Systematic Review and Meta-Analysis

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Exercise as an intervention for patients with end-stage liver disease

Systematic review

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Abstract

Background: Various etiologies of chronic liver disease often result in cirrhosis. Beside obvious liver-related complications, cirrhosis also leads to loss of muscle mass and decreased exercise capacity. In this study, our aim was to conduct a systematic review of literature to investigate the efficacy of exercise interventions in patients with cirrhosis.

Method: PubMed was used to perform the literature search. The mesh terms used were the following: (liver (and) cirrhosis (and) exercise or (exercise therapy)). The following terms were excluded: Non-alcoholic fatty liver disease (NAFLD). The search was limited to the English language and human research. The initial search was conducted on December 6, 2016 and re-reviewed May 2017.

Results: Seven studies met selection criteria. Training interventions ranged between 4 and 14 weeks in duration with an exercise frequency of 3 to 5 days per week. Most studies demonstrated an increase in maximal oxygen consumption using gas exchange techniques. Two of 3 studies demonstrated increased distance covered in the 6-minute walk test. One study showed a clinically significant decrease in hepatic venous pressure gradient, while another showed a transient increase only during exercise. There were no adverse effects of the exercise program reported.

Conclusions: Exercise in selected patients with cirrhosis can have potential benefit in endurance and functional outcome measures without adverse effect from exercise.

Abbreviations: COPD = chronic obstructive pulmonary disease, HVPG = hepatic venous pressure gradient, MELD = Model for End-stage Liver Disease, NAFLD = non-alcoholic fatty liver disease, UNOS = the United Network for Organ Sharing.

Keywords: cirrhosis, end-stage liver disease, exercise

1. Introduction

Cirrhosis is the end-stage of a number of liver diseases and is associated with significant morbidity and mortality for which the definitive treatment is liver transplantation. The United Network for Organ Sharing (UNOS) allocates organs based on severity of liver disease as documented by patients' Model for End-stage Liver Disease (MELD) scores.[1] MELD was initially developed to predict survival in patients with complications of portal hypertension undergoing elective placement of trans-jugular intrahepatic portosystemic shunts (TIPS). The initial score included serum bilirubin, creatinine, and international normalized (INR) ratio, and in 2002, MELD priority was used in the allocation of organs for patients waiting for liver transplantation.[2] Multiple studies showed that the predictive accuracy of the MELD score improved with the addition of serum sodium to the scoring system and in 2016, the Organ Procurement and Transplantation Network Policy was updated to include serum sodium.[3–5] MELD has been shown to be an independent predictor of survival in patients with cirrhosis.[6] The higher the MELD score, the sicker the patient, the more likely a patient will be offered an organ for liver transplant. In addition to its predictive capability for ranking people for transplantation priority, it is a predictor of mortality, however, MELD score is a poor predictor of post-transplant survival.[7]

In addition to variables captured by the MELD score, patients with cirrhosis suffer from a number of other comorbidities, including malnutrition, loss of muscle mass, decreased exercise capacity, and decreased muscle strength.[8,9] Furthermore, cirrhotic patients suffer from significant fatigue[10] and have a lower maximal oxygen consumption (VO_2max).[11,12] These comorbidities are associated with the severity of the cirrhosis.[9,13] In addition, oxygen consumption at peak exercise not only correlated with the severity of the liver disease, but it is also independently associated with lower survival following liver transplantation.[14] Therefore, exercise capacity can provide clinically relevant information that can allow clinicians to make informed decision a candidacy of liver transplant candidates.[15,16] In patients with cirrhosis, decreased oxygen consumption at peak exercise may result from a combination of multiple extra-hepatic complications as well as deconditioning, malnutrition-associated

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muscle weakness, anemia, cirrhotic cardiomyopathy, hepato-renal syndrome, and hepato-pulmonary syndrome for instance.[17]

As noted previously, a number of patients with cirrhosis may not be suitable candidates for liver transplantation due to poor functional status. In this context, a frequently used measure of functional status includes a 6-minute walk distance as in indicator of exercise tolerance, also referred to as aerobic capacity.[1] Given its impact on pre- and post- liver transplant prognosis, the functional status and exercise tolerance of patients with cirrhosis should be maximized before transplantation.

