Exercise Training Is Safe and Feasible in Patients Awaiting Liver Transplantation: A Pilot Randomized Controlled Trial

TO THE EDITOR:

The aim of this pilot randomized controlled trial was to investigate the safety and feasibility of an 8-week exercise training intervention for improving fitness in patients awaiting liver transplantation. We hypothesized that exercise training would not result in any serious adverse events and would be feasible. Finally, we explored whether exercise training would improve cardiorespiratory fitness (CRF), exercise capacity, muscular strength, and health-related quality of life.

Patients and Methods

Eligibility criteria were as follows: a potential candidate for liver transplantation who was between 18-69 years of age. Exclusion criteria were as follows: previous liver transplant; currently listed for another organ transplant; currently smoking; any adverse event during the initial cardiopulmonary exercise testing (CPET) indicating that it would be unsafe to participate; uncontrolled diabetes; and any orthopedic and/or neurological limitation to exercise. The protocol was approved by our institution’s human research ethics committee and was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12614000791639).

The primary outcomes of this trial were as follows:

1. Safety, determined by the number of adverse events and serious adverse events during the intervention.
2. Feasibility, assessed by attendance at prescribed exercise sessions.

Participants were randomized and stratified (by age and hepatocellular carcinoma) to an exercise training group or usual care group by an individual external to the investigation using a computer-generated allocation program. The same individual who allocated participants also generated the randomization code.

Participants attended assessments in a fasted state, where measures of CRF, exercise capacity, muscular strength, and health-related quality of life were collected. Assessments were performed at baseline and at 4 weeks (mid-intervention) and 8 weeks (post-intervention) after the commencement of the intervention. Intraoperative, perioperative, and postoperative outcomes within 90 days following transplantation were gathered from medical records.

The usual care group continued to receive standard treatment from the Queensland Liver Transplant...
Service. No additional education or information regarding exercise training or physical activity was provided. Participants randomized to exercise training completed 2 supervised and 1 unsupervised exercise sessions per week comprising of aerobic and circuit-based resistance exercises. For home-based unsupervised sessions, participants were asked to replicate the exercise prescription from the supervised sessions. The mode of aerobic exercise consisted of stationary cycling or walking. Circuit-based resistance exercise was performed using body weight or portable equipment (ie, resistance bands).

The ventilatory threshold (VT), peak oxygen uptake (VO₂peak), the oxygen uptake efficiency slope (OUES), the change in VO₂change in work-rate slope, and the ventilatory equivalents for carbon dioxide slope were determined from a CPET according to guidelines. The 6-minute walk distance (6MWD) test was used to quantify exercise capacity. The total distance walked within 6 minutes was recorded to the nearest 1 m. Isometric grip strength was measured using an electronic handgrip dynamometer. Global muscular strength was evaluated using an isometric mid-thigh pull apparatus and force platform. Health-related quality of life was evaluated using the Chronic Liver Disease Questionnaire (CLDQ).

All adverse events and serious adverse events from the commencement of the study until the final study-related procedure were recorded at each session and reviewed by a physician, who made a clinical decision whether the adverse event should be considered related to the intervention. To assess the feasibility of the intervention, the total number of exercise sessions performed and successfully completed during the 8-week period (or until liver transplantation if this occurred prior to post-intervention testing) were recorded.

Continuous data were assessed for normality using a Shapiro-Wilk test and were reported as mean ± standard deviation or as median (interquartile range), if the data were non-normally distributed. Categorical data are presented as a frequency (%) of the cohort. Linear mixed modeling assessed the change in outcomes across time and between groups, accounting for repeated measures. Group allocation (exercise training or usual care), time (baseline and 4 and 8 weeks), and the group by time interaction were considered fixed effects. When the interaction effect was significant, Bonferroni post hoc comparisons were performed. All available data were included in the analysis. Intraoperative, perioperative, and postoperative data were analyzed between the groups for all participants who received a liver transplant, using independent t tests (normally distributed) or Mann-Whitney U tests (nonnormally distributed). Categorical variables were assessed using Fisher’s exact test. Statistical significance was assumed if \( P < 0.05 \).

**Results and Discussion**

Over 15 months, 38 eligible patients were approached with 21 agreeing to participate in the intervention (Fig. 1). A total of 17 participants were assessed after 4 weeks (exercise, \( n = 8 \); usual care, \( n = 9 \)), whereas only 8 participants (exercise, \( n = 4 \); usual care, \( n = 4 \)) underwent testing after 8 weeks. During the intervention, 8 participants received a successful graft, and 2 participants in the usual care group were unable to complete the assessments at 8 weeks due to a significant deterioration in liver function.

