	14 Weeks, Moderate (12-14 on Borg RPE scale)	Hospital based, Supervised, Adherence "excellent"	Aerobic: CPET Body Composition: BIA HRQoL: CLDQ HVPG Blood Ammonia Levels	Aerobic: 1.9 unit* Improvement in Ventilatory Efficiency (VE/VCO_2) in PEP group (p=0.033) Body Composition: 0.3°* increase in phase angle (p=0.029) HVPG: Decreased by 2.5mmHg* in exercise group (p=0.05) and increased by 4mmHg* in the control group (p=0.039) at 14 weeks compared to baseline, with a significant between-group difference (p=0.009) Safety: No episodes of variceal bleeding or HE were observed. Baseline CPET identified silent ischaemia in 3 patients who were subsequently excluded
Román et	RCT	n=23 Outpatients	Recent hepatic	Int: 1 hour supervised	12 Weeks,	Hospital	Aerobic:	Aerobic:

al., 2016 (46)		with cirrhosis Mean MELD 8.2±0.4 100% CPA 70% M	decompensation, recent variceal bleeding, MELD >25, presence of HCC, Contraindication for exercise	exercise session 3 times per week. Aerobic exercise (cycle ergometry and treadmill), upper body resistance exercise (weights, bands) (n=14). Con: 1 Relaxation Programme 3 times per week (sham intervention) (n=9).	Moderate (60-70% of maximum heartrate)	based, Supervised, Patients missed a mean of 2.3 sessions Mean adherence 93.6%	CPET Body Composition: DEXA Anthropometry Risk of Falls: Timed Up and Go Test	2.00-minute increase in total CPET effort time* (p<0.001) 1.5-minute increase in ventilatory anaerobic threshold time* (p=0.009) No change in VO_{2peak}. Body Composition: 0.94kg* decrease in fat body mass (p=0.003), 1.05kg* increase in lean body mass (p=0.01), 0.38kg* increase in lean appendicular mass (p=0.03), 0.34kg* increase in lean leg mass (p=0.02), 4.25cm* increase in upper thigh circumference (p=0.009) Risk of Falls: Decreased TUG time* (p=0.02) Safety: No decompensations of cirrhosis
Zenith et al., 2014 (44)	RCT	n=19 Outpatients with cirrhosis Mean MELD 10±2.2 74% CPA 79% M	History of significant cardiac disease, CRF on dialysis, Hb <110, HIV Infection, HCC, active non-HCC malignancy, myopathy, any	Int: 3 Sessions of supervised exercise per week. Aerobic exercise with cycle ergometer for 40 minutes per session. (n=9). Con: Usual Care (UC)	8 Weeks, Moderate (Equal to heart rate at 60-80% of baseline VO_{2peak})	Hospital based, Supervised, Attendance not reported	Aerobic: CPET, 6MWD Body Composition: USS (quadriceps muscle thickness), Anthropometry HRQoL:	Aerobic: VO_{2peak} increased by 5.3mL/Kg/min* in ET group compared with usual care group (p=0.001) 6MWD increased by 41.4m* within ET group (p=0.02)

			physical impairment preventing Exercise therapy, Post-LT	including individual nutritional plan (n=10)			CLDQ, EQ-VAS (measures self-perceived health status)	Body Composition: Thigh Circumference Increased by 1.05cm* (p=0.001) and Thigh Muscle Thickness by 0.06cm/m^2* (p=0.01) in ET group compared with UC HRQoL: Activity and Fatigue sub scores of CLDQ improved by 1.24* (p=0.01) and 0.80* (p=0.01) points respectively, EQ-VAS improved by 20.4 points* (p=0.01)
Chen et al. 2020 (49)	RCT	n=17 Outpatients with cirrhosis Mean MELD-Na 17±4 0%CPA 65% M	Creatinine ≥2mg/dL, large varices without beta-blocker therapy, persistent overt HE, HCC, hepatic hydrothorax, pulmonary vascular complications of portal hypertension, cardiorespiratory or musculoskeletal contraindications for exercise	Int: Pedometer-guided physical activity intervention, with progressively incrementing step count goals, increasing by 500 steps/day each week. Fortnightly review of activity logs with education and motivational interviews to increase physical activity up until week 8. +/- Daily to weekly motivational phone calls. (n=9) Con: Normal activity levels	12 weeks, Low intensity	Home-based, monitored via personal activity tracker, 88% adherence	Aerobic: Average daily step count, 6MWD, CPET Body Composition: CT, DEXA, BIA, anthropometry HRQoL SIP Questionnaire	Aerobic: 2627 steps/day* increase in average daily step count of HB-PAP group compared to control group at week 12 (p=0.001), difference evident from week 6 onwards. Decreased number of sedentary patients (performing <2500 steps/day) in HB-PAP group compared to control group (33-17% vs 25-43%* respectively, p=0.003) by end of study. 151m* increase in mean 6MWD of HB-PAP group compared to

