Does exercise training improve physical fitness and health in adult liver transplant recipients? A systematic review and meta-analysis

Stefan De Smet, PT, PhD[1-3], *Katriona O'Donoghue, Bsc*[4], *Maud Lormans, MD*[3], *Diethard Monbaliu, MD, PhD*[3,5*], *Liset Pengel, PhD*[6*]

[1]Department of Rehabilitation Sciences, Group Rehabilitation for Internal Disorders, KU Leuven, Leuven, Belgium
[2]Department of Microbiology, Immunology and Transplantation, Nephrology and Renal Transplantation Research Group, KU Leuven, Leuven, Belgium
[3]Department of Microbiology, Immunology and Transplantation, Laboratory of Abdominal Transplantation, KU Leuven, Leuven, Belgium
[4]Peter Morris Centre for Evidence in Transplantation, Clinical Effectiveness Unit, Royal College of Surgeons of England, London, UK
[5]Department of Abdominal Transplant Surgery and Coordination, University Hospitals Leuven, Leuven, Belgium
[6] Peter Morris Centre for Evidence in Transplantation, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK

Author contribution:

Conceived the study: S.D.S., K.O., M.L., D.M., L.P. Title, abstract, and full-text screening: K.O., M.L. Study quality assessment: S.D.S., K.O., M.L. Statistical analysis: S.D.S. Interpretation of the data: S.D.S., K.O., M.L., D.M., L.P. Drafting of the manuscript: S.D.S., D.M., L.P. All authors contributed to manuscript development and read and approved the final draft. *D.M. and L.P. share last authorship.

Corresponding author's contact information:

Stefan De Smet
Department of Rehabilitation Sciences
Group Rehabilitation for Internal Disorders
KU Leuven
Herestraat 49, 3000-Leuven, Belgium
E-mail: stefan.desmet@kuleuven.be

Conflicts of interest:

The authors declare no conflicts of interest.

Funding:

S.D.S. was funded by the Transplantoux Foundation, Leuven, Belgium. D.M. is a senior researcher of The Research Foundation – Flanders and is recipient of a Centrale Afdeling Voor Fractionering chair for abdominal transplant surgery.

Acknowledgements:

The authors would like to thank the liver transplant patients for their enthusiastic participation in the focus group.

ABSTRACT:

Background: The impaired physical fitness of end-stage liver disease patients often persists after liver transplantation (LT) and compromises posttransplant recovery. This systematic review and meta-analysis evaluated evidence supporting the potential of exercise training to improve physical fitness and health-related quality of life (HRQOL) after LT.

Methods: Bibliographic searches identified all randomised controlled trials (RCTs) comparing aerobic and/or strength training *versus* usual care after LT. Risk of bias was assessed and study outcomes measuring physical fitness and HRQOL were extracted. Meta-analysis was performed if at least three studies reported on an outcome.

Results: Eight RCTs (n=334) were identified. Methodological study quality varied and was poorly reported. Meta-analyses showed a trend for favorable effects of exercise on cardiorespiratory fitness (peak oxygen uptake or 6-min walking distance; 6 studies, n=275; SMD: 0.23, 95% CI: -0.01 to 0.48), and of strength training either or not combined with aerobic training on muscular fitness (dynamometry-assessed muscle strength or 30-second sit-to-stand test; 3 studies, n=114; SMD: 0.34, 95% CI: -0.03 to 0.72). A favorable effect was found for exercise on the SF-36 HRQOL physical function subcomponent (3 studies, n=194; MD: 9.1, 95% CI: 0.3 to 17.8). No exercise-related adverse events were observed.

Conclusion: RCTs indicate that exercise training in LT recipients is safe, improves physical function aspects of HRQOL, and may benefit cardiorespiratory and muscular fitness. The strength of evidence is, however, limited by the low number of patients and study quality. More adequately powered, high-quality RCTs are warranted.

ABSTRACT WORD COUNT: 242/250

MANUSCRIPT WORD COUNT (INCLUDING ABSTRACT): 4183

KEYWORDS: Liver transplantation, physical training, peak oxygen uptake, muscle strength, cardiovascular health

ABBREVIATIONS:

6MWD: 6-minute walking distance; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BIA: bioelectrical impedance analysis; BMI: body mass index; CLQD: Chronic Liver Disease Questionnaire; FAP: Familial amyloidotic polyneuropathy disease; GGT: gamma-glutamyl transferase; HDL: high-density lipoprotein; HRQOL: Health-related quality of life; ICU: Intensive care unit; INR: international normalized ratio; IQR: interquartile range; LDL: low-density lipoprotein; LT: liver transplantation; MD: Mean difference; PND: polyneuropathy disability; NR: not reported; PT: prothrombin time; SF-12 or -36; Short-Form Health Survey-12 or -36; SMD: Standardized mean difference; VO_2peak: peak oxygen uptake

1. BACKGROUND

Patients with end-stage liver disease commonly develop sarcopenia [1] as a consequence of the multifactorial catabolic state involving increased gluconeogenesis, hypermetabolism, gastrointestinal dysfunction, systemic low-grade inflammation, hypotestosteronaemia, muscle hyperammonaemia, and physical inactivity.[2] In the early posttransplant period, catabolism is aggravated by immobilization, glucocorticosteroid therapy, surgery-induced counter-regulatory hormone production, and impaired insulin secretion and/or peripheral insulin sensitivity.[3–5] Later, while body weight rapidly recovers and exceeds pretransplant levels due to excessive intra-abdominal and subcutaneous fat accretion, at 2 years posttransplant, muscle mass typically has not recovered [6,7] and sarcopenia persists.[8,9] Whereas hand grip strength recovers within the first year after transplantation, knee extensor muscle strength remains impaired up until two years posttransplant.[5,10,11] This is problematic as impaired muscle mass and strength are known determinants of (in)dependency in activities of daily living.[12] While sarcopenia is not only associated with impaired quality of life, morbidity, and mortality in liver cirrhosis, it also predicts short- and long-term mortality after liver transplantation.[13,14]

Along with poor muscle mass and function, patients with end-stage liver disease typically present with impaired cardiorespiratory fitness levels which may impair their independency in activities of daily living.[15,16] While patients exhibit pronounced physical inactivity [17,18], end-stage liver disease affects peak oxygen consumption (VO_2peak) through its extrahepatic manifestations in the cardiovascular, respiratory, cerebral, hematological, and muscular systems. Despite successful transplantation, LT recipients typically remain less physically active than the general population [19,20] and neither muscle mass nor cardiorespiratory fitness recover to healthy norms [21], placing them at risk for metabolic syndrome [19,22] and reduced health-related quality of life (HRQOL).[23–25] Furthermore, a sedentary lifestyle, poor physical fitness, sarcopenic obesity, and pharmacological immunosuppression are well-known risk factors for cardiovascular disease. In LT recipients, these coincide with other cardiovascular risk factors such as metabolic syndrome, diabetes, dyslipidemia, and arterial hypertension, all of which increase in prevalence during the first year(s) posttransplant.[26] Cardiovascular disease is a well-established time-dependent risk factor for mortality after LT during both the shorter and longer posttransplantation time-periods.[27]

Overwhelming evidence in the general population and emerging evidence in organ transplant recipients indicate that adequate physical activity and/or exercise training can maintain and improve physical fitness and cardiometabolic health, with exercise training being more effective than physical activity interventions.[18,28–32] Individualized home-based exercise in LT candidates has recently shown to improve frailty and patient survival.[33] Exercise-based physical rehabilitation focused on restoration in physical fitness is currently not part of post-LT routine care in most transplant centers.