In the context of whether there is value for pre-transplantation intervention, a recent systematic review reported the impact on the outcomes of post-transplantation.[18] The studies assessed an Adapted Physical Activity program in patients with cirrhosis in the pre-transplant setting and its impact on 1 year post-transplant mortality and morbidity.[19] Activity, in contradistinction to prescriptive exercise, did not improve outcomes and hence the conclusion from the systematic review is that increased pre-transplantation activity is not effective in improving BMI, MELD scores, and Child score and hepatic venous pressure gradient (HVPG).[18]

Despite the importance of physical activity on the pre and post-transplant setting, there are no formal or specific recommendations for these patients.[20] In fact, exercise in patients with advanced cirrhosis has been controversial because of the theoretical risk of increased portal pressures during exercise and potential harm of inducing variceal bleeding, hepatic encephalopathy, or worsening muscle breakdown in these patients with significant sarcopenia.[20–22] In fact, these precautions are similar to previously held beliefs for other end-stage diseases such as heart failure and chronic obstructive pulmonary disease (COPD).[14,21] Given the controversial nature of these issues and lack of strong evidence for or against exercise in patients with cirrhosis, our aim was to review the current evidence from exercise intervention for patients with end-stage liver disease and determine the potential risks and benefits in these patients.

2. Methods

2.1. Search strategy

PubMed was used to perform the literature search. The mesh terms used were the following: (liver (and) cirrhosis (and) exercise or (exercise therapy)). The following terms were excluded: Non-alcoholic fatty liver disease (NAFLD). The search was limited to the English language and human research. The initial search was conducted on December 6, 2016 and re-reviewed May 2017. The search was done by the primary author (CTL). (Abstracts were reviewed by CTL, LG, and PG.) Since this study is not considered to be human subject research, approval by institutional review board is not required.

2.2. Article selection

Inclusion criteria for this review required patients to meet criteria for advanced fibrosis or compensated cirrhosis. Subjects were required to have received a prescribed exercise prescription which was accompanied by a description of type of exercise (i.e. aerobic, resistance, both), its frequency, duration, and intensity. The study required an outcome measurement that assessed either strength, aerobic capacity, functional activity level or a combination of each (i.e. an outcome such as a 6 minute walk test or VO_2 max).

Exercise was defined as a standard, repetitive intervention designed to improve aerobic capacity, muscle strength or endurance following a prescriptive approach. Studies that examined only exercise's effect on sarcopenia and/or muscle mass, studies that had no exercise prescription or exercise that was not monitored, studies that focused on the effect of exercise at 1 point in time instead of over-time and studies that focused on nutrition instead of exercise were excluded. The search with the included mesh terms above yielded 84 results (flow diagram). Titles and abstracts were reviewed, leading to the selection of 5 articles. All articles were selected on full text review. In reviewing the citations of the 5 full texts, 2 additional studies were included in the review. Given the paucity of published literature and heterogeneity of study design and outcomes, a formal meta-analysis could not be performed and a narrative review of the literature was carried out.

3. Results

A total of 7 articles met our inclusion and exclusion criteria. One study,[9] was a cohort study that investigated the effect of exercise on VO_2 max in patients with cirrhosis. Twenty-four patients were included in the study but only 4 patients out of the cohort underwent an exercise program over time. Twenty-three patients had cirrhosis secondary to alcohol and 1 patient due to viral hepatitis. All the patients had previous complications with their cirrhosis which included spontaneous bacterial peritonitis, esophageal variceal hemorrhage, and ascites but at the time of the study, all patients were well compensated. There was no mention of which specific cirrhotic complications the 4 patients in the exercise program had developed. The exercise intervention in the 4 patients was over 4 to 5 weeks and involved exercising on a treadmill or exercise bike for 45 to 60 minutes for 5 days a week. At the completion of the program, 2 patients had no improvement in their VO_2 max but the other 2 patients improved their VO_2 max by 21.2% and 27.5%. They also improved their Child–Pugh score. No mention was made of decompensation secondary to the exercise intervention.