				with personal activity tracker worn throughout study. (n=8) All patients received a standardised diet with A total protein intake of 1.2-1.5g/kg/day, light snack at night, and 12g/day of essential amino acids.				control group (p=0.03). Body Composition: Significant improvement in CT-PMI in HB-PAP group compared to control group (p=0.03) HRQoL: 4-point* improvement in ambulation domain of SIP within HB-PAP group (p=0.03) Safety: Patient inclusion contingent on absence of silent ischaemia at baseline CPET. No deterioration in MELD throughout study. One patient in exercising group admitted twice for overt HE.
Román et al., 2014 (50)	RCT	n=17 Outpatients with cirrhosis Median (Range) MELD 9.5 (7-12) 82% CPA 70% M	Recent hepatic decompensation or variceal bleeding, MELD>25, HCC, marked symptomatic comorbidities (cardiac, pulmonary, renal, untreated active depression).	Int: 1 hour supervised sessions, 3 days / week. Aerobic exercise (treadmill walking and cycle ergometry) in combination with oral leucine (10g/day) (n=8) Con: Oral leucine (10g/day) supplementation (n=9)	12 Weeks, Moderate (60-70% of maximum heart rate)	Hospital-based, Supervised, Median adherence 83.3% (range 69.4% - 97.2%)	Aerobic: 6MWD, 2MST Body Composition: Anthropometry HRQoL: SF-36	Aerobic: 6MWD increased by 80m* (29.8%) (p=0.01), 2MST increased by 50 steps* (p=0.02) Body Composition: Increased lower thigh circumference by 5cm* (p=0.02) BMI increased by 0.3kg/m^2 (p=0.05) HRQoL: Improvements in 'general health'* (p=0.03), 'vitality'*

								(p=0.01) and 'social function'* (p=0.04) domains of SF-36 Safety: No complications of cirrhosis observed in either group during the study
Wallen et al., 2019 (47)	RCT	n=17 Outpatients with cirrhosis Mean MELD 13.3±4.0 38% CPA 81% Male	Previous LT, currently listed for other organ transplant, currently smoking, adverse event during initial CPET, uncontrolled diabetes, any orthopaedic or neurological limitation to exercise	Int: 2 supervised and 1 unsupervised exercise sessions per week. Aerobic exercise with cycle ergometer or walking. Circuit-based resistance exercise using body weight or portable equipment, eg. Resistance bands. (Assessed at 4 weeks: n=8, assessed at 8 weeks: n=4) Con: Usual Care (UC) (Assessed at 4 weeks: n=9, Assessed at 8 weeks: n=4)	8 Weeks, Exercise intensity not reported	Hospital and home-based, partially supervised, 95% supervised adherence, 75% unsupervised adherence at 4 weeks. 100% and 88% adherence respectively at 8 weeks.	Aerobic: CPET, 6MWD Muscle Strength: HGS, Mid-thigh pull apparatus and force platform HRQoL: CLDQ	Aerobic, Muscle Strength, HRQoL: No significant findings in any domain Safety: No serious adverse events occurred during intervention period. One minor musculoskeletal injury to the knee occurred but did not preclude continued exercise training.
Morkane et al., 2020 (45)	NRCT	n=33 LT waitlist patients Mean MELD 13.7±4.6, 85% M	Non-cirrhotic liver disease, oncological diagnosis as primary indication for LT, contraindication to exercise training or	Int: 3 supervised 40-minute exercise sessions per week. Aerobic Exercise via interval training with cycle ergometer.	6 Weeks, Mix of moderate and severe intensity exercise	Hospital-based, Supervised, 56% (9/16) of patients completed	Aerobic: CPET Body Composition: Anthropometry Muscle Strength: HGS	Aerobic: VO_{2peak} increased by 2.3ml/kg/min* in the exercise group at week 6 (p=0.02), while VO_{2peak} decreased by 1.9ml/kg/min* at week 6 in the

