The effect of eight weeks of home based aerobic exercise training on peak exercise oxygen consumption, six-minute walk test distance, thigh muscle mass, and health related quality of life in Child Pugh class A and B cirrhosis patients

by

Calvin Paul Kruger

A thesis submitted in partial requirements for the degree of

Master of Science

in

REHABILITATION SCIENCE

Faculty of Rehabilitation Medicine

University of Alberta

ABSTRACT

Purpose: Cirrhosis patients have reduced peak aerobic power (peak VO_2) that is associated with reduced survival. Supervised endurance training is an effective therapy to increase exercise tolerance in cirrhosis. The effect of home-based endurance exercise training (HET) on improving peak VO_2 in cirrhosis patients has not been studied. The aim of this pilot study was to evaluate the safety and efficacy of 8 weeks of HET on peak VO_2, aerobic endurance, thigh muscle thickness and circumference, and quality of life.

Methods: Stable patients with Child Pugh class A and B cirrhosis were randomized to 8 weeks of HET (n=20) or usual care (controls, n=20). The HET group performed moderate-high intensity cycle exercise 3 days per week. An exercise therapist supervised a HET session biweekly. Paired t-test was used for within group comparisons and ANCOVA was used to perform between group comparisons due to baseline differences and small sample size.

Results: The cohort (n=40) was 58% male (mean age of 57 ± 8 years), and 70% had Child Pugh class A cirrhosis. The between group VO_2 difference trended to significance (1.7 (-0.33 to 3.7), p=0.09) and the between group 6-minute walk test significantly increased (33.7 (5.1 to 62.4), p=0.02). Within groups, the HET group had a significant increase in peak VO_2 from baseline (17.3 ± 4.5 to 19.0 ± 6.4 mL/kg/min, p=0.03). There was a significant increase in the thigh circumference

(50.6 ± 5.8 to 52.4 ± 6.6 cm, p=0.02) and thigh muscle thickness (1.25 ± 0.40 to 1.31 ± 0.38 cm/m2, p=0.05). There were no significant changes in quality of life and no there were no adverse events reported.

Conclusions: Eight weeks of HET shows promise as a safe and effective intervention to improve fitness outcomes in patients with liver cirrhosis.

PREFACE

This thesis is an original work by Calvin Kruger. The research project which this thesis is a part of received research ethics approval from the University of Alberta Research Ethics Board, under the project name “An 8 week randomized controlled trial assessing home based aerobic exercise therapy (HET) in Child Pugh A and B cirrhotic patients,” No. Pro00048610, May 11, 2016.

Chapters 1, and 3-6 of this thesis are the basis for the manuscript “Home Exercise Training Improves Exercise Capacity in Cirrhosis Patients: Role of Exercise Adherence,” which is currently seeking publication. The mentioned manuscript was coauthored by Margaret L. McNeely, Robert J. Bailey, Milad Yavari, Juan G Abraldes, Michelle Carbonneau, Kim Newnham, Vanessa Mathiesen, Mang Ma, Richard Thompson, Ian Paterson, Mark J. Haykowsky , and Puneeta Tandon. PT and MJH contributed to study concept and design, study conduct, data acquisition, data analysis and interpretation and drafting of the manuscript. MM, MY, MC, RT, VM, KN, MY, and IP contributed to study conduct, data acquisition, data interpretation, and drafting of the manuscript. JA contributed to data interpretation and drafting of the manuscript.

DEDICATION

This thesis is dedicated to my mother, Christine Kruger, who passed away during the course of my master's degree. A promise delivered. I love you.

ACKNOWLEDGEMENTS

Firstly, I would like to express my deepest gratitude to my supervisors both past and present: Dr. Margaret McNeely, Dr. Puneeta Tandon, and Dr. Mark Haykowsky. Thank you all for the opportunity you have given me to work under your guidance, and for your continuous academic and personal support through all phases and times of this project. Thank you all as well for your advice, your hard work on my behalf, your time, and your genuine interest in my success. Working with all of you has broadened my view of health care immensely, and has helped to guide my next steps academically and professionally, and for that, I am grateful. A thank you to Dr. Margaret McNeely for 'adopting me' as your student, integrating me into your research, and showing me clinical research in action. Thank you to Dr. Tandon for your clinical support and supervision, as well as for your teaching on working in the liver cirrhosis population and the challenges it brings. Lastly, a special thank you to Dr. Mark Haykowsky for taking me in all those years ago during my undergraduate studies to do summer research work. Without your mentorship at that time, none of this would be possible.

I would also like to thank my remaining committee member, Dr. Edith Pituskin for serving on my committee. I look forward to working with you in the coming years.

I would also like to express my gratitude to Milad Yavari and Tahira Shaikh for their assistance in data collection. You helped make this possible.

I would also like to thank my friends and my family for their support, encouragement and prayers. Thank you especially to my wife and best friend, Stephanie; you always lift me up. Without you, things are hollow.

I must also thank the participants who contributed their time and effort to this study. Without them, this study would be impossible!

A big thank you goes out to Margie's Minions. You know who you are, and your support, friendship, assistance, company, and camaraderie made you guys the best part of some quiet, lonely days. You are all great and unique people, and it was a blessing working with each and every one of you.

Lastly, thank you to God, who gives strength to the weary. I called and you answered.

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Terminology, Abbreviations, Acronyms, and Definitions

1. **Cirrhosis related**
    - **a.** Ascites – Abnormal fluid build-up in the peritoneal cavity of the abdomen, and is the most common complication of Cirrhosis.
    - **b.** Child Pugh Class – A scoring system for cirrhosis that comprises results from blood work as well as clinical assessment to predict prognosis, survival, aggressiveness of treatment, and possible need for liver transplantation.
    - **c.** Chronic Hepatic Insults – Any agent or cause of long term damage to the liver.
    - **d.** Cirrhosis – Scarring and development of regenerative nodules on the liver as the end result of long term damage to the liver.
    - **e.** Cirrhotic cardiomyopathy – a cardiac condition observed in patients with cirrhosis regardless of the aetiologies. It is characterized by the impaired systolic response to physical stress, diastolic dysfunction, and electrophysiological abnormalities, especially QT interval prolongation.[1]
    - **f.** Compensated Liver cirrhosis – A degree of severity of liver cirrhosis whereupon the liver can still perform its main functions despite tissue damage. The patient is asymptomatic.

g. Decompensated Liver cirrhosis – A degree of severity of liver cirrhosis whereupon the liver is unable to compensate for the tissue damage and the patient is symptomatic.

h. Gastroesophageal Varices – new blood vessels that have grown around the stomach and esophagus and become quite large. These vessels develop as a result of increased portal pressure due to liver cirrhosis.

i. Hepatic Encephalopathy – A term for experiences of a disturbed mental state initiated by the build-up of toxins, waste, and foreign bodies in the blood stream. This buildup impacs the central nervous system, causing the aforementioned disturbances.

j. Hepatitis B – A viral infection that has been known to cause liver cirrhosis. Hepatitis B is treatable.

k. Hepatitis C – A viral infection that has been known to cause liver cirrhosis. An antiviral treatment for Hepatitis C has become recently available.

l. MELD score – A method of predicting survival in cirrhosis via blood based values, as well as for prioritizing patients for liver transplant.

m. Non-Alcoholic fatty liver disease (NAFLD) – Liver tissue is damaged by accumulation of fatty deposits in the liver, not associated with excessive alcohol consumption. The most common cause of liver cirrhosis in developed countries and is associated with (metabolic

syndrome) obesity, insulin resistance as well as high cholesterol, high triglycerides or both.

n. Non-selective beta-blockade – Treatment with a beta blocker which is non-selective in its blockade of beta receptors, resulting in both Beta-1 and Beta 2 receptors being blocked.

o. Portal Hypertension – The increase in blood pressure in the portal venous system as a result of scarring of the liver, which impedes blood flow through the liver.

p. Prophylaxis of variceal hemorrhage – any method or treatment aimed to preventing the rupture of gastroesophageal varices

q. Splanchic Hemodynamics – The attributes of blood flow through the gastrointestinal system.

r. Variceal Band Ligation – A method of variceal prophylaxis whereupon varices are tightly bound in areas which may be vulnerable to rupture.

s. TIPS – Transjugular intrahepatic portosystemic shunt. Insertion of a stent into a hepatic vein to allow blood flow to bypass the liver, thereby lowering portal pressure and decrease the risk of variceal bleeding.

2. Exercise related

a. Aerobic Capacity –is the maximum volume of oxygen that the body can consume during maximal exercise, using at least 60% of the musculature, and while breathing air at sea level. This volume is

expressed as an absolute rate in litres per minute (L/min) or as a relative rate in millilitres per kilogram of bodyweight per minute (mL/kg per minute).

b. Peak VO_2 – a measure of aerobic capacity. VO_{2peak} is the term used most commonly in clinical populations when a true maximal value is not attained due to testing conditions or when the test is limited by the participant's symptoms.

c. Borg Scale of perceived exertion – A scale from 6 – 20 where the individual rates their subjective level of exertion during exercise.

d. Ejection Fraction – The percentage of blood ejected from a ventricle with each heart beat.

3. Outcomes

a. Six-minute walk test (6MWT) – A walking test of aerobic endurance. The total distance achieved in six minutes of walking a marked distance and is associated with survival predictions.

b. Six-minute walk distance (6MWD) – The distance achieved on the six-minute walk test.

c. CLDQ – Chronic liver disease questionnaire

d. HADS – Hospital anxiety and depression scale

e. EQ-VAS – Euro-Qol Visual Analogue Scale. Part of a larger questionnaire upon which patients rate their own overall health status on a scale of 0 to 100.