This systematic review and meta-analysis aims to investigate the existing clinical evidence on the effectiveness and safety of exercise training in LT recipients as a means to improve physical fitness and HRQOL.

2. METHODS

2.1 Patient involvement

As part of the study protocol development, a focus group consisting of five LT recipients (aged 38 to 75; 1 woman, 4 men; LT 5 months to 9 years prior) was organized to identify the most important study outcome of the present systematic literature review from the perspective of the patients. These patients identified 'functional physical fitness', which they defined as 'the capacity to move freely, independently, comfortably, and confidently without instability or restrictions' as the primary outcome of interest for this study.

2.2 Protocol publication and ethics statement

This study's protocol was registered in PROSPERO (CRD42019123883) on February 27, 2019. The review was conducted in accordance with the 2009 PRISMA guidelines.[34] Given the nature of this study, using already published data, no ethical approval was sought.

2.3 Literature review search strategy

A bibliographic search was conducted from database inception through March 25th 2021 in: PubMed, Ovid EMBASE, Web of Science, The Cochrane Library, Transplant Library, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform. Vocabulary terms and keywords were combined for the population, intervention, and outcomes (**Supplemental Table 1**). Study titles and abstracts were screened independently by two investigators (KO, ML), who then reviewed the full-text versions of potentially eligible manuscripts and convened to agree on the selection of publications. Bibliographies of eligible publications were hand searched for titles not identified via electronic database searches. No language or date limits were applied.

2.4 Inclusion and exclusion criteria

Patient population – The study population included adult (≥18 year) LT recipients, irrespective of gender, time after discharge from the ICU, and etiology of liver disease.

Intervention – All interventions consisting of aerobic (endurance and interval) and peripheral muscle strength training, implemented after ICU discharge and lasting at least two weeks or a total of eight sessions were considered. Both supervised and home-based training interventions were included.

Comparator – Usual care or minimal intervention.

Study outcomes – The primary outcomes were parameters of physical fitness: cardiorespiratory-, muscular-, and motor fitness, morphological traits, and metabolic health (**Table 1**), and HRQOL. Secondary outcomes included adherence to the training program, fatigue, long-term physical activity behaviour, graft function, and adverse events.

Type of study designs – Randomized controlled trials.

2.5 Data extraction and analysis

Two investigators (KO, ML) independently extracted relevant study data using a prepiloted data collection form. A third investigator (SDS) identified discrepancies between data sets. Discrepancies were resolved through discussion, until consensus was reached.

2.6 Risk of bias assessment

Eligible publications were assessed for risk of bias using the Cochrane Risk of Bias Tool, independently by a minimum of two investigators (SDS, KO, ML).[35] Discrepancies were identified by a third investigator (LP) and resolved through discussion. As only seven full-text RCTs were included in the review, publication bias was not formally assessed.

2.7 Statistical analysis

Meta-analysis was performed if at least three studies reported on an outcome. Pooled intervention effects were calculated as mean differences (MD) or standardized mean differences (SMD) using postintervention means and SD of the intervention and control groups. Analyses were done using RevMan software (V5.3, The Cochrane Collaboration, 2014). The overall effect was assessed with $P<0.05$ being considered as statistically significant. Heterogeneity was assessed by visual inspection of forest plots and by quantitative evaluation using Chi^2 and I^2 tests. Because eligible studies were expected to have small sample sizes, Chi^2 P value <0.10 was considered indicative of significant heterogeneity; I^2 test ≥50% was considered indicative of substantial heterogeneity. If moderate or significant heterogeneity was present, a sensitivity analysis was performed whenever possible. Random-effects models were used because training characteristics (mode, volume, intensity, supervision) were expected to differ among studies. Subgroup analyses were planned to evaluate the role of training mode (strength, aerobic, and combined strength and aerobic training), training volume (≤1500 min *versus* >1500 total training minutes), training intensity (low, moderate, and high-intensity training [29]), and intervention delivery mode (supervised *versus* home-based), provided that subgroups included at least three studies.

3. RESULTS

3.1 Literature search strategy

After elimination of duplicates, literature search yielded 1,625 titles, of which 1,605 were excluded based on title and abstract (**Figure 1**). Following full-text screening of the remaining 20 records, 10 records did not meet the inclusion criteria. Eight full-text articles and two conference abstracts originating from eight independent studies (n=334 patients) were included.[36–45]

3.2 Study characteristics

A summary of the study characteristics and results is presented in **Table 2**. All except one study [45] initiated the study intervention within the first year after LT. Interventions lasted 2-10 months and involved supervised [38–44] and/or home-based [36–39,45] exercise training. Since Tomás *et al.* 2013 [39] performed only partial randomization to the subgroups home-based *versus* supervised training (personal communication), this meta-analysis considered both supervised and home-based programs together. Apart from one study that combined strength training with a walking program [37] and another study that investigated early postoperative strength training [44], all study interventions comprised moderate- to high-intensity aerobic exercise training with or without muscle strength exercises. Two studies combined exercise intervention with dietary advice.[36,45] Most studies failed to accurately describe their comparator of usual care; in one study, the control group was assigned a low-intensity intervention consisting of progressive walking.[37]

3.3 Assessment of study quality

The risk-of-bias assessment is summarized in **Figure 2**. Only Moya-Nájera *et al.* [42,43] and Hickman *et al.* [45] reported the use of random sequence generation. Mandel *et al*. and Hickman *et al*. were the only studies reporting on the randomization strategy, concealing allocation using envelopes and/or recruiting a blinded investigator.[37,45] Despite the nature of exercise interventions not allowing adequate blinding of participants, Mandel *et al*. addressed performance bias by ensuring that both exercise and control groups received a similar number of contacts (phone calls or office visits) and by assigning the control group to a low-intensity exercise intervention (progressive ambulation program), which would allow patients to anticipate clinical benefits.[37]

The study by Hickman *et al*. was considered at risk for detection bias because study participants acted as outcome assessors.[45] So was the study by Mandel *et al.*, because of investigators being in charge of both coaching and outcome assessment.[37] Basha *et al.* was considered not at-risk for detection bias, since they only investigated objective outcomes (body composition and blood lipid profile) unlikely to be affected.[41] Other studies did not report on blinding of outcome assessors, leaving detection bias risk unclear.