			testing	Con: Usual Care. [Patients matched to those in the exercise group based on age, sex and MELD.] All patients received standardized nutritional assessment (via RFH Global Assessment Data Collection Form) and advice at baseline and at 6 weeks.		the full program of 6 weeks		control group (p=0.03). <u>Muscle Strength:</u> Increase in mean HGS in exercise group of 3kg (p=0.05).
Berzigotti et al., 2017 (42)	Obsv.	n=50 Outpatients with cirrhosis with HVPG ≥6mmHg and BMI ≥26kg/m^2 Mean MELD 9±3 92% CPA 62% M	Previous or ongoing ascites, previous or ongoing jaundice, severe bacterial infections leading to hospitalisation, HE, HCC, alcohol abstinence < 6months, untreated varices, CP score >8, presence of TIPS, previous LT, IHD, orthopaedic problems limiting exercise	One supervised 60-minute session per week, gym-based aerobic and resistance exercise. Abdominal workout and pump was avoided. Patients also encouraged to increase their standard daily physical activity (*ie unsupervised aspect).* Personalised hypocaloric normoproetic diet	16 Weeks, Moderate (10-12 on Borg RPE scale)	Hospital-based Supervised, 88% adherence	<u>Aerobic:</u> CPET <u>Body Composition:</u> Anthropometry, BIA <u>HRQoL:</u> CLDQ <u>HVPG</u> <u>Adipokines:</u> Leptin	<u>Aerobic:</u> VO_{2peak} increased by 4.4ml/kg/min*(p<0.0001) <u>Body Composition:</u> 5kg Decrease in BW* (p<0.0001) associated with a significant decrease in fat mass* (p<0.0001) and no change in lean mass, decreased waist circumference* (p<0.0001) <u>HRQoL:</u> Improvement in global score* (p<0.001) and in all domains* of the CLDQ (p<0.0001) <u>HVPG:</u> HVPG decreased by 1.6mmHg* (p<0.0001)

								A ≥10% BW loss was associated with a greater decrease in HVPG* (p=0.024) Adipokines: Leptin decreased by 9.4ng/mL* (p<0.0001)
Hiraoka et al., 2017 (53)	Obsv.	n=33 Outpatients with cirrhosis 91% CPA 39% M	Uncontrollable ascites, HbA1c > 7.0%, motor disturbance, viable HCC	Aerobic intervention via walking exercise (prescribed 2000 steps increase on average daily step count calculated over 3 weeks at baseline). Patients also received 13.5g BCAA supplementation as a late evening snack.	12 Weeks, Low intensity	Home-based, Unsupervised, 94% of patients completed the study	Aerobic: Average Daily Step Count Muscle Strength: Cycle ergometer (leg strength), HGS Body Composition: BIA Laboratory Data	Aerobic: 59.5%* increase in Average Daily Step Count at 3 months (p=0.02) Muscle Strength: 11%* increase in leg strength (p<0.01) and 5.6%* increase in HGS (p<0.01) at 3 months Body Composition: 1.3%* increase in muscle volume at 3 months (p<0.01) Laboratory Data: 0.94 point* increase in BCAA/Tyrosine ratio at 3 months (p=0.001)
Williams et al., 2019 (57)	Obsv.	n=18 LT waitlist patients Median (IQR) MELD 13 (12-26) 50% M	History of cardiovascular instability, significant HE (grade ≥2), inpatient at time of screening, inability to consent	Aerobic exercise via a walking program and accelerometer. Patients were given daily step targets that incremented each week based on previous performance, as	12 Weeks, Moderate (12-14 on Borg RPE scale)	Home-based, Unsupervised with weekly phone calls for first 6 weeks, no phone calls	Aerobic: ISWT, Average daily step count Functional Capacity: SPPB HRQoL:	Aerobic: Median ISWT increased by 50m* at 6 weeks (p≤0.01) and 210m* at 12 weeks (p≤0.01) Median average daily step count increased by 2700/day* at 12 weeks (p≤0.01)