4. **Blood work definitions:**

   a. Serum Albumin – a blood protein responsible for transport of molecules through blood. Tested in Child Pugh scoring. Normal range is 3.4-5.4 grams / deciliter. Lower values indicate higher disease severity.

   b. Bilirubin – Blood compound partially responsible for breakdown of old red blood cells. Tested in Child-Pugh and MELD scoring. The cause of yellow skin in jaundice. Normal range is 0.1 – 1 mg/dL. Elevated levels indicate more severe disease.

   c. Creatinine – Product of muscle metabolism. Tested in MELD scoring. Normal range is 0.5 – 1 mg/dL in women and 0.7 – 1.2 mg/dL in men, although normal levels increase with increased muscle mass. Elevated levels result in a higher MELD score, indicating a more severe disease state.

   d. Alanine aminotransferase (ALT) – Enzyme produced in liver to assist in protein breakdown. Normal range is from 7-56 units/L. Elevated levels in blood stream can indicate liver damage.

   e. Aspartate Aminotransferase (AST) – Enzyme produced in liver to assist in amino acid metabolism. Normal range is 8 - 43 U/L in females and 8 – 48 U/L in males. Elevated levels in blood stream can indicate liver damage.

f. Electrolytes – Electrolytes such as sodium and potassium are elements that are important for the cells in the body to function. Electrolytes allow cells to generate energy, maintain the stability of their walls, and to generate electrical impulses, contract muscles, and move water and fluids within the body.

g. Complete Blood Count (CBC) – A blood test used to evaluate overall health. Includes measures of red blood cells, white blood cells, platelets, hemoglobin and hematocrit.

h. International Normalized Ration (INR) – The ratio of the amount of time a healthy person takes to coagulate vs the test sample from a patient. Tested in both MELD and Child Pugh scoring. Normal range is 0.8 – 1.2 seconds. An elevated INR indicates a higher risk of bleeding without clotting. This indicates an elevated risk in the case of variceal rupture.

CHAPTER 1: INTRODUCTION

1.1 Brief Introduction

It is estimated that one in 10 Canadians has some form of liver disease. Cirrhosis is defined by the development of regenerative nodules on the liver, which are covered by bands of fibrotic tissue and develop in response to chronic liver injury. [2] The most common causes of cirrhosis include non-alcoholic fatty liver disease, alcoholism, and viral sources such as hepatitis B and hepatitis C. [3] Cirrhosis is classified based on the presence of signs and symptoms. Cirrhosis is classified as *compensated* when the liver is still able to function even though tissue damage is present. [3] In contrast, decompensated cirrhosis occurs when the damage is so extensive that liver function is compromised and symptoms develop. [3] The symptoms of decompensated cirrhosis can include jaundice, hepatic encephalopathy, sarcopenia, edema and development of gastroesophageal varices. These symptoms can also contribute to decreased physical function and quality of life. Importantly, individuals with decompensated cirrhosis suffer from a higher mortality rate than that of the general population. [4]

Poor aerobic capacity has been shown to negatively correlate with increased mortality in clinical populations. Aerobic exercise training has consistently demonstrated benefit across clinical populations for its effectiveness in increasing aerobic capacity and decreasing mortality; however, there is a paucity of research studies examining physical activity and exercise training in patients with cirrhosis

of the liver. The lack of research in the area is likely due to concerns over the feasibility and safety of exercise given patient symptoms and the high risks associated with liver disease. The purpose of the present study was to examine the safety, feasibility and preliminary efficacy of a home-based aerobic exercise training program for patients with liver cirrhosis.

1.2 Statement of the Problem and Purpose of the Thesis

The aim of this study is to fill a gap in knowledge around exercise training for patients with Child Pugh Class A and B liver cirrhosis. While there have been previous exercise training studies in this population, these studies had small sample sizes (n=5, n=4, n=19), and only one of these three studies compared an exercise group to a control group. [5] Moreover, studies to date have examined supervised hospital or clinic based programs.

Home exercise training (HET) offers advantages over supervised hospital or clinic based programming. Namely, transportation and costs associated with facility-based programming, which are potential barriers to exercise for this patient population are removed. In the home setting exercise training can be performed daily and at a time convenient for the patient. [6] At present, it is unknown whether a HET program can be delivered safely and effectively to patients with Child Pugh class A and B liver cirrhosis. The specific aims of the current study were to evaluate the safety, feasibility and preliminary efficacy of an eight-week HET program on

peak VO_2, six-minute walk distance, quality of life measures and muscle mass, in patients with Child Pugh class A and B liver cirrhosis.

1.3 Objectives

Primary objective:

1. To determine the safety, feasibility and preliminary efficacy of eight weeks of home exercise training (HET) on Child Pugh class A and B liver cirrhosis patients on exercise capacity as measured by peak VO_2, as well as to assess the safety and feasibility of such a program.

Secondary objectives

1. To determine the efficacy of HET on thigh muscle mass. This will be measured via resting ultrasound (Mindray©, Shenzhen, China) on the quadriceps, using cross-sectional muscle thickness as the measure.
2. To determine the efficacy of HET on quality of life, via the CLDQ.
3. To determine the efficacy of HET on anxiety and depression via the Hospital Anxiety and Depression Scale (HADS).
4. To determine the efficacy of HET on aerobic endurance, as measured by the six-minute walk test.

1.4 Hypotheses

Hypothesis 1: The primary hypothesis is that a home exercise-training (HET) program will prove safe and feasible in patients with cirrhosis of the liver.

Hypothesis 2: A significant improvement in peak VO_2 will be observed in participants in the eight-week HET group when compared to the usual care group (UC).

Hypothesis 3: Eight weeks of HET will result in significant improvements in cross sectional measures of thigh muscle mass, quality of life measures, and six-minute walk distance.

Delimitations

1. The sample consisted of 23 male and 17 female (n=40) Child Pugh class A and B patients (mean age: 56.7 ± 8.2 years) referred to the Cirrhosis Care Clinic at the University of Alberta Hospital.
2. Cardiopulmonary testing was performed on a Monark Cycle ergometer in the ABACUS research center at the Mazankowski Alberta Heart Institute.
3. HET sessions were to be performed a minimum of 3 times per week at the participant's home, totalling 24 training sessions over eight weeks.
4. Muscle mass was evaluated using an ultrasound machine (Mindray©, Shenzhen, China).
5. Health related quality of life was evaluated via CLDQ (Chronic Liver Disease Questionairre), HADS (Hospital Anxiety and Depression Scale) and EQ-VAS.

Limitations

1. Participants in the study were volunteers. These patients were referred to the Cirrhosis Care Clinic at the University of Alberta Hospital.
2. The randomly selected sample of participants represents the population of patients with cirrhosis between the ages of 18 and 70 years.

Significance of the Study

This study will be the first randomized controlled trial to determine the effects of a HET program on aerobic capacity and endurance, muscle mass, and quality of life in pre-transplant cirrhosis patients with a history of complications relating to liver cirrhosis. These complications include the presence of gastroesophageal varices, ascites, hepatic encephalopathy and sarcopenia. This study will help determine the safety and feasibility of a HET program as a possible therapeutic option to improve clinical outcomes and exercise tolerance in individuals with Child Pugh class A and B liver cirrhosis.

CHAPTER 2: LITERATURE REVIEW

This literature review will serve to introduce the pathophysiology and potential complications of liver cirrhosis as well as describe the current methods used in the assessment of severity of liver cirrhosis. This chapter will also serve to describe the relationships between aerobic capacity and liver cirrhosis, as well as the literature examining the effect of exercise on aerobic capacity, endurance, muscle mass and health related quality of life in patients with liver cirrhosis.

2.1 Overview of Liver Cirrhosis

It is estimated that one in 10 Canadians, or more than three million people, has some form of liver disease. The most common forms of liver disease — viral hepatitis, fatty liver disease and liver cancer — are all on the rise which means that the increase in death rates from these diseases and their complications will continue to climb if there is no effective intervention. [7] Liver disease is the 5th leading cause of death in the Canadians between the ages of 45-64 years of age (http://www.statcan.gc.ca/pub/82-625-x/2015001/article/14296-eng.htm), and is responsible for approximately one million, or 2% of worldwide deaths per year. [8] In addition to this, the treatment cost of liver disease in the United States ranges from 14 million to 2 billion dollars per year, depending on disease etiology and severity. [9]

Cirrhosis refers to scarring or fibrosis of tissue in the liver and is a complication of liver disease. Cirrhosis occurs when the liver tissue is healing following injury, and scar tissue replaces normal healthy tissue in the liver. Cirrhosis is the end result of damage to the liver tissue that may result from excessive consumption of alcohol, Non-Alcoholic Fatty Liver Disease (NAFLD), chronic hepatitis B or C infection [10], autoimmune diseases, and destruction of the bile ducts. [2, 11, 12] As a result of the tissue fibrosis, blood flow through the portal vein in the liver becomes compromised, causing an increase in the resistance to blood flow. This increased resistance results in portal hypertension, or high blood pressure in the portal venous system [13], and is the root cause of common liver cirrhosis complications. Portal hypertension is classified by causes originating in different locations in the portal venous system [13]:

1. before it reaches the liver (prehepatic)
2. within the liver (intrahepatic)
3. between the liver and the heart (post-hepatic)

Disease progression to a decompensated state is associated with morbidity as well as mortality. [2] Current treatment approaches focus on symptom management of cirrhosis and prevention of complications, as there are currently no treatments to reverse the fibrotic tissue formations or nodules that develop on the liver in late stage cirrhosis. Symptom management of cirrhosis comprises lifestyle interventions such as prescribing a low sodium diet, pharmacological interventions including diuretics to reduce ascites [14] and beta blocker prescription to reduce

the risk of variceal bleeding; and procedures such as endoscopic band ligations for prophylaxis of variceal haemorrhage.[15] Currently, liver transplantation is the only option for treatment of advanced liver cirrhosis.[16]

The available treatment options for both compensated and decompensated cirrhosis can have several drawbacks. In the case of variceal band ligation and transplantation, the treatments are invasive. Additionally, patients requiring liver transplantation often face long wait times of around one year, during which time there is increased risk of further decompensation, morbidity and mortality.[16] As of 2012, the mortality rate for patients on the wait list for transplantation was 24-30%. [15, 17] Therefore, there is a need for treatments focussed on optimizing the health of patients with cirrhosis and mitigating the risks of morbidity and mortality for those waiting for transplantation. [18] Exercise, due to its known benefits on physical functioning, quality of life and survival, may prove beneficial for patients with liver cirrhosis who may or may not be awaiting transplantation.