Two studies were at risk of attrition bias because of dropout rates that were either high [37], unequal between control and exercise groups [39], insufficiently justified [39], and/or because of unclear handling of missing values.[37]

Most studies were at low risk of reporting bias, with the exception of the study by Tomás *et al*., who reported on the outcomes fatigue and HRQOL in a 2011 conference abstract [38], but not in the subsequent 2013 original article.[39]

Lastly, Garcia *et al.* was considered at unclear risk for 'other potential sources of bias', because of a low sample size and between-group differences in gender distribution and age.[40]

Overall, study quality was heterogeneous, with many categories of bias considered at unclear risk due to poor reporting.

3.4 Meta-analysis of primary outcomes

Cardiorespiratory fitness:

Meta-analysis of six studies (n=275) [36,37,39,40,42,45] showed a trend for favourable effects of exercise training on cardiorespiratory fitness as evaluated by VO_2peak and 6-minute walking distance (6MWD) (SMD: 0.23, 95% CI: -0.01 to 0.48, P=0.06; Chi^2=2.57, P=0.77; I^2=0%; **Figure 3**). Insufficient studies were available for meta-analysis of VO_2peak in isolation. Pooled analysis of four studies (n=106) [37,39,40,45] showed no favourable effects of exercise training on 6MWD in isolation (MD: 26 m, 95% CI: -12 to 65 m, P=0.18; Chi^2=3.92, P=0.27; I^2=23%).

Mandel *et al.* investigated the effects of strength training in *de novo* LT recipients.[37] Aside from a progressive ambulation program delivered to both the exercise and control group, the study intervention did not include an aerobic exercise intervention. Exclusion of Mandel *et al.* was performed to assess whether the anticipated lack of strength training effects on cardiorespiratory fitness may have affected previous meta-analyses. However, exclusion of Mandel *et al.* did not change the outcome in either of both aforementioned meta-analyses (data not shown).

Muscular fitness:

Three studies assessed knee-extensor muscle strength by dynamometry.[36,39,42] One study assessed lower body muscle (strength-) endurance by means of a 30-second sit-to-stand test.[37] Pooled analysis on data from the four full-text articles (n=233) [36,37,39,42] showed no favourable effect of exercise training on lower body muscular fitness (SMD: 0.18, 95% CI: -0.13 to 0.49, P=0.27; Chi^2=3.82, P=0.28; I^2=22%; **Figure 4**).

To explore the effect of strength training in particular, either or not performed in conjunction with aerobic exercise, a subgroup analysis of three studies (n=114) [37,39,42] was conducted and showed a trend towards improved lower body muscular fitness (SMD: 0.34, 95% CI: -0.03 to 0.72, P=0.07; Chi^2=1.77, P=0.41; I^2=0%; **Figure 5**).

Motor fitness:

Only Moya-Nájera *et al.* evaluated changes in postural balance and global motor fitness (Timed Up and Go test); both improving after a 6-month exercise training program.[43] Tomás *et al.* reported on a cohort of 39 *de novo* LT recipients with familial amyloidotic polyneuropathy (FAP), and documented an improvement in the polyneuropathy disability score of 1 patient who participated in home-based training.[39]

Morphology:

Fat percentage was reported by four studies [36,39,41,42], however, the Krasnoff *et al.* study showed apparent errors in data reporting.[36] Meta-analysis of the three remaining studies (n=119) showed no significant effect of exercise training, whilst showing significant heterogeneity (MD: -1.5%, 95% CI: -5.1 to 2.1%, P=0.42; Chi^2=11.77, P=0.003; I^2=83%). The small number of studies did not allow a sensitivity analysis.

Four studies evaluated body composition, either by DXA scan [36,39] or bioelectrical impedance analysis (BIA) [41,42], and reported variable findings. Krasnoff *et al.* documented that both exercise and usual care groups experienced a significant increase in body weight, lean body mass, fat mass, and fat percentage.[36] However, similar to Moya-Najera *et al*., they did not find a significant difference in body composition between these groups.[42] In the FAP patient study, Tomás *et al*. found an increase in total body skeletal muscle mass that was greater in those allocated to supervised training than in those allocated to home-based training or usual care; no differences were found for fat mass or percentage, and proximal femur bone mineral density was found to be higher in usual care than in those undertaking supervised training.[39] Basha *et al.* reported a significant reduction in fat percentage and increase in muscle percentage in the exercise group relative to the usual care group.[41]

Moya-Nájera *et al.* reported that lower back and hamstring flexibility assessed by the sit and reach test was improved in the exercise group relative to the usual care group.[43]

Metabolic health:

Only two studies reported on metabolic health parameters. Basha *et al.* reported that *de novo* LT recipients after a 3-month supervised strength and aerobic training program showed significantly lower cholesterol and triglyceride levels compared to usual care.[41] Conversely, Hickman *et al.* found that a two-month aerobic and strength program along with a Mediterranean diet failed to improve metabolic syndrome severity score or laboratory markers of metabolic health.[45]

Health-related quality of life:

Because literature is scarce and a large variability exists in outcome measures used to quantify HRQOL, the meta-analysis was limited to the 'physical function' measure of SF-36 in three studies (n=194) (**Figure 6**).[36,37,42] A significant effect was found in favour of exercise training (MD: 9.1, 95% CI: 0.3 to 17.8, P=0.04; Chi^2=3.75, P=0.15; I^2=47%).

3.5 Secondary outcomes

Adherence:

Five studies reported on adherence rates to the allocated exercise program, and found them to be high for supervised programs, but variable for home-based programs.[36,37,40,42,45] The definitions of adherence varied according to study set up and are detailed in **Table 1**. Actual dropout rates in exercise *versus* control groups are discussed below. Moya-Nájera *et al.* and Garcia *et al.* reported an adherence rate of 94% and 100%, respectively, to the allocated supervised programs of strength and/or aerobic training.[40,42] In contrast, Krasnoff *et al.* found a 37% adherence rate to a home-based aerobic exercise and dietary intervention [36], whereas Mandel *et al.* reported an 82% adherence rate to a home-based strength training program with written exercise instructions, daily exercise logs, and bi-weekly telephone calls.[37] Last, Hickman *et al.* reported 52% and 71% attendance rates to virtually-delivered exercise and diet videoconferences, respectively.[45]

Fatigue:

In an abstract, Tomás *et al.* reported that fatigue did not improve in transplanted FAP patients allocated to home-based or supervised strength and aerobic training.[38]

Liver function:

Three studies reported on laboratory values of liver and kidney function.[36,37,42] Although group-specific data from baseline to the follow-up were not provided, all three studies reported that lab values of liver and kidney function remained in normal post-LT ranges in both exercise training and usual care groups.

Adverse events and dropouts:

Few studies reported on safety other than clarifying reasons for dropout.[37,44,45] Hickman *et al*., Ergene *et al*. and Mandel *et al*. specifically reported that no exercise-related adverse events were documented.

Five studies reported on dropout rates [36,37,39,42,43,45], which varied from 8 [39] to 56% [37] in the exercise groups, and from 0 [42,43] to 44% [37] in the usual care groups (**Table 1**). Pooled dropout rates in the exercise and usual care groups were 45 (n=74/164) and 46% (n=80/174), respectively.