				well as advised 30 minutes of 'brisk walking a day. Functional resistance exercises for upper and lower body performed biweekly with an exercise worksheet and video demonstrations as a guide. (Assessed at baseline: n= 18, Assessed at 6 weeks: n= 12, Assessed at 12 weeks: n = 9)		thereafter. <u>First 6 weeks adherence:</u> 82% to average daily step count, 90% to resistance exercise. <u>Week 7-12 adherence:</u> 53% to average daily steps, 78% to resistance exercise.	EQ-5D-5L, HADS	<u>Functional Capacity:</u> SPPB improved by 2.5* at 12 weeks (p=0.02) <u>HRQoL:</u> EQ-5D-5L improved by 17.5%* after 12 weeks (p=0.04) <u>Safety:</u> No reported adverse events related to the HBEP
Hiraoka et al. 2019 (54)	Obsv.	n=18 Outpatients with cirrhosis receiving BCAA supplements 50% CPA 56% Male	Refractory ascites, motor disturbance, HCC, exercise restriction owing to chronic heart failure or chronic respiratory, pancreatic or renal disease	Baseline average daily step count evaluated via pedometer over a period of 2-3 weeks. Following this, 1000mg/day L-carnitine supplementation and a 2000 step/day increase to average daily step count was commenced. Average daily steps, muscle function and muscle mass were assessed monthly	24 Weeks, Low intensity	Home-based, Unsupervised, Adherence to exercise not reported	<u>Aerobic:</u> Average daily step count <u>Muscle Strength:</u> HGS, Cycle Ergometer <u>Body Composition:</u> BIA <u>Muscle Cramping:</u> Numerical Pain Score, frequency of cramping	<u>Aerobic:</u> 1,282 steps/day* increase in average daily step count at 6 months (p<0.01) <u>Muscle Cramping:</u> Reduced frequency of muscle cramping complaints from 6.3/month at baseline to 3.1/month* and 2.1/month* at 3 and 6 months respectively (p=0.025, Holm's method)

				throughout the 6-month study				
Konishi et al. 2011 (55)	Obsv.	n=17 patients with CHC, 3 with cirrhosis 100% CPA 35% M	Presence of HCC, pregnancy, unable to perform prescribed exercise, SPB ≥180mmHg, IHD or severe arrhythmia	8-week diet-only intervention of prescribed target energy intakes, followed by a 24-week pedometer-guided aerobic intervention of ≥8000 steps/day ≥3 days/week on a flat field at a prescribed exercise intensity. Nutritional counselling continued for further 6-months via dietician-delivered sessions occurring every second month.	24 weeks, Light (50% of target heart rate calculated using the Karvonen formula)	Home-based, Unsupervised, monitored via pedometer, 47% of patients achieved target ADS	Aerobic: Average daily step count Body Composition: BIA, CT, anthropometry HRQoL: SF-36 Insulin Resistance: HOMA-IR Adipokines, Cytokines: TNF-α, IL-6, adiponectin, leptin	Aerobic: Significant* increase in average daily step count at 6 months compared to start of study (p=0.003) Body Composition: Median BMI decreased by 0.2kg/m^2* (p=0.004), median fat weight decreased by 2.2kg* (p=0.008), median SFA decreased by 34.6cm^2* (p=0.001), and median VFA decreased by 11.4cm^2* (p=0.041) after 6 months of exercise HRQoL: Trend towards improvement in the 'vitality' score of the SF-36 (p=0.087) Insulin Resistance: Median HOMA-IR decreased by 0.6* after 6 months of exercise (p=0.023) Adipokines: Median serum Leptin levels decreased by 9,300pg/mL*