2.2 Complications of liver cirrhosis

The development of symptoms and complications such as ascites, jaundice, hepatic encephalopathy, and bleeding of varices, denotes disease progression to a decompensated state and all result from portal hypertension. [12, 13, 19, 20] The symptom burden and high risks associated with a decompensated state may be barriers, or possibly contraindications, to exercise therapy. Increased portal pressure can contribute to the growth of extraneous blood vessels in the

gastrointestinal system, and especially on the esophagus. Blood is shunted to these extraneous vessels due to the higher pressure in the portal vein. Varices with thin walls are at high risk of rupture, causing serious and possibly fatal hemorrhaging. Risks are further increased with any increased blood pressure such as occurs with high intensity exercise. [21] Varices are generally treated with the prescription of beta blockers, or through procedures such as band ligation or transjugular intrahepatic portosystemic shunt (TIPS) to reduce the risk of bleeding from vein rupture. [22, 23]

Hepatic encephalopathy is another common complication of liver cirrhosis and is defined as deterioration in brain function resulting from acute liver failure or chronic liver disease. [24] Hepatic encephalopathy results when there is shunting of the blood by collateral vessels to the systemic circulation without the normal filtering and cleaning of the blood first through the liver. Consequently, drugs, bacteria, toxins, and ammonia, normally metabolized by the liver, remain in the blood stream. These substances can then accumulate in the systemic circulation and are toxic to the individual.[13] With hepatic encephalopathy, the patient is often confused, and has difficulty with memory and concentration affecting his or her ability to carry out daily activities. The symptoms can lead to anxiety and negatively impact quality life. In individuals with severe hepatic encephalopathy impairments in mental and neuromotor functioning can further deteriorate, and lead to extreme drowsiness, convulsions and coma. [25, 26]

Ascites is another common complication of cirrhosis and is indicative of advanced liver disease. Ascites is defined as the accumulation of fluid in the peritoneal cavity of the abdomen. [27] This accumulation of fluid causes weight gain and increased intra-abdominal pressure leading to abdominal pain and dyspnea (shortness of breath). [25] Ascites is generally managed medically through the prescription of diuretics and by having the individual maintain a low sodium diet, in some cases a therapeutic paracentesis is performed to relieve pressure and symptoms. [28]

2.3 Models used to assess Severity and Prognosis

There are two classification models that are commonly utilized to assess and predict morbidity and mortality in patients with liver cirrhosis. These are the Child-Pugh (CP) classification system (Tables 1 and 2), and the Model for End stage Liver Disease (MELD) (Table 3).[29, 30] This thesis classifies disease severity using both these models.

2.3.1 The Child Pugh model

The Child Pugh (CP) classification model is commonly used clinically and in research disciplines .[2] It is derived from the measurement of five factors, three of which are obtained via blood sample, and two of which are obtained via direct questioning of the patient: total bilirubin, serum albumin, international normalized ratio (INR), presence of ascites, and presence of and severity of hepatic encephalopathy. Each variable is scored from 1-3 points, and the sum, which will be between 5 and 15, determines the CP classification. Patients can be classified

as CP class A (5-6 points), B (7-9 points) or C (10-15 points), with class C being the most severe classification.[2] The CP is used to predict survival, as shown in Table 2.

Table 1. Child Pugh classification system [31, 32]

Measure	**1 Point**	**2 Points**	**3 Points**
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Slight, or controlled by diuretics	Moderate, despite treatment
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4

Table 2. One and two-year median survival times according to Child Pugh Class [2]

Child Pugh Class	**Child Pugh Score**	**Median 1 Year Survival**	**Median 2 Year Survival**
A	5-6	95%	90%
B	7-9	80%	70%
C	10-15	45%	38%

2.3.2 The Model for End Stage Liver Disease (MELD)

The MELD is based on: serum creatinine, total bilirubin, and INR. These laboratory values are inserted into a logarithmic formula, resulting in scores ranging from 6 to 40, with higher scores indicating a more severe disease state. [33] The MELD was developed to predict survival rates while removing the subjective components of

determining severity of ascites or encephalopathy in the CP model. Due to this objectivity, the MELD is used to determine the need for liver transplantation. MELD predicted survival rates are shown in Table 3.

Table 3. One and Two year predicted survival by MELD score (Said, 2004)

MELD Score	Predicted 1-year survival	Predicted 2-year survival
0-9	93%	90%
10-19	86%	80%
20-29	71%	66%
30-39	37%	33%

2.4 Reduced aerobic capacity in Liver cirrhosis: Prevalence, Association with morbidity and mortality, and Effect of Aerobic Exercise Training

2.4.1 *Reduced aerobic capacity in liver cirrhosis patients: Prevalence*

Patients with liver cirrhosis often demonstrate a reduced maximum aerobic capacity. [34] Aerobic capacity defined by peak VO_2 is the maximum amount of oxygen consumed (transported and utilized) by an individual at their symptom limited peak exercise. [34] VO_2 measurement is considered to be the gold standard measure of aerobic capacity and fitness. Assessment of VO_2 is often done on a cycle ergometer or treadmill so as to incorporate the pulmonary, cardiovascular, hematopoietic, and skeletal muscle responses to exercise.

[35]VO_2 is defined by cardiac output and the amount of oxygen extracted from blood to tissue. Compromises in any of the above systems may impact the defining components of VO_2, thereby reducing aerobic capacity. [34]

There have been several studies demonstrating reduced peak VO_2 in patients with liver cirrhosis when compared to either healthy controls or predicted age and gender based values. [5, 36] While the decline is most marked in cirrhosis populations with the most severe states of liver disease, even in individuals with compensated cirrhosis, peak VO_2 values remain depressed when compared to healthy age matched controls. [37, 38] As previously mentioned, there are several possible mechanisms for this decrease in peak VO_2 including those related to the cardiovascular, pulmonary, hematopoietic and musculoskeletal systems such as loss of cardiac output, anemia, and ineffective transfer of oxygen from the lungs to the blood as well as from the blood to the muscle. Moreover, cirrhosis may be accompanied by complications that may affect both oxygen transport and utilization such as cirrhotic cardiomyopathy [1], and sarcopenia. [39]

Normally during exercise, cardiac output is significantly increased via an increase in heart rate and stroke volume. [40] Cirrhotic cardiomyopathy is a cardiac condition related to liver cirrhosis, which may impede the normal increase in cardiac output that occurs with exercise. [41] Cirrhotic cardiomyopathy is characterized by impaired contractility of the heart in response to stressors, altered diastolic relaxation, and electrophysical abnormalities. [1, 41] The inability of the

cirrhotic heart to adapt heart rate to meet physical demands is called chronotropic incompetence, and it results in limited exercise capacity. [38, 41]

In addition to the possible cardiac consequences of liver cirrhosis, there are also pulmonary abnormalities associated with cirrhosis. Ventilation-perfusion mismatch, intrapulmonary shunts, and diffusion-perfusion defect all have an effect on gas exchange and transportation [42], while hepatopulmonary syndrome (HPS) specifically impairs gas exchange in the lungs due to dilation in vessels carrying blood for oxygenation. It has been shown that those with HPS have a significantly reduced aerobic capacity. This reduced capacity falls below levels of cirrhotic controls (without HPS) with both low and normal blood oxygen levels. [43] Together, these abnormalities may impair gas exchange within the lungs as well as limit oxygen transportation.

Other factors which may also play a role in the reduction seen in aerobic capacity in patients with cirrhosis include anemia, the use of beta blocker therapy to decrease risk of variceal rupture, as well as a generalized loss of muscle mass. [42]

2.4.2 Peak VO_2: Relatedness to Clinical outcomes and Mortality

Peak VO_2 is a clinically significant measure in both healthy and clinical populations. Myers *et al.,* in a study including 6213 men with and without cardiovascular disease, showed that for every 3.5 ml/kg/min reduction in peak VO_2 (equal to one metabolic equivalent or 1 MET) there was an associated 12% increase in the risk

of mortality. [44] When adjusting for cardiovascular risk factors, peak VO_2 has also been shown to be an independent predictor of all-cause mortality. [45] Gulati *et al.* followed 5271 asymptomatic women with cardiovascular disease for eight years, and found that a 1 MET increase in peak VO_2 (3.5 ml/kg/min) was associated with a 17% increase in survival. [45]

There have been several studies showing an association between aerobic capacity and survival in both pre and post liver transplant populations, as well as with rehospitalization rates of patients post-transplant. [43, 46, 47] Epstein *et al.* reported an increased rate of mortality 100 days post transplantation in those with a reduced (<50% predicted peak VO_2) aerobic capacity. [43] Dharancy *et al.* found a link between pre-transplant peak VO_2 and 1-year survival post transplantation. In an examination of patients who underwent transplantation, it was found that those with a decreased peak VO_2 (<60% predicted peak VO_2) had a lower 1-year survival rate as compared to those with a higher VO_{2peak} before transplantation. [42] Additionally, those with depressed pre-transplantation VO_{2peak} scores trended to having longer post-transplantation hospital stays for recovery, and required supplemental oxygen for a significantly longer period of time. [42] Bernal *et al.* studied the relationship between peak VO_2 and one-year survival in groups of patients who underwent liver transplantation as compared to those who did not. In their sample of 399 patients, it was found that among those who did not undergo transplantation, there was a 34.6% mortality rate. The patients who succumbed to the disease had on average significantly lower peak VO_2 scores than those who

survived. Moreover, among patients who underwent a transplantation procedure, it was found that post transplantation, those with the lowest 25% of VO_{2peak} scores had extended length of hospitalization. [47]

Summarizing this evidence, we can conclude that (1) peak VO_2 is a valuable and important clinical measure for predicting outcomes; and (2) interventions, such as exercise, prescribed to improve aerobic capacity may optimize the quantity of life of patients with cirrhosis and inform future therapeutic practices.

