Eight Weeks of Exercise Training Increase Aerobic Capacity and Muscle Mass and Reduce Fatigue in Patients With Cirrhosis

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BACKGROUND & AIMS: **Patients with cirrhosis have reduced exercise tolerance, measured objectively as decreased peak exercise oxygen uptake (peak VO_2). Reduced peak VO_2 is associated with decreased survival time. The effect of aerobic exercise training on peak VO_2 has not been well-studied in patients with cirrhosis. We evaluated the safety and efficacy of 8 weeks of supervised exercise on peak VO_2, quadriceps muscle thickness, and quality of life.**

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METHODS: **In a prospective pilot study, stable patients (79% male, 57.6 ± 6.7 years old) with Child–Pugh class A or B cirrhosis (mean Model for End-Stage Liver Disease score, 10 ± 2.2) were randomly assigned to groups that received exercise training (n = 9) or usual care (controls, n = 10) at the University of Alberta Hospital in Canada from February through June 2013. Supervised exercise was performed on a cycle ergometer 3 days/week for 8 weeks at 60%–80% of baseline peak VO_2. Peak VO_2, quadriceps muscle thickness (measured by ultrasound), thigh circumference, answers from Chronic Liver Disease Questionnaires, EQ-visual analogue scales, 6-minute walk distance, and Model for End-Stage Liver Disease scores were evaluated at baseline and at week 8. Analysis of covariance was used to compare variables.**

RESULTS: **At week 8, peak VO_2 was 5.3 mL/kg/min higher in exercise group compared with controls (95% confidence interval, 2.9–7.8; $P = .001$). Thigh circumference ($P = .001$), thigh muscle thickness ($P = .01$), and EQ-visual analogue scale determined self-perceived health status ($P = .01$) was also significantly higher in the exercise group compared with controls at week 8; fatigue subscores of the Chronic Liver Disease Questionnaires were lower in the exercise group compared with controls ($P = .01$). No adverse events occurred during cardiopulmonary exercise testing or training.**

CONCLUSIONS: **In a controlled prospective pilot trial, 8 weeks of supervised aerobic exercise training increased peak VO_2 and muscle mass and reduced fatigue in patients with cirrhosis. No relevant adverse effects were observed. Larger trials are needed to evaluate the effects of exercise in patients with cirrhosis. ClinicalTrials.gov number: NCT01799785.**

Keywords: Liver Disease; Fibrosis; Clinical Trial; Cardiovascular.

Cirrhosis is the final common pathway of a wide range of chronic hepatic insults. Cirrhosis is characterized by diffuse nodular hepatic fibrosis and progressive hepatic dysfunction and is associated with significant morbidity and mortality.[1] In addition to dysfunction of the involved organ, patients also have decreased exercise tolerance measured objectively as decreased peak exercise oxygen uptake (peak VO_2).[2–4] Although the decline in peak VO_2 is most marked in patients with the most severe hepatic dysfunction, even in patients with early stage cirrhosis, it is up to 40% lower than in healthy controls.[2,5] The postulated mechanisms of impairment include cardiovascular and skeletal muscle dysfunction resulting in decreased oxygen delivery to and/or impaired oxygen extraction by the

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Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CLDQ, Chronic Liver Disease Questionnaire; CP, Child–Pugh; ET, supervised aerobic exercise training; EQ-VAS, EQ-visual analogue scale; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; peak VO_2, peak oxygen uptake; RD, registered dietitian; 6MWD, 6-minute walk distance; UC, usual care.

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active muscles.[2] The reduction in exercise tolerance is not only common but is also clinically significant. Several studies have demonstrated an independent association of this parameter with pre– and post–liver transplantation morbidity and mortality.[3,4,6]

In healthy and clinical populations, peak VO_2 is modifiable with aerobic exercise training (ET).[7] The exercise-mediated increase in peak VO_2 has been associated with decreased morbidity and mortality[8] and concurrent improvements in relevant secondary outcomes including fatigue,[9] depression,[10] and quality of life.[9] To date, the impact of ET on peak VO_2 (and relevant secondary outcomes) in patients with cirrhosis remains unclear. Available data are based on uncontrolled series including five[11] and four[12] patients studied more than 20 years ago. This paucity of data may in part be related to concerns about the safety of an exercise intervention in the setting of cirrhosis. In 1996 Garcia–Pagan et al[13] demonstrated that moderate exercise was associated with significant reductions in hepatic perfusion and increases in portal pressure. Importantly, this study was followed by data showing that the use of a nonselective beta-blocker effectively prevented the exercise-induced rise in pressure.[14]