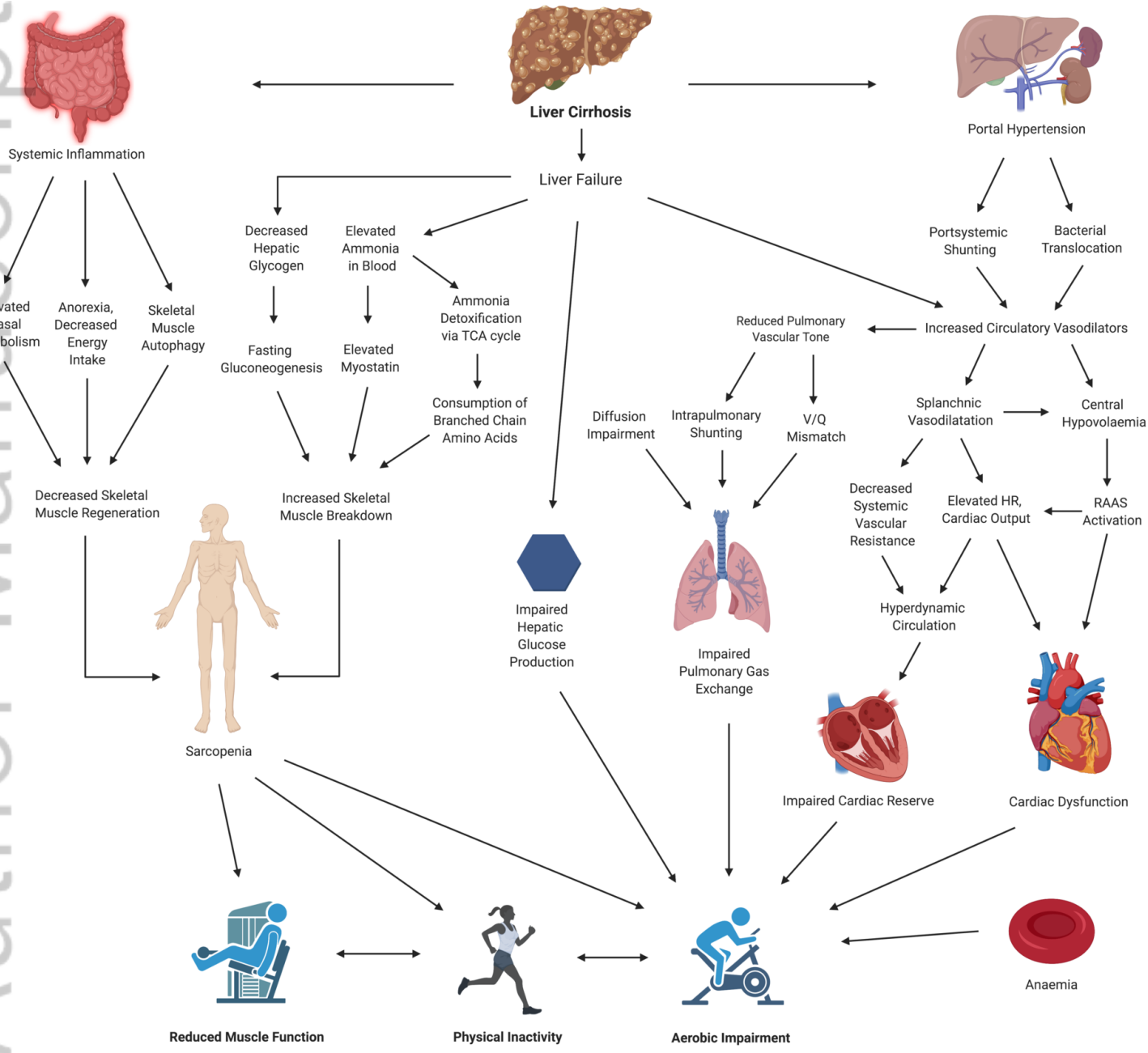
								(p=0.002) Safety: No liver function parameters worsened in any participant during the study period
Pattullo et al. 2013 (56)	Obsv.	n=16 patients with insulin-resistant CHC and BMI ≥30kg/m^2, 6 with cirrhosis Mean MELD 9±2.3 83% CPA 44% M	DM, pregnancy, pulmonary vascular complications, large oesophageal varices or gastric varices, medical condition precluding a sudden increase in physical activity or potentially compromising safety	Pedometer-monitored intervention. Baseline step count assessed over 3 days, followed by implementation of a daily step count target 3000 steps above baseline average. Gradual incrementing of average daily step count to reach ultimate target of ≥10,000 steps/day. Individualised nutritional plan designed to lose 0.5-1kg/week and improve insulin resistance. Cirrhotic patients recommended ≥1.2g/kg protein per day. Individually tailored behaviour therapy to facilitate behaviour change.	24 Weeks, low intensity	Home based, unsupervised, "Excellent" Adherence – 100% completion of 24-week protocol	Aerobic: Average daily step count Body Composition: Anthropometry HRQoL: FIS Insulin Resistance: HOMA-IR, Hepatic ISI Adipokines, Cytokines: TNF-α, IL-6, adiponectin, leptin	Aerobic: Significant increase in average daily step count at week 24 compared to week 0* (p=0.001) Body Composition: 8.2kg* loss in median weight (p<0.001), 4.69kg/m^2* loss in median BMI (p<0.001), and 11cm* loss in median waist circumference (p<0.001) at week 24 compared to week 0 HRQoL: 26.5-point* improvement in FIS score (p=0.006) and 4-point* improvement in MADRS score (p<0.001) at week 24 compared to week 0 Insulin Resistance: Median HOMA-IR decreased by 1.54* at week 24 compared to week 0 (p<0.001). 8 participants (50%) were no longer insulin resistant (HOMA-