2.4.3 VO_{2peak}, Aerobic exercise training, and Liver Cirrhosis

It has been well documented that aerobic exercise training can bring about change in peak VO_2 in clinical and healthy populations of a wide range of demographics. [48-51] Improvements in peak VO_2 score of 10% or more are possible in healthy individuals through aerobic exercise training. [51] However, the effect of AET on patients with liver cirrhosis has not been thoroughly explored. A total of 4 studies have been performed examining the effect of aerobic exercise training in the liver cirrhosis population. [5, 36, 52, 53]

A 1983 study by Ritland *et al.* found that AET produced increases in predicted VO_{2peak}, based on results of submaximal endurance testing in nine patients. Patients were instructed to exercise in a method of their choice (swimming, biking, or running) in a home-based aerobic training program and assessed after 4-6 weeks and again at 10-12 weeks. At each time point, estimated peak VO_2

increased by 19% ($p<0.05$) at the 4-6 week time frame and 29% ($p<0.01$) at the 10 to 12 week timeframe, from baseline measures. [52] In this population, exercise training had no deleterious effects to patients' clinical condition or liver function as assessed by laboratory values. It is important to note however, that the patients included did not show signs and symptoms of decompensation, making this a relatively low risk study, with limited generalizability to the cirrhosis population as a whole. [52]

In 1990, Campillo *et al.* examined the results of 4-5 weeks of aerobic training in 4 patients, all of whom had experienced at least one comorbidity associated with cirrhosis, but were deemed well enough to participate. [53] Patients exercised on a bike or treadmill in a supervised setting for five weeks at 45-60 minutes per day, 5 days per week at 50-60% of peak VO_2. Results varied by patient, with two patients improving their peak VO_2 by 21.2% and 27.5%, and two patients demonstrating no significant changes.

In a more recent randomized trial of 19 CP class A and B liver cirrhosis patients, Zenith *et al.* found that eight weeks of supervised exercise training (n=9) 3 times per week at 60 - 80% of baseline peak VO_2 on a cycle ergometer produced a 5.3 ml/kg/min increase in peak VO_2 when compared to a control group (n=10).[5]

In another recent randomized controlled trial of 23 CP class A patients with liver cirrhosis, Roman et al., prescribed 12 weeks of supervised treadmill walking,

performed three times per week to a maximum of 30 minutes per session, at an intensity of 60-70% maximum heart rate to the exercise group. [36] In contrast to the results of Zenith *et al*, the exercise intervention in the Roman study did not result in a significant improvement in peak VO_2 as compared to a relaxation group.[5]

2.5 The 6 Minute Walk Test Distance as a predictor of Mortality in Cirrhosis

The six-minute walk test (6MWT) is a clinically useful test that provides clinicians with an easily obtained estimate for aerobic capacity that is not as costly or time consuming as cardiopulmonary exercise testing. The six-minute walk test has been established as an independent predictor of mortality in cirrhosis patients. [54, 55] Mizuno *et al.* found that there was a strong negative correlation between MELD score and six-minute walk distance (6MWD) in pre-transplant candidates with an r= -0.593, and a p= 0.042. Consistent with these findings, Galant *et al.* also found a significant negative correlation between 6MWD and MELD score [56], and Yadav *et al.* demonstrated that patients that had lower 6MWD had significantly higher MELD scores, indicating a more severe disease state.[57] Carey *et al.* also found that in 121 pre-transplant patients the optimal 6MWD cut-off for mortality prediction was <250 meters, and every 100-meter increase from the cut-off representing a mortality reduction of 52%. [55] Similarly, Periera *et al.* found that among pre-

transplant cirrhosis patients, those that had a 6MWD of less than 410 meters had a survival rate of 55%, while those who walked more than 410 meters had a survival rate of 97%. [58] In addition to these findings, in a one-year follow up study, Alameri *et al.* found a difference in the mean 6MWD between cirrhosis survivors and non-survivors, with 317 meters being achieved in surviving cirrhosis patients and 245 meters achieved for those that did not survive (p=0.021). [50] The 6MWT may then offer useful and clinically applicable data regarding submaximal endurance and submaximal aerobic capacity in liver cirrhosis populations.

Table 1. Summary of studies that have examined the effects of aerobic exercise training on peak VO_2 and or 6MWT in patients with liver cirrhosis.

Author, year	Participants	Gender, mean age	CP/MELD score	Aerobic activity	Duration
Present study	HET: n=20 UC: n=20	23 male, 17 female. 57 years	CP: 6.3 MELD: 9.4	Home based, bicycle	8 weeks
Roman *et al.,* 2016	AET: n=15 Relaxation: n=10	17 male, 6 female 62.5 years	CP: 5.4 MELD: EX:8.2 Relax: 9.1	Supervised, bicycle, treadmill.	12 weeks
Macías-Rodríguez et al., 2016	Therapy: n= 14 UC: n = 15	19 male, 6 female. 52 years.	CP: 6 MELD: 10.5	Supervised training, bicycle	12-13 weeks (40 sessions)
Zenith, 2014	AET: n=9 UC: n=10	15 male, 4 female. 57.6 years	CP: 6.1 MELD: 10	Supervised training, bicycle	8 weeks
Campillo *et al.* 1990	AET: n=4 (subgroup from larger study)	4 male, no mean. Mean age of whole group: 44.8	Not present, mean of main group:7.2 (CP:B)	Home based: treadmill or bicycle	4-5 weeks
Ritland *et al., 1983*	AET: n=9	8 female, 31 years 1 male, 18 years	Not present	Home based running, swimming or bicycle	4-6, 10-12 weeks

Frequency	Intensity	VO_2 change	6MWT change	Adverse events	Limitations
30-60 min, 3x/week	60-80% VO_2peak	1.7ml/kg/min within exercise group (p=0.03). No change b/w groups	33.7 m between groups, p=0.02	None	Predominantly CP class A (70%).
60 mins, 3x/week	60-70% of HRmax	AET: 1.6 ml/kg/min No p value, no between group change.	Not evaluated	None	Predominantly male (74%), control was relaxation group.
40 mins, 3x/week	12-14 on 20-point borg scale	-0.9ml/kg/min p=0.605 within AET group. No between group calculation.	Not evaluated	None	Predominantly Male (76%) Predominantly CP class A (100%), Nutritional therapy intervention.
32.5-47.5 mins, 3x/week	60-80% VO_2peak	5.3ml/kg/min Between group change	23.5 m between groups, p=0.19	None	Predominantly Male (79%), Predominantly CP class A (74%).
45-60 Mins, 5x/week	50-60% VO_2max	21.2% and 27.5% in 2 patients, no change in 2 patients.	Not evaluated	None	All males, No control, Peak VO2 predicted using Bruce Protocol and equations
30 Mins, 3-4x/week	75% HRmax	6ml/kg/min (19%) after 4-6 weeks, 9ml/kg/min (29%) after 10-12 weeks	Not evaluated	None	Small sample, no control, predominantly female sample, VO2max estimated using Astrand formula (HR based)

Abbreviations: HET: Home based exercise training, AET: Aerobic exercise training (supervised), UC: Usual Care, HRmax: maximum heart rate, 6MWT: Six Minute walk test

2.6 Reduced Muscle Mass in Cirrhosis: Prevalence, Association with Mortality and Effect of Aerobic Exercise training

2.6.1.1 Reduced Muscle Mass in Cirrhosis: Prevalence and mortality

Loss of skeletal muscle mass, also known as skeletal muscle wasting, or sarcopenia is common among liver cirrhosis patients, and has been found in approximately 40% of patients under consideration for liver transplant. [59] There are a variety of causes and factors that can contribute to sarcopenia, including malnutrition, decreased hepatic protein synthesis, hypermetabolism, loss of appetite, medications, and inflammatory cytokines. [4] Loss of muscle mass has been shown to be an independent predictor of survival in pre-transplant and post-transplant cirrhosis patients: Albertino *et al.* found that in 212 cirrhosis patients, muscle mass as measured by mid upper arm circumference was an independent predictor of survival. [60] In addition to this, Montano-Loza *et al.* found that muscle mass as measured centrally at the 3rd lumbar vertebral level was associated with death from sepsis, as well as functioned as an independent predictor of survival in pre-transplant patients. [59] Gender differences were also found in patients waiting for transplant, with half of all male patients and 12% of female patients presenting with sarcopenia. Compared to liver cirrhosis patients without sarcopenia, those with sarcopenia had significantly reduced survival (19 months in sarcopenia, 34 months in non-sarcopenia, $p = 0.005$). [59]