Health-related dropouts may be worth noting in the light of safety evaluation. Moya-Nájera *et al*. reported that n=4/26 dropped out from exercise training, compared to n=0/28 participants in usual care.[42,43] Two of these four dropouts related to loss of vitality associated with hepatitis C virus recurrence. Mandel *et al.* reported a dropout rate of n=14/25 patients in the exercise group, *versus* n=11/25 in usual care.[37] In the exercise group, health-related dropouts were due to death (n=1), hospitalizations related to immunosuppression (n=7), knee pain (n=1), groin abscess formation (n=2), and renal failure (n=1). In usual care, health-related dropouts were due to death (n=1), hospitalizations related to immunosuppression (n=5), and fall injury unrelated to the study intervention (n=1). Krasnoff *et al*. reported a dropout rate of n=11/60 and n=11/81 in the intervention and usual care group, respectively.[36] Health-related dropouts in the intervention and control group included death (n=4 *vs*. 2, respectively) and illness (n=4 *vs*. 3, respectively).

4. DISCUSSION

Randomized controlled trials into the effects of aerobic and strength training after LT are scarce. Only eight RCTs were identified, which moreover presented with challenges of small sample sizes, a risk of bias due to the difficulty of applying blinded research in this setting, and poor methodological reporting. Despite these limitations and significant heterogeneity in study design, meta-analysis showed a statistically significant benefit of exercise training on the physical function subcomponent of the SF-36 HRQOL, as well as a trend for statistical significance for a favorable effect of exercise training on cardiorespiratory fitness, and of strength training on muscular fitness. The evidence from this systematic review and meta-analysis is encouraging. It indicates the need for well-designed RCTs in larger cohorts of patients, and this review highlights specific challenges that will need to be addressed when designing and interpreting these studies.

Although few studies reported on prospectively collected adverse events, across the selected RCTs, both aerobic and strength training interventions were found to be safe.[37,44,45] This review was restricted to RCTs because after LT, patients will experience changes in physical fitness that occur naturally and are independent of exercise. While a broader selection of studies may have allowed for wider insight in the safety aspect of exercise training, any future clinical trials should include prospective safety evaluations.

As per this study's design, the selected RCTs focused on strength training [37,44], others on aerobic training [36,40], but the majority [38,39,41–43,45] included both components. The duration of exercise programs was variable, though all lasted for at least two months and were therefore of sufficient duration to expect detectable training adaptations.[46] Although the objective was to identify optimal training mode, volume, intensity, and delivery method, a larger number of studies would be required to enable such investigation.

A small focus group with LT recipients held in preparation of the present review protocol suggested that, from a patient perspective, motor fitness should be considered an important training goal as it may contribute to 'functional physical fitness'. Few of the selected RCTs investigated postural balance and motor fitness other than by 6MWD. Moya-Nájera *et al.* reported that postural balance and the timed up-and-go-test (coordination, agility, and dynamic balance) were highly responsive to a six-month intervention of concurrent aerobic, strength, balance, and flexibility exercise.[43] Future studies should likewise address these outcomes.

The currently available data falls short in the evaluation of the impact of exercise training on metabolic and cardiovascular health. Two studies evaluated markers of metabolic health but reported contrasting findings.[41,45] The two largest studies did not indicate an important role for exercise training in the attenuation of fat mass accretion.[36,42] Long-term effects on cardiovascular events remain to be investigated. This is surprising, as metabolic and cardiovascular comorbidities after LT are abundant and exercise training is likely to positively impact metabolic and cardiovascular health.[26,32,41]

Risk of bias analysis of the selected RCTs revealed inadequate methodological reporting, in particular regarding selection and detection bias. The study quality was also compromised because of performance bias, which seems inherent to research involving physical exercise interventions. In an attempt to address this, Mandel *et al*. allocated a low-intensity progressive ambulation program to the control group, along with a follow-up schedule similar to that of the intervention group. Despite the lack of blinding, such approach leads to participants in both groups to experience subjective anticipatory benefits. Last, the average sample size was small (n=42) and most studies did not report whether an *a priori* power calculation was performed.

The nature of both the study patient population and study intervention warrant caution when translating the conclusions of this review to clinical practice. Most studies used strict in- and exclusion criteria related to age, etiology of liver failure, single *versus* multi-organ transplantation, and medical contraindications to exercise. In addition, willingness to participate in a physical exercise program requires a certain attitude, belief, and commitment from the patient. In the two largest studies, 11% (n=19/170) and 45% (n=45/99) of eligible study subjects declined to participate.[36,42,43] Moreover, adherence rates were variable across supervised and home-based programs, and in some studies dropout rates were substantial.[37] As a result, across the five studies that provided numbers of contacted study subjects, only 43% (n=338/779) were randomized, and only 33% (n=260/779) were eventually included in the final analyses.[36,37,39,42,43,45] The study population of this review thus represents a medically preselected (sub)group of LT patients who were willing and able to complete a physical exercise training program. Last, one study in particular investigated exercise training in patients suffering from FAP, a progressive neurodegenerative disease for which LT is currently considered the best treatment option to halt disease progression.[39] For FAP patients who typically exhibit malabsorption and malnutrition, a certain extent of weight gain, preferably driven by muscle mass, is considered beneficial. In other studies, LT was performed primarily as a treatment for advanced liver cirrhosis from various etiologies, where rapid posttransplant weight gain is generally considered problematic, as it is primarily driven by fat accretion and often leads to sarcopenic obesity.[5–8,10]

Two meta-analyses within the scope of the present study have recently been published.[47,48] Choo *et al.* (2022) evaluated the effects of supervised exercise training in both chronic liver disease and LT patients. [47] The authors included only one RCT in LT patients. Janaudis-Ferreira *et al.* (2021) evaluated the effects of exercise training *versus* control across all solid organ transplant recipient types and included only two RCTs in LT patients.[48] The present review includes eight unique RCTs in LT patients. Therefore, based on a stronger body of evidence and in line with the aforementioned meta-analyses, our findings may provide further support for the favorable effects of exercise training on cardiorespiratory and muscular fitness, and HRQOL after LT.

The present study holds several clinical implications. First, exercise training at moderate intensity is safe and benefits both mental and physical well-being after LT. Training programs should include both aerobic and muscle strengthening exercises to improve both cardiorespiratory and muscular fitness. Furthermore, postural stability exercises are advised to improve motor fitness and hence support activities of daily living.[12,43] Finally, both researchers and clinicians should beware of selection bias and training adherence. Home-based programs require thoughtful implementation strategies to ensure adequate adherence to the training program.

Further well-designed and adequately powered RCTs are warranted to identify the most effective training and implementation strategies, and to evaluate a standardized set of clinical (e.g., survival, cardiovascular health, graft function, physical fitness), patient-reported (e.g., HRQOL, depression, anxiety, social roles), and health-economic outcomes during the short and longer term follow up.