The median age of the cohort was 49 years (IQR, 40–60 years) with 81% being male. The average Model for End-Stage Liver Disease (MELD) score was 13.3 ± 4.0, and 62% had Child-Pugh B or C disease. The primary diagnosis for advanced liver disease was alcoholic liver disease (24%), hepatitis C virus (10%), or a combination of both (29%). Almost half (43%) of the participants had a diagnosis of hepatocellular carcinoma. Gastroesophageal varices were present in 81% of the cohort, where 52% had varices of grade 2 or higher. Hypertension, diabetes, and chronic kidney disease were present in 29%, 33%, and 5% of the cohort, respectively. No ischemic changes indicating the presence of coronary artery disease were identified during CPET.

**SAFETY**

No serious adverse events occurred during the intervention period. There were no episodes of variceal bleeding or hepatic encephalopathy. One adverse event (musculoskeletal injury to the knee) occurred in 236 testing and training hours during the intervention. The knee injury did not preclude continued exercise training. There was no significant group by time interaction for the MELD score during the intervention (\( P = 0.56 \)). These data illustrate that exercise training does not appear to precipitate...
complications associated with advanced liver disease and is well tolerated.

**FEASIBILITY**

Exercise training adherence was 95% (supervised) and 75% (unsupervised) for the 8 participants who completed training until the mid-intervention time-point. For the 4 participants who were available at 8 weeks, adherence to exercise training for the supervised and unsupervised sessions were 100% and 88%.

Our findings showed that all participants randomized to exercise, including those with a calculated MELD score ≥15, demonstrated good adherence to the training sessions.

**EFFICACY**

Median time from study enrollment to liver transplantation was 80 days (IQR, 37.8-232.3 days) and was not significantly different between groups ($P = 0.80$). No significant between-group differences were found for
any intraoperative, perioperative, or postoperative outcomes. There were no deaths at 90 days following liver transplantation.

No significant group by time interactions were found for any CPET variable (Table 1). The interaction effect trended toward significance for relative (P = 0.053) and absolute VT (P = 0.06) and for absolute peak VO₂ (P = 0.07). There was a trend toward a significant group by time interaction for the 6MWD (P = 0.054). A significant group by time interaction (P = 0.04) for isometric grip strength was observed. However, after Bonferroni corrections, no significant between-group differences were found. No group by time interactions were observed for peak force derived from the isometric midthigh pull (P = 0.70) or for any MLDQ domain.

Although we did not demonstrate a statistically significant between-group difference in the VT, the observed improvement of 3.9 mL/kg/minute (29%) in the exercise-training group after 8 weeks may be clinically important. This increase is greater than the minimal clinically important change in VT of 2 mL/kg/minute, which is suggested to shift patients at high risk for perioperative morbidity toward a low-risk stratification.(3) Other clinically important improvements with exercise included changes in the 6MWD and isometric grip strength. Our results show that modification of these measures with aerobic and circuit-based resistance training appears possible.

Based on data from this study to detect a change in the VT with an effect size of 1.13 and a 60% dropout rate, 58 participants would be required to enter a 2-group randomized controlled trial.

Limitations include the homogeneity of the sample (male, 81%; Caucasian, 86%), meaning that the findings may not be generalizable to all patients.
awaiting liver transplantation. Although no liver-related adverse events occurred during the interventional period, the current investigation was not statistically powered to fully evaluate the safety of exercise training in this cohort. The final limitation was the small number of participants who were initially recruited and available for testing at 8 weeks, which would impact on the statistical power to detect significant changes in the secondary outcomes. Given a large proportion of participants received a graft during the study period, this investigation provides insight into the feasibility of exercise interventional research in this cohort.

In summary, the main findings from this study are that patients with advanced liver disease are able to safely undertake and adhere to an exercise training program. Although no significant improvements for efficacy measures were found, this study provides pilot data to adequately investigate clinically meaningful outcomes in a larger study.

Matthew P. Wallen, Ph.D. 1
Shelley E. Keating, Ph.D. 1
Adrian Hall, M.B.B.S. 4
Ingrid J. Hickman, Ph.D. 5
Toby G. Pavey, Ph.D. 7
Aidan J. Woodward, M.B.B.S., Ph.D. 2,3
Tina L. Skinner, Ph.D. 1
Graeme A. Macdonald, M.B.B.S., Ph.D. 2,3,6
Jeff S. Coombes, Ph.D. 1

REFERENCES