2.6.1.2 Complications and Exercise Interventions

Sarcopenia is not only related to increased mortality, but also to the decreased overall quality of life seen in cirrhosis patients [61], and is associated with other symptoms seen in liver cirrhosis, such as hepatic encephalopathy, portal hypertension, and ascites. [4] While the mechanism for sarcopenia in liver cirrhosis is unknown, there has been some speculation that the loss of muscle mass is due to unbalanced amino acid concentrations in the body, as well as due to hyperammonemia, or buildup of ammonia in the muscle cells, that results in a series of molecular events, leading to sarcopenia. [62]

There are several treatment methods for sarcopenia that have been investigated, although with limited success. [63] These include diet modification to include more protein or amino acids [64], hormone treatment [64, 65], and treatments to reduce ammonia in the body. [66] Exercise is treatment option that has been attempted with varying amount of success depending on exercise type. [67] According to Dasarathy *et al.,* endurance exercise alone may increase aerobic capacity but may not be sufficient to reverse sarcopenia. [61, 68] Exercise programs with combined resistance training and aerobic training as well as studies of resistance training alone have thus far not been investigated in cirrhosis patients, despite the potential to alleviate sarcopenia. [68] The dearth of literature in exercise training in those with cirrhosis, especially resistance training, may be due to the potential risk of rupturing varices in the gastrointestinal system as a result of the increased portal

pressure. Any significant increase in pressure could cause internal bleeding and possibly fatal hemorrhaging. [20]

While resistance exercise has not been evaluated, randomized studies have reported short term improvements in sarcopenia from aerobic exercise training in cirrhosis patients.[5, 53, 69] Campillo *et al.* investigated the effects of aerobic exercise training on muscle mass in four patients with liver cirrhosis. After 4 – 5 weeks of cycle ergometer or treadmill training, 5 days a week for 45 – 60 minutes per session at 50-60% peak VO_2, they found that muscle mass as measured by mid arm muscle area improved in two of the four patients. [53] Zenith *et al.* also investigated the effect of supervised cycle ergometer exercise training on 9 Child-Pugh class A and B liver cirrhosis patients, and after eight weeks of training found that when compared to a control group (n = 10), the exercise group (n = 9) had a significant increase in thigh muscle circumference as well as thickness as measured by compression index. [5] Outside of these studies, there is limited data available on the effect of exercise training on muscle mass in liver cirrhosis.

Within other clinical populations as well as healthy populations, the effect of exercise on muscle mass has been well documented, and studies have indicated that in these populations, aerobic and strength training are effective in increasing muscle mass as well as slowing or reversing muscle loss. In a study of cardiac transplant patients, for example, long term aerobic exercise training has been found to produce a two kilogram increase in lean muscle mass. [70] Furthermore,

it has been shown that aerobic training is associated with increases in thigh muscle cross sectional area as measured by computed tomography in clinical populations.[71, 72] Given the relative lack of literature in this area in regards to cirrhosis, and association between mortality and sarcopenia, the further investigation of the relationship of exercise training and muscle mass in liver cirrhosis is warranted and of clinical importance.

2.7 Health Related Quality of Life and Cirrhosis

Health related quality of life (HRQOL) can be summarized as how well a person functions in their life, their perceived well being in the domains of physical, mental and emotional domains of health as the aspects of self-perceived well being related to or affected by the presence of a disease or treatment. [73, 74] An assessment of HRQOL incorporates measures of a patients' perceptions, appraisals and attributions towards their own illness, the impairments associated, and their health state. Because patients are concerned with not only the quantity of their life, but also the quality, measures of HRQOL are important to clinicians as endpoints for assessment of treatment effectiveness beyond physical and functional outcomes. [75] Liver cirrhosis patients often experience increased fatigue, anxiety, depression, and a loss of self-esteem that can negatively impact work life. [76-78] In addition to these effects, there are physical complications which can cause a further decrease in perceived quality of health. These complications include muscle weakness and muscle mass loss, ascites, cramps, and hepatic encephalopathy. [68-70] There are several studies showing that

HRQOL is significantly lower in those with liver cirrhosis as compared to healthy controls, and that as disease progresses QOL degrades further. [76-78]

There are currently few studies assessing aerobic exercise training and HRQOL in liver cirrhosis. However, Roman *et al.* found that in a 12-week moderate intensity aerobic exercise program in 14 liver cirrhosis patients, significant improvements were found in the domains of general health, vitality, and social function. [36] In a study of 9 patients with Child-Pugh class A and B liver cirrhosis, Zenith *et al.* found a significant difference between exercise and control groups in the EQ-VAS, as well as a significant improvement in the fatigue subdomain of the CLDQ in the exercise group. [5]

In the absence of a robust amount of literature examining the relationship between HRQOL and AET in cirrhosis patients, other populations must be examined for relationships between exercise and HRQOL. There is currently a significant volume of literature assessing the benefits of exercise in several subdomains of quality of life. These domains include psychological and psychosocial wellbeing [79, 80] depression [81, 82], anxiety [83], self-image, confidence, and improvement in energy. [84, 85]

Related to energy level, fatigue has been found to be a common symptom of liver cirrhosis patients [86]; however, exercise has been shown to have a reducing

effect on symptoms of fatigue. In a review of 12 epidemiological studies, Puetz *et al.* found consistent findings indicating a strong, dose dependent relationship between physical activity, vitality, and decreased fatigue. [87]

2.8 Safety Concerns: The effect of Aerobic Exercise on Portal Pressures and Variceal Rupture

Of significant concern in patients with cirrhosis is the safety of exercise. While there is still limited data on benefits and harms of exercise in this population, a main concern is that exercise will cause an increase in portal pressure, leading to increases in pressure in gastroesophageal varices, and subsequent varicose vein rupture and internal bleeding. [21] These effects if severe may lead to death. In support of this concern, an increase in portal pressure has been found to correlate with an increased risk of internal bleeding via varices rupture. [21] In a 1996 study of eight patients with liver cirrhosis, Garcia-pagan *et al.* found an increase in portal pressure as measured by hepatic venous pressure gradient (HVPG), as well as a decrease in portal blood flow when patients exercised at 30% of peak power output.[88] This level of exercise, which corresponds roughly to brisk walking, would be considered moderate intensity activity. When patients were exercised at 50% of peak power output, this effect on portal pressure and blood flow was even further pronounced. Thus, the concern related to increased portal pressure caused by exercise and the associated risks of gastroesophageal variceal bleeding may be justified.

The risk of bleeding, however, can be mitigated via the use of a non-selective beta blocker to prevent the exercise induced increase in portal pressure. Bandi *et al.* performed a double blinded placebo controlled study of splanchic hemodynamic response in liver cirrhosis patients with portal hypertension, as measured by hepatic venous pressure gradient (HVPG). [89] Patients assigned to the placebo group experienced increased portal pressures at baseline and during moderate cycling exercise, while patients in the group receiving propranolol (beta blocker) were found to have a significant reduction in portal pressure both at baseline and during exercise. As a result of this mitigation of a raised HVPG, the risk of a variceal rupture is decreased.

2.9 Summary and Rationale

It has been shown that aerobic capacity, muscle mass and quality of life are decreased in individuals with liver cirrhosis. At present, there is a paucity of literature on the effect of exercise training on these outcomes, thus, there is limited data supporting the safety and effectiveness of aerobic exercise interventions. While there is limited data in the liver cirrhosis population, there is strong evidence supporting exercise training in healthy and other clinical populations, demonstrating that exercise interventions are associated with improvement in aerobic capacity, muscle mass, and quality of life, all areas of concern to patients with cirrhosis. Due to this potential benefit, further research investigating the effects of aerobic exercise training in a liver cirrhosis population is warranted, particularly in patients where measures have been taken to reduce risks

associated with increased portal pressure and where appropriate variceal prophylaxis is in use.

Chapter 3: Methods

3.1 Overview of study design

“The effect of eight weeks of home based aerobic exercise training on peak exercise oxygen consumption, six-minute walk test distance, thigh muscle mass, and health related quality of life in Child Pugh class A and B cirrhosis patients” was as randomized controlled trial conducted at the University of Alberta in Edmonton, Alberta, Canada, from September of 2014 to October of 2015. Patients meeting eligibility requirements were randomized to a home exercise training group (HET), or a usual care group (UC) for eight weeks.

3.2 Ethics Approval

This investigation was approved by the Health Research Ethics Board at the University of Alberta. The study was registered at www.clinicaltrials.gov (Identifier: NCT02267421). All patients gave informed consent prior to their participation in this study.

3.3 Participants

A convenience sample of patients was recruited during their visits to the Cirrhosis Care Clinic at the University of Alberta Hospital. Patients were screened for inclusion and exclusion criteria.

3.4 Inclusion Criteria

1. Liver Cirrhosis diagnosed via compatible radiological appearance or by biopsy.

2. Child Pugh Class A or B liver cirrhosis

3. Age ≥ 18 and ≤ 70 years

4. Guideline based primary prophylaxis in place for patients displaying gastroesophageal varices. Prophylactic options include:

    a. Non-selective beta-blockade

    b. Endoscopic band ligation to the point of variceal eradication

3.5 Exclusion Criteria

1. Patient is post liver transplantation

2. Patient has significant cardiac disease, defined as an ejection fraction <60% or a history of coronary artery disease, or a positive stress test (≥1mm ST segment depression)

3. Chronic renal failure on dialysis

4. Hemoglobin measurement <110g/L

5. Human Immunodeficiency Virus infection (HIV)

6. Hepatocellular Carcinoma (HCC)

7. Active non-HCC related malignancy

8. Myopathy

9. Presence of a physical impairment or orthopedic abnormality that would prevent HET.

10. Failure to Consent

3.6 Baseline Evaluation

Patients meeting study eligibility were provided with an information sheet (Appendix A), which outlined the purpose, procedures, risks and possible benefits involved with participation in this study. The patient's written informed consent was obtained (Appendix B). Baseline data collection took place over two separate days within a seven-day period.