5. CONCLUSION

This study indicates that exercise training in LT recipients is safe, benefits the physical function aspect of HRQOL, and may lead to improved cardiorespiratory and muscular fitness. While clinical recommendations highlight the importance of physical activity and exercise in all types of solid organ transplantation, robust evidence to support this in LT recipients is still lacking. Well-designed and adequately powered RCTs are warranted.

6. REFERENCES

1. Kim HY, Jang JW. Sarcopenia in the prognosis of cirrhosis: Going beyond the MELD score. *World J Gastroenterol*. 2015;21(25):7637-7647. doi:10.3748/wjg.v21.i25.7637

2. Ebadi M, Bhanji RA, Mazurak VC, Montano-Loza AJ. Sarcopenia in cirrhosis: from pathogenesis to interventions. *J Gastroenterol*. 2019;54(10):845-859. doi:10.1007/s00535-019-01605-6

3. Schakman O, Kalista S, Barbé C, Loumaye A, Thissen JP. Glucocorticoid-induced skeletal muscle atrophy. *Int J Biochem Cell Biol*. 2013;45(10):2163-2172. doi:10.1016/j.biocel.2013.05.036

4. Schricker T, Lattermann R. Perioperative catabolism. *Can J Anesth*. 2015;62(2):182-193. doi:10.1007/s12630-014-0274-y

5. Plank LD, Metzger DJ, McCall JL, et al. Sequential changes in the metabolic response to orthotopic liver transplantation during the first year after surgery. *Ann Surg*. 2001;234(2):245-255. doi:10.1097/00000658-200108000-00015

6. Keogh JB, Tsalamandris C, Sewell RB, et al. Bone loss at the proximal femur and reduced lean mass following liver transplantation: a longitudinal study. *Nutrition*. 1999;15(9):661-664. http://www.ncbi.nlm.nih.gov/pubmed/10467609

7. Hussaini SH, Oldroyd B, Stewart SP, et al. Effects of orthotopic liver transplantation on body composition. *Liver*. 1998;18(3):173-179. http://www.ncbi.nlm.nih.gov/pubmed/9716227

8. Tsien C, Garber A, Narayanan A, et al. Post-liver transplantation sarcopenia in cirrhosis: A prospective evaluation. *J Gastroenterol Hepatol*. 2014;29(6):1250-1257. doi:10.1111/jgh.12524

9. Jeon JY, Wang H-J, Ock SY, et al. Newly developed sarcopenia as a prognostic factor for survival in patients who underwent liver transplantation. *PLoS One*. 2015;10(11):e0143966. doi:10.1371/journal.pone.0143966

10. Kaido T, Tamai Y, Hamaguchi Y, et al. Effects of pretransplant sarcopenia and sequential changes

in sarcopenic parameters after living donor liver transplantation. *Nutrition*. 2017;33:195-198. doi:10.1016/j.nut.2016.07.002

11. Krasnoff JB, Vintro AQ, Ascher NL, Bass NM, Dodd MJ, Painter PL. Objective measures of health-related quality of life over 24 months post-liver transplantation. *Clin Transplant*. 2005;19(1):1-9. doi:10.1111/j.1399-0012.2004.00306.x

12. Wang DXM, Yao J, Zirek Y, Reijnierse EM, Maier AB. Muscle mass, strength, and physical performance predicting activities of daily living: a meta-analysis. *J Cachexia Sarcopenia Muscle*. 2020;11(1):3-25. doi:10.1002/jcsm.12502

13. Montano-Loza AJ. Clinical relevance of sarcopenia in patients with cirrhosis. *World J Gastroenterol*. 2014;20(25):8061-8071. doi:10.3748/wjg.v20.i25.8061

14. Ferreira AP, Machado MV. Impact of pretransplant frailty and sarcopenia on the post-transplant prognosis of patients with liver cirrhosis: a systematic review. *Eur J Gastroenterol Hepatol*. 2021;33(1S):e883-e897. doi:10.1097/meg.0000000000002291

15. Ney M, Haykowsky MJ, Vandermeer B, Shah A, Ow M, Tandon P. Systematic review: pre- and post-operative prognostic value of cardiopulmonary exercise testing in liver transplant candidates. *Aliment Pharmacol Ther*. 2016;44(8):796-806. doi:10.1111/apt.13771

16. Shephard RJ. Maximal oxygen intake and independence in old age. *Br J Sports Med*. 2009;43(5):342-346. doi:10.1136/bjsm.2007.044800

17. Dunn MA, Josbeno DA, Schmotzer AR, et al. The gap between clinically assessed physical performance and objective physical activity in liver transplant candidates. *Liver Transplant*. 2016;22(10):1324-1332. doi:10.1002/lt.24506

18. Booth FW, Roberts CK, Thyfault JP, Ruegsegger GN, Toedebusch RG. Role of inactivity in chronic diseases: Evolutionary insight and pathophysiological mechanisms. *Physiol Rev*.

2017;97(4):1351-1402. doi:10.1152/physrev.00019.2016

19. Kallwitz ER, Loy V, Mettu P, Van Roenn N, Berkes J, Cotler SJ. Physical activity and metabolic syndrome in liver transplant recipients. *Liver Transplant*. 2013;19(10):1125-1131.

20. van Adrichem EJ, Dekker R, Krijnen WP, Verschuuren EAM, Dijkstra PU, van der Schans CP. Physical activity, sedentary time, and associated factors in recipients of solid-organ transplantation. *Phys Ther*. 2018;98(8):646-657. doi:10.1093/PTJ/PZY055

21. Williams TJ, McKenna MJ. Exercise limitation following transplantation. *Compr Physiol*. 2012;2(3):1937-1979. doi:10.1002/cphy.c110021

22. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: A case for fitness as a clinical vital sign: A scientific statement from the American Heart Association. *Circulation*. 2016;134(24):e653-e699. doi:10.1161/CIR.0000000000000461

23. Rongies W, Stepniewska S, Lewandowska M, et al. Physical activity long-term after liver transplantation yields better quality of life. *Ann Transplant*. 2011;16(3):126-131.