In the study by Ritland et al, 9 patients with autoimmune hepatitis were prescribed exercise for 30 minutes, 3 to 4 times a week targeting 75% of maximal heart rate, for 10 to 12 weeks.[21] Measurements of VO_2 max and work load capacity were performed at baseline and then every 2 weeks during the intervention period. Patients were classified as having "chronic active hepatitis" and a note was made that 5 of the 9 patients had cirrhosis but there was no mention of the other 4 patients. None of the patients had any signs of decompensation. At the end of the training period, oxygen consumption had improved by 19% at weeks 4 to 5 and by 29% at weeks 10 to 12. These were statistically significant improvements. There were no reported complications due to the exercise intervention.

In another study, Roman et al performed a randomized non-blinded control trial in which 20 patients with previous decompensated cirrhosis, but who were well compensated at the study start date, were randomized into an exercise group and a non-exercise group.[23] All 20 patients received leucine as a potential supplement to improve functional status and increase muscle mass. The primary end-points in this study were exercise capacity as measured by a 6 minute walk test and a 2 minute step test, muscle mass and health-related quality of life. (Strictly speaking, the 6MWT does not measure exercise capacity but moderately correlates with endurance). The exercise intervention was a 12 week program that involved three 1-hour sessions a week on a treadmill or indoor bicycle. For the exercise group, the average 6 minute walk test improved from 365 meters to 445 meters over 12 weeks which was statistically significant. The control group average decreased from 385 meters to 320 meters which was not statistically significant. No adverse events occurred during the total 24 week study period.

In a study by Zenith et al which was a randomized controlled trial in which patients with Childs-Pugh class A or B cirrhosis randomized to an 8-week program of bicycle ergometry 3 times a week starting at 30 minutes and increasing session length by 2.5 minutes each session.[24] The control group participated in their usual activity. There were 9 patients in the exercise group and 10 patients in the control group. A number of variables were measured including VO_2 max, quadriceps muscle thickness, quality of life, and 6-minute walk test. They found an average increase of 5.3 mL/kg/minute, an average increase of 23.5 meters on the 6-minute walk test, and improved quality of life measures in the exercise group, all of which were statistically significant improvements compared to the usual activity group except the improvement of the 6 minutes walk distance. Importantly there were no adverse events in the patients in the exercise group. All but 1 patient in the exercise group had a history of esophageal varices. Five of the 9 patients in the exercise group had cirrhosis secondary to Hepatitis C or alcohol but the other 4 had cirrhosis secondary to "other" causes.

In a study by Debette-Gratien et al, 13 cirrhotic patients on a liver transplant list were put through an exercise program modeled after the COPD pulmonary rehabilitation program.[19] Patients underwent 2 sessions per week for 12 weeks performing both cycle ergometry and weight training for at least 20 minutes each. In this non-randomized trial, a statistically significant improvement in the VO_2 max was noted from 21.5 ml/kg/min to 23.2 ml/kg/min. There was also a statistically significant improvement of the 6 minute walk test from 481 meters to 521 meters. They also noted significant improvements in muscle strength. The average MELD score for these patients was around 13. Four of the patients had cirrhosis from alcohol, 2 from hepatitis B or C, and 1 from congenital fibrosis. One patient was on the transplant list due to polycystic liver disease. Three of the patients actually had hepatocellular carcinoma. No harms or decompensation occurred during the study.

The next study was performed by Roman et al In this randomized control trial, 23 patients with cirrhosis were randomized to an exercise program or a relaxation program.[25] The exercise program consisted of three 1 hour sessions per week for 12 weeks using either cycle ergometry or a treadmill. There were a total of 14 patients in the exercise group with an average MELD of 8 and all patients having a history of decompensations in the past. They found a non-statistically significant improvement in VO_2 max in the exercise group and a statistically significant improvement in the timed up and go test. They also found a statistically significant improvement in lean body mass and lean leg mass. No complications occurred during the study.