3.6.1 Day One: Cardiopulmonary Exercise Test

Cardiopulmonary exercise testing (Appendix F) was administered by an exercise physiologist and assistant, along with physician supervision at the Mazankowski Heart Institute at the University of Alberta Hospital. Heart rate and blood pressure were taken before, during and after testing to ensure that these parameters were within and remained in a safe range. An electronically braked cycle ergometer was used. Power output was set at 15 watts, and increased by 15 watts every two minutes until the aerobic threshold was reached based on RER remaining at or above 1.0 on for a period of time, and not decreasing below this point on average

until testing was completed. At this point, power output was increased by 15 watts every minute until volitional exhaustion occurred. In the last 30 seconds of each stage, participants were asked to rate their perceived exertion on a Borg scale, numbered from 6 to 20, with 6 being the least difficult, and 20 being the most difficulty. A Physioflow was used to monitor heart rate continuously during the testing. Blood pressure was also measured via sphygmomanometer at the end of each exercise stage (every two minutes). After the test was finished, the highest amount of oxygen consumed over one minute was used as the peak VO_2 score.

3.6.2 Day two: Clinic Baseline Evaluations:

Day two baseline evaluations were administered at the Cirrhosis Care Clinic at the University of Alberta Hospital. Data collected was recorded on Baseline Data Collection Sheets (Appendix D). Data collection consisted of the completion of assessments of quality of life, general medical history taking, thigh muscle ultrasound, a six-minute walk test, and requisition for bloodwork.

1) *Recording of general medical history and review of current medications.*

Medications, complications, patient comorbidities, etiology of liver cirrhosis, and general medical history was first collected. These data were confirmed through information available through Netcare.

2) *Nutritional Assessment*

As per standard of care, two-day diet records were distributed to participants, along with instructions on their use. Patients were asked to fill in and return the diet records for analysis by the Cirrhosis Care Clinic registered dietician. Diet records

were used to estimate caloric intake, protein intake, and to provide nutritional counselling to participants. Nutritional counselling guidelines were to be based on the European Society of Enteral and Parenteral Nutrition Guidelines (ESPEN) guidelines [90], and the *Nutrition Support Manual (Adult)* and *Daily Nutrient Recommendations for Liver Disease*, which is provided by Alberta Health Services (AHS).

3) Thigh Muscle Mass and Circumference Measurement

Thigh Muscle thickness was assessed using a portable ultrasound machine (Mindray©, Shenzhen, China) on the right quadriceps muscle (rectus femoris, vastus lateralis, vastus medialis and vastus intermedius muscles). Measurements were taken at marked points that were at one-third and at one-half of the distance between the top of the patella and the iliac crest, as these measurement sites have been previously validated. [5] Two measurements were recorded at each of these measuring points. The first was a compression reading, where the ultrasound probe was pushed down on the muscle to compress the muscle against the femur bone. Pressure was applied until the muscle would no longer compress, at which point, the image was recorded and a measurement was taken. The second measurement taken was a feathering measurement where the probe was held to the skin, but no pressure was applied to the thigh. Measurements at both points of the thigh were averaged over 2 readings and recorded. Thigh circumference was assessed via tape measure at the one-third point of the thigh. This measurement acts as a muscle mass correlate.

4) Assessment of Quality of Life

Patients independently completed the following quality of life questionnaires, with help available for interpreting questions as requested.

A) Chronic Liver Disease Questionnaire (CLDQ)

The CLDQ (Appendix G) is a 29-item self-administered health related quality of life survey. It was developed for use with all causes/ types of liver disease and stages of liver cirrhosis. The CLDQ questionnaire contains items in the domains of fatigue, activity, emotional function, abdominal symptoms, systematic symptoms, systemic symptoms, and worry, all rated on a 7-point Likert scale. Higher total and domain scores indicate lower frequency of experiencing related symptoms. Means were computed for both an overall score as well as for each domain subscale.

B) Hospital Anxiety and Depression Scale (HADS)

The HADS (Appendix H) consists of 14 items and two subscales measuring anxiety and depression levels using a 4-point (range: 0-3) Likert scale. Scores for each subscale range from 0-21 when summed. Higher scores indicating higher levels of depression and/or anxiety, depending on the item.

C) EuroQoL-Visual Analogue Scale (EQ-VAS)

The EQ-VAS (Appendix I) is a component of the EuroQol Descriptive System; a standardized measure of health status that quantitatively records a patients self-rated health on a 100-point visual analogue scale. [91] Patients were asked to rate their perceived health state on the 100-point scale with scale end points labeled

“Best imaginable health state” (score of 100) and “Worst imaginable health state” (score of zero).

5) 6-Minute Walk Distance

A 6-minute walk test was performed adhering to American Thoracic Society guidelines. [92] Patients were instructed to cover as much distance as possible at a steady walking pace, in six minutes while walking back and forth in a straight, flat, 25-meter distance marked hallway. Distance was marked every meter. Participants were instructed to slow down and rest if they felt it was necessary, and to resume walking when they felt able. The total distance traveled during the six-minute period was recorded.

6) Bloodwork requisition and liver cirrhosis disease severity

Each patient was provided with a bloodwork requisition form and instructed to have blood work done within two days of their appointment. In order to examine disease severity, liver function, and enzymes, the following items were assessed in the blood work: serum albumin, bilirubin, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), electrolytes, complete blood count (CBC), and international normalized ratio (INR). Liver disease severity was determined from this blood work using the Child-pugh classification system, as well as the MELD score.

7) Adherence

Data on adherence to exercise sessions as well as to the prescribed program was collected. Adherence was considered complete if patients completed ≥ 80% of their prescribed exercise sessions, and having 80% (of the 80% above i.e. 64%) of sessions within their target heart rate range.

3.7 Randomization

After completing both days of baseline assessment, patients were randomized to the home exercise training group (HET) or the usual care group (UC) via an internet randomization plan (http://www.randomization.com*).* The randomization sequence was generated by a clinician external to the study team, who then placed the group assignment in sealed, opaque, sequentially number envelopes. Patients were randomized after completion of their baseline assessments. Investigators were informed of patient group assignments.

3.8 The home-based exercise training program

Patients meeting eligibility requirements were randomized to receive HET or UC for eight consecutive weeks. A home exercise training protocol was implemented for this study due to several advantages:

1. It is more cost-effective to deliver the intervention
2. It allows the patient to exercise when convenient for them
3. Because of 1 and 2, the intervention is more feasible over the long term

Patients randomized to the HET group were visited by an exercise training assistant to deliver and set up a cycle ergometer (Schwinn 170 Upright bike, Chicago, USA), as well as to provide instruction on use of the bike and education on the exercise training program. Participants were also provided with a heart rate monitor and an exercise diary, and instructed in their use for monitoring and recording workouts respectively. Patients were also taught to use the Borg scale of physical exertion (scale of 6-20) [93] as a method to rate their own exertion during exercise.

Aerobic exercise was chosen as the mode of exercise, as even with appropriate variceal prophylaxis in place, there remains a lack of data on the safety and efficacy of resistance training in this population. Patients were prescribed an aerobic exercise program to be performed between 60% and 80% of heart rate reserve (Appendix K). For patients prescribed beta-blockers, 60-80% of their beta blocked heart rate reserve was used or an intensity level of 14 to 15 (somewhat hard to hard) on the Borg scale prescribed. Patients were asked to exercise a minimum of 3 times per week, starting at 30 minutes per session for the first two weeks. Subsequent to this, training sessions increased in duration by 5 minutes every week from week three to eight to a maximum of 60 minutes per session in the eighth week. Participants performed a warm up before exercise and cool down after exercise of five minutes each. Warm up and cool down were to be completed at a lower intensity than the exercise session, also measured by Borg scale at an intensity of 8-9 on the 6-20 point Borg scale, or by heart rate at an intensity of 40% of heart rate reserve. Participants were contacted by phone weekly, and visited

biweekly for exercise session observation and monitoring. During the session, patients were asked about any adverse events experienced during training. This included cardiovascular or pulmonary events, extreme fatigue or muscle weakness, variceal bleeding, paracentesis, infections, hospitalizations, or any other effects related or unrelated to exercise they may have experienced.

3.9 Usual Care Group

Patients in the UC group were asked to continue with their regular daily activities, without starting any new exercise or exercise program for the duration of the study.

3.10 Follow-up Evaluations

After the eight-week intervention period, participants in both groups underwent the follow-up evaluation. Follow-up tests were administered by the same staff, following the same testing procedures as the baseline assessments. Results were recorded on the End of Study Data Collection Sheet (Appendix E).

3.11 Outcome Measures

Vhange in peak VO_2 from baseline to follow-up at the end of the 8-week intervention period was the primary outcome. Secondary outcome measures also followed this timeline, and are as follows: changes in quadricep muscle thickness as determined by bedside ultrasound, thigh circumference as measured by measuring tape, six-minute walk distance, health related quality of life.