24. van Ginneken BTJ, van den Berg-Emons TJG, Kazemier G, Metselaar HJ, Tilanus HW, Stam HJ. Physical fitness, fatigue, and quality of life after liver transplantation. *Eur J Appl Physiol*. 2007;100(3):345-353. doi:10.1007/s00421-007-0435-6

25. Dunn MA, Rogal SS, Duarte-Rojo A, Lai JC. Physical function, physical activity and quality of life after liver transplantation: A review. *Liver Transplant*. 2020;26(5):702-708. doi:10.1002/lt.25742

26. D’Avola D, Cuervas-Mons V, Martí J, et al. Cardiovascular morbidity and mortality after liver transplantation: The protective role of mycophenolate mofetil. *Liver Transplant*. 2017;23(4):498-509. doi:10.1002/lt.24738

27. Tovikkai C, Charman SC, Praseedom RK, Gimson AE, Van Der Meulen J. Time-varying impact

of comorbidities on mortality after liver transplantation: A national cohort study using linked clinical and administrative data. *BMJ Open*. 2015;5(5):1-10. doi:10.1136/bmjopen-2014-006971

28. Li C, Xu J, Qin W, Hu Y, Lu H. Meta-analysis of the effects of exercise training on markers of metabolic syndrome in solid organ transplant recipients. *Prog Transplant*. 2018;28(3):278-287. doi:10.1177/1526924818781576

29. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43(7):1334-1359. doi:10.1249/MSS.0b013e318213fefb

30. Piepoli MF, Davos C, Francis DP, Coats AJ, ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *Br Med J*. 2004;328(7433):189-192. doi:10.1136/bmj.37938.645220.ee

31. Ruegsegger GN, Booth FW. Health benefits of exercise. *Cold Spring Harb Perspect Med*. 2018;8(7):a029694. doi:10.1101/cshperspect.a029694

32. Pinckard K, Baskin KK, Stanford KI. Effects of exercise to improve cardiovascular health. *Front Cardiovasc Med*. 2019;6:69. doi:10.3389/fcvm.2019.00069

33. Lin F-P, Visina JM, Bloomer PM, et al. Prehabilitation-driven changes in frailty metrics predict mortality in patients with advanced liver disease. *Am J Gastroenterol*. 2021;116(10):2105-2117. doi:10.14309/ajg.0000000000001376

34. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097

35. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk

of bias in randomised trials. *BMJ*. 2011;343(7829):1-9. doi:10.1136/bmj.d5928

36. Krasnoff JB, Vintro AQ, Ascher NL, et al. A randomized trial of exercise and dietary counseling after liver transplantation. *Am J Transplant*. 2006;6(8):1896-1905. doi:10.1111/j.1600-6143.2006.01391.x

37. Mandel DW. Comparison of targeted lower extremity strengthening and usual care progressive ambulation in subjects post-liver transplant: A randomized controlled trial (Chapter 3: Randomized clinical trial of targeted lower extemity resistance training vs. progressiv. *Open Access Dissertrations*. Published online 2009.

38. Tomás M, Santa-Clara H, Monteiro E, et al. A supervised versus home-based exercise program effects on liver transplanted familial amyloidotic polyneuropathy patients: walking, fatigue and quality of life. *Physiotherapy*. 2011;97(S1):eS1241-eS1242.

39. Tomás MT, Santa-Clara H, Bruno PM, et al. The impact of exercise training on liver transplanted familial amyloidotic polyneuropathy (FAP) patients. *Transplantation*. 2013;95(2):372-377. doi:10.1097/TP.0b013e31827220e7

40. Garcia AMC, Veneroso CE, Soares DD, Lima AS, Correia MITD. Effect of a physical exercise program on the functional capacity of liver transplant patients. *Transplant Proc*. 2014;46(6):1807-1808. doi:10.1016/j.transproceed.2014.05.023

41. Basha MA, Mowafy ZE, Morsy EA. Sarcopenic obesity and dyslipidemia response to selective exercise program after liver transplantation. *Egypt J Med Hum Genet*. 2015;16(3):263-268. doi:10.1016/j.ejmhg.2014.12.006

42. Moya-Nájera D, Moya-Herraiz Á, Compte-Torrero L, et al. Combined resistance and endurance training at a moderate-to-high intensity improves physical condition and quality of life in liver transplant patients. *Liver Transplant*. 2017;23(10):1273-1281. doi:10.1002/lt.24827

43. Moya-Nájera D, Moya-Herraiz Á, Gargallo P, Calatayud J, Escrig-Sos J, Colado JC. Clinical relevance of a balance training program on liver transplant patients. A randomized controlled trial. *Transplantation*. 2019;103(5):965-972. doi:10.1097/TP.0000000000002415

44. Ergene T, Koç ŞN, Karadibak D. The early strength training program improves muscle strength and functional capacity in liver recipients (Poster presentation). *Turkish J Gastroenterol*. 2019;30:S788-S789. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02006311/full%0Ahttps://www.embase.com/search/results?subaction=viewrecord&id=L629793582&from=export%0Ahttp://dx.doi.org/10.5152/tjg.2019.050919

45. Hickman IJ, Hannigan AK, Johnston HE, et al. Telehealth-delivered, cardioprotective diet and exercise program for liver transplant recipients: A randomized feasibility study. *Transpl Direct*. 2021;7(3):e667. doi:10.1097/TXD.0000000000001118

46. Je C. The impact of duration on effectiveness of exercise, the implication for periodization of training and goal setting for individuals who are overfat, a meta-analysis. *Biol Sport*. 2016;33(4):309-333. doi:10.5604/20831862.1212974

47. Choo YJ, Cho CW, Chang MC. Effects of supervised exercise on aerobic capacity and quality of life in patients with chronic liver disease and patients who underwent liver transplantation. *Int J Rehabil Res*. 2022;45(1):1-11. doi:10.1097/mrr.0000000000000502

48. Janaudis-Ferreira T, Tansey CM, Mathur S, et al. The effects of exercise training in adult solid organ transplant recipients: A systematic review and meta-analysis. *Transpl Int*. 2021;34(5):801-824. doi:10.1111/tri.13848

49. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Heal Rep*. 1985;100(2):126-131.

50. WHO. *WHO Guidelines on Physical Activity and Sedentary Behaviour*.; 2020.

https://www.who.int/publications/i/item/9789240015128

51. Pelliccia A, Sharma S, Gati S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J*. 2021;42(1):17-96. doi:10.1093/eurheartj/ehaa605

52. Ortega FB, Cadenas-Sánchez C, Sánchez-Delgado G, et al. Systematic review and proposal of a field-based physical fitness-test battery in preschool children: The PREFIT battery. *Sport Med*. 2014;45(4):533-555. doi:10.1007/s40279-014-0281-8

53. Taylor HL, Buskirk E, Henschel A. Maximal oxygen intake as objective measure of cardio-respiratory performance. *J Appl Physiol*. 1955;5(1):73-80.

Table 1. Common terminology used in the present study.

Term	**Definition used in the present paper**
Physical activity	Any bodily movement produced by skeletal muscles that requires energy expenditure.[49,50]
Physical exercise/physical training/exercise training	A subcategory of physical activity that is planned, structured, repetitive, and purposefully focused on improvement or maintenance of one or more components of physical fitness.[50]
Physical fitness	Physical fitness refers to a state of well-being characterized by (i) traits and capacities related to present and future health, and (ii) the ability to carry out primarily physical-related functions and daily activities with vigour and alertness, without undue fatigue, and with sufficient energy to enjoy leisure-time pursuits and respond to emergencies.[49] We specifically refer to health-related physical fitness, a term encompassing the following five components: cardiorespiratory fitness, muscular fitness, motor fitness, morphological traits, and metabolic health.[51]
Cardiorespiratory fitness	The overall capacity of the cardiovascular, respiratory, and muscular system to supply and combust oxygen for execution of physical activity.[52,53] Typically assessed by cardiopulmonary exercise testing and expressed as peak oxygen consumption. Field tests such as a 6-min walk test and an incremental shuttle walk test are expressed in distance and are often used to estimate cardiorespiratory fitness in clinical populations.
Muscular fitness	The characteristics of a specific muscle or muscle group regarding muscular strength (force generation with a single maximal effort), muscular endurance (capacity to resist repeated contractions over time or a voluntary contraction for a prolonged period of time), and muscular (explosive) power (high-velocity maximal force production in as short a time as possible).[51,52]
Motor fitness	Physical traits related to speed (ability to perform a movement within a short period of time), agility (ability to rapidly change body position in space with speed and accuracy), and balance (ability to maintain equilibrium while stationary or moving).[49,52]
Morphological component of physical fitness	Morphological characteristics such as BMI, body composition, subcutaneous fat distribution, abdominal visceral fat, bone density, and flexibility.[51]
Metabolic health	Traits related to glucose tolerance, insulin sensitivity, lipid and lipoprotein metabolism, and substrate oxidation characteristics.[51]