Therefore, provided adequate prophylaxis against variceal hemorrhage is in place, on the basis of successful results in a wide range of populations, the aim of this pilot study was to evaluate the efficacy of 8 weeks of supervised ET on peak VO_2, muscle mass, and quality of life in patients with Child–Pugh (CP) class A and B cirrhosis. We hypothesized that compared with patients receiving usual care (UC), supervised ET would be associated with improvements in these outcomes in the absence of adverse events.

Materials and Methods

This randomized controlled pilot study was conducted at the University of Alberta Hospital in Edmonton, Alberta, Canada, from February to June 2013. All potentially eligible patients were consecutively screened during clinic visits at the Cirrhosis Care Clinic, and all provided signed informed consent. Study approval was granted by our local Health Research Ethics Board, and the study was registered at ClinicalTrials.gov (study ID: NCT01799785). All co-authors had access to the study data and reviewed and approved the final manuscript.

Patient Selection

Inclusion criteria were (1) cirrhosis diagnosed by compatible radiologic appearance or biopsy, (2) CP class A (CP-A) or B (CP-B), (3) age $\geq$18 and $\leq$70 years, and (4) guideline-based primary prophylaxis in place for high-risk gastroesophageal varices (either nonselective beta-blockade or endoscopic band ligation to the point of variceal eradication).[15]

Subjects were excluded if they had (1) significant cardiac disease (ejection fraction $<$60% or history of coronary artery disease, positive exercise stress test [$\geq$1 mm ST segment depression]), (2) chronic renal failure on dialysis, (3) hemoglobin $<$110 g/L, (4) human immunodeficiency virus infection, (5) hepatocellular carcinoma (HCC), (6) active non-HCC related malignancy, (7) myopathy, (8) any physical impairment or orthopedic abnormality preventing ET, or (9) post–liver transplantation.

Randomization was performed by using a computer randomization plan (http://www.randomization.com/). Treatment assessments were concealed by sealed envelope. Patients and investigators were informed of the study group assignment after completion of the baseline assessment. The primary outcome was change in peak VO_2 from baseline. Secondary outcome measures included changes in quadriceps muscle thickness as measured by ultrasound, thigh circumference, 6-minute walk distance (6MWD), quality of life, and safety as determined by the occurrence of variceal hemorrhage or deteriorations in liver biochemistry, CP, and Model for End-Stage Liver Disease (MELD) scores.

Before and after the intervention, the following assessments were performed (see Supplementary Methods for additional details).

Cardiopulmonary exercise test. This was performed on an electrically braked cycle ergometer.[16] The initial power output was set at 15 W and increased by 15-W increments every 1–2 minutes until volitional exhaustion. Continuous expired gas analysis was performed with a metabolic measurement system (Innocor; Innovision, Copenhagen, Denmark). Blood pressure and heart rate were monitored, and the highest oxygen consumed during a 1-minute period was used as the peak VO_2 score.[16]

Nutritional assessment. A registered dietician (RD) recorded height, weight, and body mass index (BMI) and calculated calorie and protein intake that was based on 2-day diet records.

Muscle mass and thigh circumference. A portable ultrasound machine (Mindray, Shenzhen, China) was used to measure the depth of the right quadriceps muscle (the rectus femoris and vastus intermedius).

Six-minute walk distance. A standardized 6-minute walk test was performed according to American Thoracic Society Guidelines.[17]

Quality of life measures. The Chronic Liver Disease Questionnaire (CLDQ)[18] and EQ-visual analogue scale (EQ-VAS)[19] were used to assess quality of life and self-perceived health status, the latter on a scale of 0–100.

Laboratory tests and liver disease severity. Serum albumin, bilirubin, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), electrolytes, complete blood count, and international normalized ratio were performed, and CP and MELD were calculated.