								IR ≤2.0) at week 24* (p=0.008). Significant improvement in Hepatic ISI at week 24 compared to week 0 (p=0.009) Adipokines, Cytokines: 1.33ng/ml* decrease in serum Leptin at week 24 compared to week 0 (p=0.028) Safety: One patient with cirrhosis developed clinical ascites by week 4, however this responded to diuretics and the patient continued the study.
Debette-Gratien et al., 2015 (43)	Obsv.	n=8 Outpatients with cirrhosis Mean MELD 13±6 63% CPA 75% M	Patients presenting with a physical or mental disability or any other somatic problem prohibiting physical exercise.	Two supervised one-hour exercise sessions per week, for 12 weeks. Aerobic exercise with cycle ergometer for ≥20 minutes, resistance exercise with a weight bench for 20 minutes.	12 weeks, Moderate (Exercise performed at VT)	Hospital-based, Supervised, "Good" adherence	Aerobic: CPET, 6MWD Muscle Strength: IQS HRQoL: SF-36	Aerobic: Mean VO_{2peak} values increased by 1.7mL/kg/min* (p<0.008) 6MWD increased by 40m* (p<0.02) Mean maximal power values increased by 13W* (p<0.02) Mean ventilatory threshold power increased by 10W* (p<0.02) Muscle Strength: Mean IQS improved by 7kg* force (p<0.008) HRQoL:

								Improved 'perceived general state of health'* (p=0.02) and 'change of health in the previous year'* (p=0.02)
Nishida et al. 2016 (52)	Obsv.	n=6 Outpatients with cirrhosis 100% CPA 0% M	Congenital BCAA metabolism abnormalities, poorly controlled DM or concomitant corticosteroid therapy, enteral nutrition within previous 3 months, HCC, Child-Pugh stage B or C disease, inability to undertake exercise	Aerobic intervention via bench step exercises at an intensity corresponding to individual's AT, for 140 minutes per week. Group exercise sessions once per month to maintain subject motivation. 12.45g/day oral BCAA supplementation, and maintenance of usual dietary habits throughout the 12-month study.	12 Months, Moderate intensity (exercise performed at VT)	Home-based, Intermittently supervised, Adherence 100%	Aerobic: AT (Mets), average daily step count Body Composition: BIA, CT, Anthropometry HRQoL: SF-8 Insulin Resistance: HOMA-IR, Glycated Albumin, CLD-HbA1c	Aerobic: Increase of 1.5 Mets* (39%) in Anaerobic Threshold at 12 months (p=0.03) Insulin Resistance: Significantly decreased Glycated Albumin at 12 months (p=0.03)

Abbreviations: 2MST, 2-minute step test; 6MWD, 6-minute walk distance; ADS, Average daily step count; AT, Anaerobic threshold; BCAA, Branched-chain amino acids; BIA, Bioelectrical impedance analysis; CHC, Chronic hepatitis C; CLDQ, Chronic liver disease questionnaire; Con, Control group; CPA, Child Pugh score class A; CPET, Cardiopulmonary exercise test; CRF, Chronic renal failure; CSA, Cross-sectional area; CT-PMI, CT-based psoas muscle index; DEXA, Dual-energy X-ray absorptiometry; DM, Diabetes mellitus; EQ-5D-5L, EuroQol 5-dimension 5-level; EQ-VAS, EQ-visual analogue scale; FIS, Fatigue impact scale; HADS, Hospital anxiety and depression score; Hb, Haemoglobin; HCC, Hepatocellular carcinoma; HE, Hepatic encephalopathy; HGS, Handgrip strength; HIV, Human immunodeficiency virus; HOMA-IR, Homeostatic model of assessment of insulin resistance; HVPG, Hepatic venous pressure gradient; IHD, Ischaemic heart disease; Int, Intervention group; IQR, Interquartile Range; IQS, Isometric quadriceps strength; ISI, Insulin sensitivity index; ISWT, Incremental shuttle walk test; LT, Liver transplantation; M, Male; MADRS, Montgomery-Asberg depression rating scale; MELD, Model for end stage liver disease; Mets, Metabolic equivalents of task; NRCT, Non-randomised control trial; Obsv, Observational study; RCT, Randomised control trial; RPE, Rating of perceived exertion; SF-36, Short form-36 questionnaire; SF-8, Short form-8 questionnaire; SFA, Subcutaneous fat areas; SIP, Sickness impact profile questionnaire; SPB, Systolic blood pressure; SPPB, Short physical performance battery; TIPS, Transjugular intrahepatic portosystemic shunt; TUG, Timed up & go test; VFA, Visceral fat areas; VT, Ventilatory Threshold.