Table 2 | Summary of study characteristics and results:

Author, year, country, publication type	**Population**	**Intervention and comparator**	**Outcome measures and results**
1. Hickman *et al.* 2021. Australia Full-text article	**Recruitment and randomization:** - n assessed for eligibility: 131 - n randomized/completed: 35/27 - Time after LT: 4 (IQR: 2-6) years **Control group:** - n randomized/completed: 12/11 - % male: 83% (including 1 dropout) - Age: 50 ± 15 y (including 1 dropout) **Exercise + diet group:** - n randomized/completed: 23/16 - % male: 65% (including 7 dropouts) - Age: 51 ± 15 y (including 7 dropouts)	**Intervention:** - Type: aerobic + strength + diet - Duration: 2 months - Frequency: aerobic training: accumulation of 150 min of moderate to vigorous aerobic exercise per week; strength training: 2x/week - Supervision: home-based, guided through telerehabilitation **Comparator:** - Usual care	*Primary outcome(s): feasibility and safety* **Cardiorespiratory fitness:** - 6MWD: no between-group differences **Morphology:** - Body weight: trend (P=0.06) to decrease compared to control - BMI: trend (P=0.05) to decrease compared to control - Waist circumference: no between-group differences **Metabolic health:** - Blood pressure: no between-group differences - Fasting blood glucose: no between-group differences - Total cholesterol, LDL, HDL, and triglycerides: no between-group differences - Metabolic syndrome severity score: no between-group differences **HRQOL:** - The mental but not physical component score of the SF-12 improved compared to the control **Adherence:** - Participants attended on average in 52% of the 8 intended exercise videoconferences and 71% of the 6 intended diet videoconferences - Greater shift towards the Mediterranean diet compared to control **Adverse events:** - No study-related adverse events - No participant reported feeling unsafe while exercising

2. Ergene *et al.* 2019. Turkey Abstract	**Recruitment and randomization:** - n assessed for eligibility: NR - n randomized/completed: NR/29 - n female/male: n=9/20 - Age: 53 ± 12 y - Time after LT: immediately **Control group:** - n randomized/completed: NR/15 **Exercise group:** - n randomized/completed: NR/14	**Intervention:** - Type: strength - Duration: 2 months - Frequency: 2 sessions/day, 5 days/week - Supervision: combination of supervised and home-based **Comparator:** - Routine postoperative care	*Primary outcome(s): peripheral muscle strength, 'physical performance' (sit-to-stand test), and functional exercise capacity (6MWD)* **Cardiorespiratory fitness:** - 6MWD: improved compared to control **Muscular fitness:** - Knee extensor muscle strength: improved compared to control - 30-s sit-to-stand test: improved compared to control **Adverse events:** - There were no adverse events in either group
3. Moya-Nájera *et al.* 2019. Spain Full-text article	**Recruitment and randomization:** - n assessed for eligibility: 162 - n randomized/completed: 54/50 - Time after LT: 6 months **Control group:** - n randomized/completed: 28/28 - % male: 85% - Age: 55 ± 9 y **Exercise group:** - n randomized/completed: 26/22 - % male: 82% - Age: 57 ± 7 y	**Intervention:** - Type: aerobic + strength + flexibility + balance - Duration: 6 months - Frequency: 2x/week - Supervision: supervised **Comparator:** - Usual care	*Primary outcome(s): static and dynamic balance* **Muscular fitness:** - Hip extensor strength: improved compared to control **Motor fitness:** - Static and dynamic postural balance: improved compared to control - Timed up and go test: improved compared to control **Morphology:** - Sit and reach test: improved compared to control **Adherence:** - 94% adherence (45/48 sessions attended) **Adverse events:** - Not reported, but the authors did conclude that the intervention was 'safe'
4. Moya-Nájera *et al.* 2017. Spain Full-text article	Identical to Moya-Nájera *et al.* 2019	Identical to Moya-Nájera *et al.* 2019	*Primary outcome(s): cardiorespiratory fitness (VO_2peak), muscle strength, body composition, HRQOL, and liver function* **Cardiorespiratory fitness:** - VO_2peak: improved compared to control **Muscular fitness:** - 'Global' strength: improved compared to control

			- Knee extensor muscle strength: no between-group differences **Morphology:** - Body weight and fat tissue percentage: no between-group differences **HRQOL:** - Physical functioning and vitality scores of SF-36: improved compared to control **Adherence:** - Identical to Moya-Nájera *et al.* 2019. **Liver function:** - AST, ALT, GGT, ALP, total bilirubin, PT, and INR: no between-group differences
5. Basha *et al.* 2015. Egypt Full-text article	**Recruitment and randomization:** - n assessed for eligibility: NR - n randomized/completed: NR/30 - Time after LT: 'since' 6 months - Only patients with BMI>30 kg/m² **Control group:** - n randomized/completed: NR/15 - % male: NR - Age: 51 ± 3 y **Exercise group:** - n randomized/completed: NR/15 - % male: NR - Age: 50 ± 3 y	**Intervention:** - Type: aerobic + strength + flexibility - Duration: 3 months - Frequency: 3x/week - Supervision: supervised **Comparator:** - Usual care	*Primary outcome(s): body composition and blood lipid profile* **Morphology:** - Fat and muscle tissue percentage: respectively decreased and increased compared to control **Blood cholesterol and triglycerides** - Blood cholesterol and triglycerides: decreased compared to control
6. Garcia *et al.* 2014. Brazil Full-text article	**Recruitment and randomization:** - n assessed for eligibility: NR - n randomized/completed: NR/15 - Time after LT: 6 to 12 months **Control group:** - n randomized/completed: NR/6 - % male: 50% - Age: 39 ± 15 y	**Intervention:** - Type: Aerobic - Duration: 2-3 months (24 sessions) - Frequency: 2-3x/week - Supervision: supervised **Comparator:** - Usual care	*Primary outcome(s): functional capacity (6MWD) and resting energy expenditure* **Cardiorespiratory fitness:** - 6MWD: improved over time (within-group effect) in the exercise group but not in the control group (group or interaction effects were not evaluated). **Other:**