3.12 Sample size

The sample size calculation was based off the expected change in peak VO_2, the primary outcome. Based on a previous study [5], improvement was expected to be approximately 5.3 ml/kg/min after HET when compared to UC. With a between group standard deviation of 5ml/kg/min [5], alpha level of $p<0.05$, and a power of 80%, it was estimated that a total of 28 subjects were needed. Given the high potential for dropouts as well as for decreased efficacy of HET as compared to supervised exercise, the target recruitment was conservatively increased by 40% for a total of 40 subjects (n=20 home exercise training, and n=20 control). (Appendix L)

3.13 Statistical Analyses

Statistical Analyses was performed using SPSS version 19 (SPSS INC., Chicago, IL, USA). Variables were described using means and standard deviations, or proportions. Depending on variable distribution, Chi-squared and paired t-tests were used to determine if there were differences in baseline characteristics or results between study groups. To take advantage of RCT design, the primary statistical analysis was the determination of between group differences using the analysis of covariance (ANCOVA). ANCOVA was chosen as it accounts for individual changes within patients, changes between groups, and for differences in baseline values and is robust to violations of normality assumptions. Statistical significance was established at a 2-tailed p-value of <0.05. (Table 4)

Table 4. Variables and Statistics used

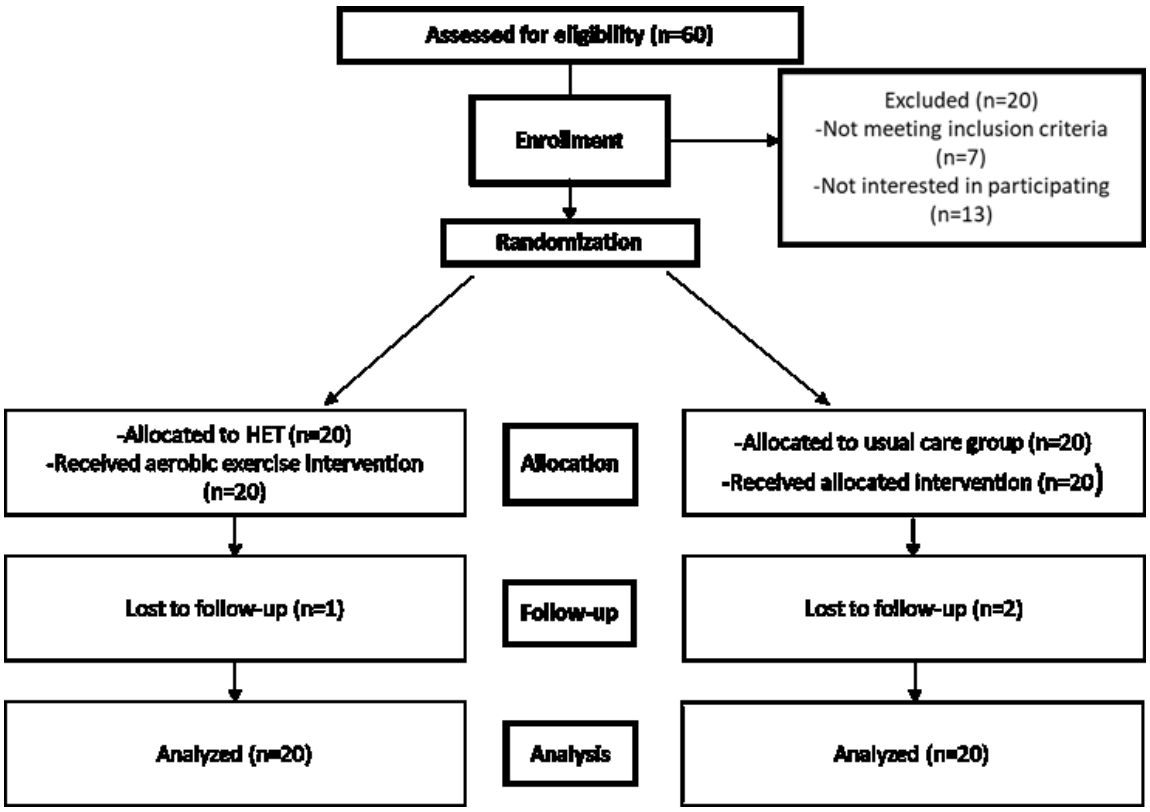
Variable	**Descriptive Statistic**	**Inferential Statistic (between and within groups)**
Peak VO_2	Mean and Standard deviation	ANCOVA and students' t-test
6MWT	Mean and Standard deviation	ANCOVA and students' t-test
Thigh Circumference	Mean and Standard deviation	ANCOVA and students' t-test
CLDQ measures	Mean and Standard deviation	ANCOVA and students' t-test
Lab Values	Mean and Standard deviation	ANCOVA and students' t-test
Age	Mean and Standard deviation	ANCOVA and students' t-test
Body Weight	Mean and Standard deviation	ANCOVA and students' t-test
Child Pugh score	Mean and Standard deviation	ANCOVA and students' t-test
Meld Score	Mean and Standard deviation	ANCOVA and students' t-test
Adherence	Mode, Mean and Standard deviation	Chi-squared, students' t-test ANCOVA

CHAPTER FOUR: RESULTS

4.1 Flow of Patients Through the Study

Figure 1 shows the flow of patients through the study. Sixty patients were screened and approached at one of two tertiary liver clinics in Edmonton, Alberta (University of Alberta Hospital, and the Royal Alexandra Hospital) between October 2014 and September 2015. Of the 60 approached, 40 agreed to participate (66.7%). Therefore, data were available and analyzed for all 40 patients recruited. 3 patients were lost to follow up, and were analyzed as intent to treat.

Figure 1. Flow of patients through the study.



4.2 Patient Characteristics

The participants included 40 male and female patients (23 male, 58%).

Baseline patient characteristics are shown in Table 5. Eighty percent were Caucasian (n=32), and the mean age for all participants was 56.7 ± 8.2 years. Seventy percent of participants were classified as Child Pugh class A, with a mean CP score of 6.3 ± 1.3 and a mean MELD score of 9.4 ± 2.9. Fifty-eight percent (n = 23) of participants had either Hepatitis C or alcohol related liver disease. No patients had clinically detectable ascites or hepatic encephalopathy on baseline evaluation, however, thirty-five percent (n = 14) of participants were taking diuretic therapy during the study. Seventy-three percent (n = 29) of patients had a history of varices. Six patients met criteria for primary (pharmacological) variceal prophylaxis (two in HET group, four in Usual Care group), and four patients met criteria for secondary (endoscopic or TIPS) variceal prophylaxis (one in HET group, three in Usual Care group). One patient in the UC group had a well-functioning transjugular intrahepatic portosystemic shunt (TIPS) in place, and was therefore not counted as actively meeting criteria for variceal prophylaxis. Four patients were active smokers, all in the HET group. Two patients, one in each group reported weekly alcohol consumption.

Table 5. Baseline Patient Characteristics

Characteristic	**Exercise training group (n = 20)**	**Usual Care Group (n=20)**
Age (years)	**53.0±8.3**	**56.4±8.5**
Male, n (%)	**50%**	**64%**
Caucasian, n (%)	**15 (75%)**	**17 (85%)**
Etiology of cirrhosis n (%)		
Alcohol Induced	**5 (25%)**	**6 (30%)**
NASH	**5 (25%)**	**5 (25%)**
Hepatitis C	**7 (35%)**	**5 (25%)**
Other	**3 (15%)**	**4 (20%)**
Severity of liver disease		
MELD score	**9.1**	**9.7**
Child Pugh Score	**6.35**	**6.26**
Child Pugh A/B	**70%/30%**	**70%/30%**
Use of Diuretics, n (%)	**7 (35%)**	**3 (15%)**
History of Varices, n (%)	**70%**	**75%**
Variceal Prophylaxis, n (%)		
Not required/TIPS	**0 (0%)**	**1 (5%)**
Primary Prophylaxis	**2 (10%)**	**4 (20%)**
Secondary Prophylaxis	**1 (5%)**	**3 (15%)**
Medications, n (%)		

Beta Blocker	**3 (15%)**	**5 (25%)**
Diuretics	**9 (45%)**	**5 (25%)**
Labs		
Hemoglobin (g/L)	**133.5±15.7**	**132.5±14.7**
Platelet count	**111.5±53.9**	**136.7±95.1**
Albumin (g/L)	**38.1±4.5**	**37.8±4.4**
Creatinine (umol/L)	**81.42±42.0**	**69.65±18.9**
Bilirubin (umol/L)	**24.8±16.5**	**36.05±50.24**
INR	**1.23±0.3**	**1.34±0.5**
ALT (U/L)	**47.5±36.7**	**44.15±36.3**
BMI	**28.9±5.1**	**28.9±4.2**
Peak VO_2 absolute (L/min)	**1.87±0.66**	**2.21±0.52**
Peak VO_2 (ml/kg/min)	**17.3±4.5**	**21.0±6.1**

Data presented as mean **±** *S.D. with the exception of gender, ethnicity, disease etiology, disease severity, and prophylactic methods, where values are frequency counts. For all comparisons, p > 0.05. The etiology of liver cirrhosis in the 'other' category include: cryptogenic, hepatitis b and primary biliary cirrhosis. See definitions section for abbreviations.*

4.3 Primary Outcome Measure: Effect of 8 weeks of HET or UC on Peak VO_2

At baseline, the relative Peak VO_2 was significantly higher in the UC group than in the HET group (mean peak VO_2 21.0 ± 6.1 ml/kg/min in UC group versus 17.3 ± 4.5 ml/kg/min in HET group, p=0.03). Following the intervention period, the mean change in peak VO_2 between the groups favoured the HET group but was not statistically different (+0.15 L/min; 95% CI: -0.03 to 0.32, p = 0.10 and +1.7 mL/kg/min; 95% CI: -0.33 to 3.7, p = 0.10). Within group differences via paired t-test showed a significant improvement in peak VO_2 within the HET group only, when indexed to body weight (17.3 ± 4.5 mL/kg/min baseline to 19.0 ± 6.4 mL/kg/min, p= 0.03). There was also significant improvement in peak VO_2 in the HET group in absolute terms (1.44 ± 0.4 mL/min at baseline to 1.57 ± 0.56 L/min; p = 0.04). (Table 6) There were no significant changes within the UC group for relative peak VO_2 when indexed to body weight or with absolute peak VO_2 measures (p= 0.80 body weight indexed, p= 0.98 absolute).