*: p<0.05



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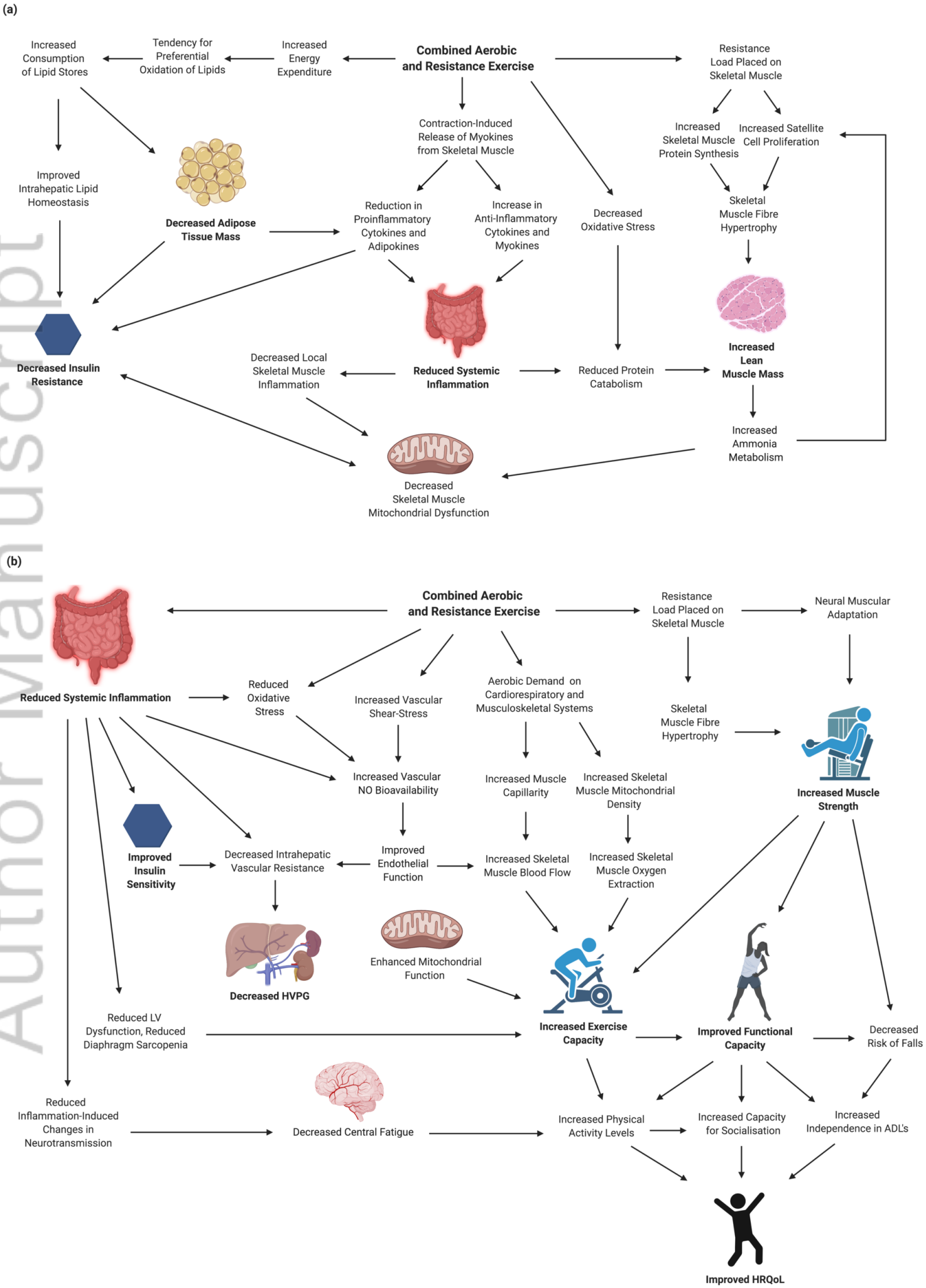

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