Finally, Macias-Rodriguez et al carried out a randomized controlled trial examining the effect of exercise on the HVPG over time. The study included 11 cirrhotic patients in the exercise group who underwent three 40-minute sessions per week using cycle ergometry for 14 weeks. Originally 14 patients with cirrhosis started the study but 1 was removed at the beginning due to silent ischemia and 2 stopped early due to gastrointestinal complications but not decompensations. HVPG was measured at the beginning of the study and at the end of the study plus secondary measures such as VO_2 max was measured. A statistically significant drop of HVPG was noted in the exercise group, from 14.5 to 11.5. The control group had an average increase of 4 and there was a statistically significant difference at the end of the study period between the exercise and control groups. No significant changes were noted in VO_2 max. Average MELD in the exercise group was 9. No decompensations were noted.[26]

4. Discussion

Our systematic narrative review suggests that exercise in patients with cirrhosis provides some beneficial impact. In most studies, this benefit was noted as an improvement in VO_2 max or improvement in endurance as measured by the 6-minute walk test or functional measure such as the timed up and go. These findings are clinically relevant since a decrease in mortality has been documented in cirrhotic patients with an improved VO_2 max or improved 6-minute walk test. In this context, Macias-Rodriguez et al noted an actual decrease in the HVPG which interestingly went from an average of 14.5 to 11.5.[26] The significance of this decrease in portal pressure can be reflected in the reduction of clinically significant portal hypertension ($HVPG > 12$), which places patients at risk of variceal bleeding.[26] In contrast, the study by Garcia-Pagan et al showing a potentially harmful but transient increase in portal pressures during exercise.[20] It is possible that this increase may have been, in fact, related to worsening liver disease, rather than exercise itself.

In the studies that measured a 6-minute walk test as an outcome variable, 2 out of 3 showed potential improvements. The overall conclusion of these studies suggests that the best benefits are gained by those patients with worse baseline functional impairments.

An important aspect of exercise recommendation is the fact that it should be considered as any other medical intervention for patients with cirrhosis. In fact, it is critical to recognize exercise recommendation must be provided to patients as prescription that must target the specific needs of the patients. In this context, it is important to recommend the right kind of exercises, the right intensity and frequency and to understand the physiological impact of exercise in the patients with cirrhosis, so that they are not unduly stressed. In fact, the current data suggest that patients with cirrhosis have reduced exercise capacity, low VO_2 max and sarcopenia/loss of muscle mass.[27,28] In this context, aerobic exercise must target the first 2 issues. On the other hand, resistance exercise can address issues of strength and lean mass.[29] Although resistance training has been shown to increase lean mass and muscle strength and may have functional benefit, it has not been shown to improve post-transplant outcomes, but as expected, exercise after liver transplantation improves aerobic capacity and strength.[30] Finally, a single bout of moderate exercise in cirrhotic patients can cause a shift in substrate utilization with an increase in lipid oxidation in the post-exercise period. Additionally, it can increase insulin sensitivity only during euglycemia but not during the more physiological condition of hyperglycemia.[31] In this context, single bouts of moderate exercise may not have a beneficial effect on the metabolic status of patients with chronic liver disease such as those with NAFLD. Nevertheless, this hypothesis must be tested in future well-designed studies of cirrhotic patients with NAFLD.

In conclusion, this systematic narrative review showed that moderate intensity either aerobic exercise or resistance training, 4 days/week, 20 minutes, for at least 8 weeks in selected patients with cirrhosis can have positive physiological impact related to their cardiorespiratory system, despite the small possibility of transient elevation of portal pressures. In all of the studies reviewed, there was no harm documented by any cirrhotic patients who underwent exercise while there was potential benefit in endurance and functional outcome measures. These findings suggest that exercise in cirrhotic patients can be considered safe and potentially beneficial. Nevertheless, future studies are needed to establish the efficacy and safety of different exercise regimens in patients with cirrhosis.

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Author contributions

CTL and PG participated in the study design and drafted the manuscript. LG participated in the interpretation of the data and revised the manuscript. ZMY conceived of the study, participated substantially in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

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