	Exercise group: - n randomized/completed: NR/9 - % male: 67% - Age: 52 ± 15 y		- Resting energy expenditure: improved over time (within-group effect) in the exercise group but not in the control group (group or interaction effects were not evaluated) **Adherence:** - All participants of the exercise group completed all 24 training sessions
7. Tomás *et al.* 2013. Portugal Full-text article	**Recruitment and randomization:** - n assessed for eligibility: 120 - n randomized/completed: 48/39 - Time after LT: 2 to 12 months - Only patients with FAP **Control group:** - n randomized/completed: 23/16 - % male: 81% - Age: 33 ± 8 y **Supervised exercise group:** - n randomized/completed: 9/8 - % male: 63% - Age: 34 ± 8 y **Home-based exercise group:** - n randomized/completed: 16/15 - % male: 27% - Age: 35 ± 4 y	**Intervention:** - Type: aerobic + strength + balance - Duration: 6 months - Frequency: 3x/week - Supervision: either supervised or home-based **Comparator:** - Usual care	*Primary outcome(s): walking capacity (6MWD), muscle strength, and body composition* **Cardiorespiratory fitness:** - 6MWD, covered distance: no between-group differences - 6MWD, covered distance multiplied by body weight: increased more in the supervised exercise group compared to the home-based exercise group and usual care **Muscular fitness:** - Knee extensor muscle strength: no between-group differences - Handgrip muscle strength: no between-group differences **Motor fitness:** - PND score: One patient in the home-based exercise group improved her PND score from IIIA (walking with help of one walking aid) to II (impaired walking but without use of any walking aid). **Morphology:** - Total body skeletal muscle mass: improved in the supervised exercise group compared to the home-based exercise group and control group - Fat mass and percentage: no between-group differences - Proximal femur bone mineral density but not total bone mineral density was higher after the intervention in the control group compared to the supervised exercise group

8. Tomás *et al.* 2011. Portugal Abstract	**Recruitment and randomization:** - n assessed for eligibility: NR - n randomized/completed: NR/37 - Time after LT: 2 to 12 months **Control group:** - n randomized/completed: NR/14 - % male: 79% - Age: 34 ± 10 y **Supervised exercise group:** - n randomized/completed: NR/8 - % male: 63% - Age: 34 ± 7 y **Home-based exercise group:** - n randomized/completed: NR/15 - % male: 27% - Age: 35 ± 5 y	**Intervention:** - Type: aerobic + strength - Duration: 6 months - Frequency: 3x/week - Supervision: either supervised or home-based **Comparator:** - Usual care	*Primary outcome(s): walking capacity (6MWD), fatigue, and HRQOL* **Cardiorespiratory fitness:** - 6MWD covered distance multiplied by body weight: improved in the supervised exercise group only (no further details provided) **HRQOL:** - SF-36: no between-group differences **Fatigue:** - Multidimensional Assessment of Fatigue questionnaire: no between-group differences
9. Mandel, D.W. 2009. USA Full-text article (Ph.D. dissertation chapter)	**Recruitment and randomization:** - n assessed for eligibility: 74 - n randomized/completed: 50/25 - Time after LT: 6 to 12 weeks **Control group:** - n randomized/completed: 25/14 - % male: NR - Age: 53 ± 8 y **Exercise group:** - n randomized/completed: 25/11 - % male: NR - Age: 54 ± 12 y	**Intervention:** - Type: ambulation program + strength - Duration: 3 months - Frequency: 3-4x/week - Supervision: home-based **Comparator:** - Usual care: ambulation program	*Primary outcome(s): strength and physical function (ability to perform activities)* Note: whenever posttest data at 3 months was not available, data assessed at 2 months was used for analysis. **Cardiorespiratory fitness:** - 6MWD: no between-group differences **Muscular fitness:** - 30-s sit-to-stand test: improved compared to control - Number of heel rise repetitions till failure: trend (P=0.065) for improvement compared to control - Number of bridge repetitions till failure: improved compared to control **HRQOL:** - The SF-36 and CLQD: no between-group differences **Adherence:** - Execution of the muscle strengthening and/or the walking program for at least 50% of the time was

			defined as adherent. 12 out 14 participants of the control group adhered to the ambulation program. 9 out of 11 participants of the exercise group adhered to the training and ambulation program. **Liver function:** - Albumin, total protein, creatinine, ALP, ALT, AST, and bilirubin: remained within normal post-LT ranges in both the control and exercise group **Adverse events:** - No verbal reports of severe muscle/joint pain or other adverse events from participants in either group. - A substantial number of participants could not complete the study for medical reasons, primarily due to immunosuppressant medications resulting in hospitalizations
10. Krasnoff *et al.* 2006. USA Full-text article	**Recruitment and randomization:** - n assessed for eligibility: 292 - n randomized/completed: 151/119 - Time after LT: 2 months **Control group:** - n randomized/completed: 86/70 - % male: 40% - Age: 51 ± 10 y **Exercise + diet group:** - n randomized/completed: 65/49 - % male: 39% - Age: 50 ± 11 y	**Intervention** - Type: aerobic + diet - Duration: 10 months - Frequency: ≥3x/week - Supervision: home-based **Comparator:** - Usual care	*Primary outcome(s): cardiorespiratory fitness (VO_2peak)* **Cardiorespiratory fitness:** - VO_2peak: improved compared to control **Muscular fitness:** - Knee extensor muscle strength: no between-group differences **Morphology:** - Fat mass: no between-group differences - Lean body mass: no between-group differences **HRQOL:** - SF-36: subscales general health and mental health improved compared to control **Adherence:** - Adherence was defined as ≥50% adherence to both the exercise prescription and diet recommendations. 37% (n=18) adherence in the intervention group. **Liver function:**

			- ALP, total bilirubin, AST, and ALT: no between-group differences

6MWD: 6-minute walking distance; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CLQD: Chronic Liver Disease Questionnaire; FAP: Familial amyloidotic polyneuropathy disease; GGT: gamma-glutamyl transferase; HDL: high-density lipoprotein; HRQOL: Health-related quality of life; INR: international normalized ratio; IQR: interquartile range; LDL: low-density lipoprotein; LT: liver transplantation; NR: not reported; PND: polyneuropathy disability; PT: prothrombin time; SF-12 or -36; Short-Form Health Survey-12 or -36; VO_2peak: peak oxygen uptake

Figure legends

Figure 1 | Flow chart of search process and study selection

Figure 2 | Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3 | Forest plot of pooled effect of exercise training on cardiorespiratory fitness assessed by VO_2peak and 6MWD.

Figure 4 | Forest plot of pooled effect of exercise training on lower body muscular fitness assessed by dynamometry or 30-second sit-to-stand test.

Figure 5 | Forest plot of pooled effect of exercise training on lower body muscular fitness assessed by dynamometry or 30-second sit-to-stand test in a subanalysis restricted to studies implementing muscle strengthening exercises.

Figure 6 | Forest plot of pooled effect of exercise training on physical function subcomponent of the SF-36 questionnaire.