Table 6. Baseline and study end cardiorespiratory measures.

	AET group			Control group			Difference between mean changes (95% CI)	ANCOVA P value between groups
	Baseline	**Study End**	**Within group p value**	**Baseline**	**Study end**	**Within group p value**		
Peak VO_2 (L/min)	1.44 ± 0.40	1.57 ± 0.56	0.04	1.87 ± 0.66	1.87 ± 0.70	0.98	0.15 (-0.03 to 0.32)	0.095
Peak VO_2 (ml/kg/min)	17.3 ± 4.5	19.0 ± 6.4	0.03	21.0 ± 6.1	21.2 ± 6.3	0.80	1.7 (-0.33 to 3.7)	0.098
Peak Power output (W)	120.0 ± 41.7	125.0 ± 52.2	0.27	149.8 ± 50.9	146.5 ± 59.9	0.47	12.5 (-0.08 to 25.0)	0.051
Peak Heart Rate (BPM)	130.4 ± 23.0	126.5± 22.4	0.09	139.8 ± 22.3	138.2 ± 22.7	0.72	-4.0 (-11.4 to 3.5)	0.29
Peak Systolic BP	157.4 ± 23.7	150.4 ± 20.0	0.04	157.5 ± 21.0	152.5 ± 16.4	0.07	-0.56 (-7.4 to 6.3)	0.87

Data presented as mean ± S.D.

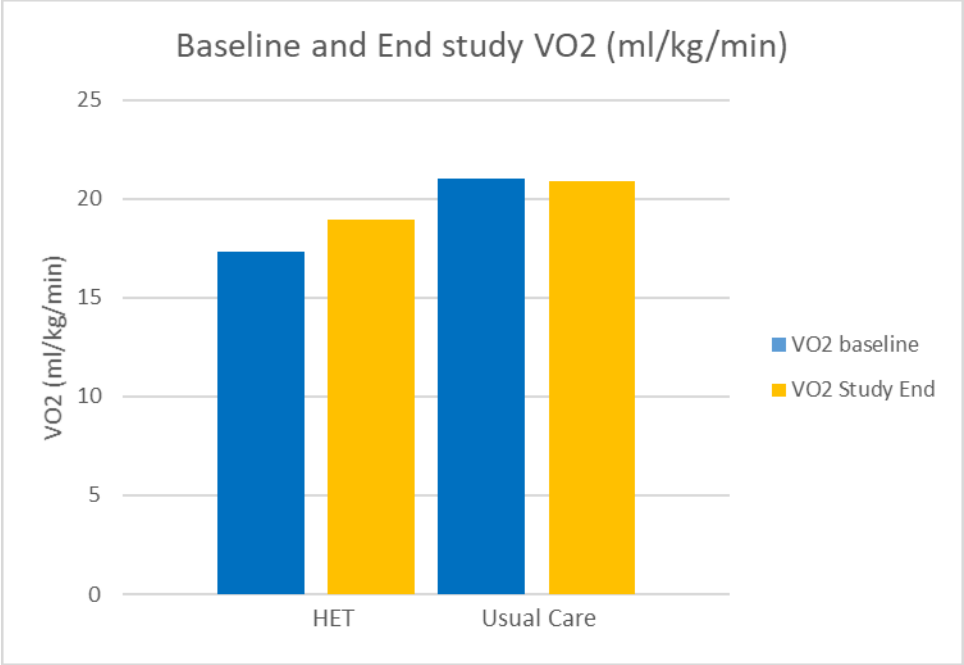


Figure 2. Baseline and End Study VO_2 (ml/kg/min)

Data presented as means.

4.4 Secondary Outcomes measures: Effect of 8 weeks of HET or UC on Six-minute walk distance, Thigh muscle circumference, Thigh muscle thickness, and quality of life measures

The changes in the secondary outcome measures are presented in Table 7. When examining between group changes, the HET group showed a statistically significant increase in 6MWD when compared to the UC group (mean of 33.7 meters, 95% CI: 5.1 to 62.4, p=0.02). Looking at within group changes via paired t-test, neither the HET group or the UC group exhibited significant changes (HET: 476.0 ± 89.8 meters baseline to 490.7 ± 104.1 meters post eight weeks, p = 0.08), (UC: 520.8 ± 92.2 meters baseline to 500.4 ± 91.8 meters post eight weeks, p = 0.08).

When compared to the UC group, the HET group showed no statistically significant change in thigh circumference (cm) (1.20, CI: -0.58 to 2.98, p = 0.18). There was however, significant change within the HET group (50.6 ± 5.8 cm baseline to 52.4 ± 6.6 cm post, p = 0.024). There was no significant change in the UC group thigh circumference (51.2 ± 5.8 cm baseline to 51.8 ± 5.5 cm post eight weeks, p = 0.23).

The HET group did not show significant improvement in thigh muscle compression or feathering index (thigh muscle thickness as measured by ultrasound, with the muscle compression corrected for height squared) when compared to the UC group in either feathering conditions (Feather index: 0.005, CI: -0.08 to 0.09, p = 0.91), or compression conditions (Compression Index: 0.04, CI: -0.04 to 0.12, p=0.33).

There were no statistically significant improvements in the CLDQ total or any of the CLDQ domains between the HET and UC groups. However, the systemic systems domain trended to significance (0.55 points, CI: -0.06 to 1.15, p = 0.07). The HET group showed significant change within group in the emotional function CLDQ subdomain (5.31 ± 1.04 baseline to 4.84 ± 1.22 post eight weeks, p = 0.03). The HET group approached and trended towards significance in the Systemic Symptoms CLDQ domain (4.84 ± 1.22 baseline to 4.53 ± 1.36 post eight weeks, p= 0.07). The UC group trended towards significance in the abdominals symptoms CLDQ domain (4.93 ± 1.82 baseline to 5.32 ± 1.71 post eight weeks, p = 0.06). There were no statistically significant differences in any other CLDQ domains.

The EQ-VAS did not show significant change either between or within groups, although results approached significance between groups with a difference between mean change of a mean 7.01 points (CI: -16.6 to 2.6, p = 0.15) on a zero to 100-point scale.

The HADS did not show a significant change in within or between groups as a whole, or either within the anxiety or depression subdomains.

Table 7. Baseline and End of Study secondary outcome and anthropomorphic measurements

	AET group			Usual Care			Difference between mean changes	ANCOVA p-value
	Baseline	Study end	Within group p-value	Baseline	Study End	Within group p-value		
Six Minute walk distance (m)	476.0 ± 89.8	490.7 ± 104.1	0.08	520.8 ± 92.2	500.4 ± 91.8	0.08	33.7 (5.1 to 62.4)	0.02
Thigh Circumference (cm)	50.6 ± 5.8	52.4 ± 6.6	0.024	51.2 ± 5.8	51.8 ± 5.5	0.23	1.20 (-0.58 to 2.98)	0.18
Average Feather Index (cm/m^2)	1.25 ± 0.40	1.31 ± 0.38	0.05	1.21 ± 0.26	1.27 ± 0.24	0.07	0.005 (-0.08 to 0.09)	0.91
Average Compression index (cm/m^2)	0.75 ± 0.27	0.77 ± 0.25	0.30	0.75 ± 0.18	0.73 ± 0.19	0.72	0.04 (-0.04 to 0.12)	0.33
BMI (kg/m^2)	29.3 ± 5.2	29.3 ± 5.1	0.74	28.9 ± 5.1	29.2 ± 5.0	0.90	0.12 (-0.6 to 0.85)	0.73
Body Weight (kg)	84.6 ± 15.6	84.8 ± 14.7	0.85	88.1 ± 16.9	89.1 ± 16.4	0.82	-0.005 (-2.0 to 2.0)	0.99
Quality of life								
CLDQ								
Total	5.06 ± 1.09	4.76 ± 1.16	0.13	5.22 ± 1.36	5.03 ± 1.34	0.29	0.15 (-0.40 to 0.66)	0.57
Abdominal Symptoms	5.43 ± 1.54	5.30 ± 1.43	0.66	4.93 ± 1.82	5.32 ± 1.71	0.06	-0.23 (-0.91 to 0.45)	0.49
Systemic Symptoms	5.01 ± 1.12	4.53 ± 1.36	0.07	5.04 ± 1.51	5.10 ± 1.49	0.72	0.55 (-0.06 to 1.15)	0.07
Activity	5.08 ± 1.42	4.73 ± 1.50	0.20	5.32 ± 1.71	4.77 ± 2.13	0.21	-0.12 (-1.11 to 0.86)	0.80
Emotional Function	5.31 ± 1.04	4.84 ± 1.22	0.03	5.63 ± 1.32	5.46 ± 1.33	0.23	0.34 (-0.14 to 0.82)	0.16
Worry	5.30 ± 1.33	5.18 ± 1.37	0.59	5.42 ± 1.69	5.34 ± 1.75	0.83	0.08 (-0.71 to 0.88)	0.83
Fatigue	4.28 ± 1.53	4.14 ± 1.35	0.55	4.46 ± 1.52	4.16 ± 1.68	0.24	-0.12 (-0.77 to 0.53)	0.72

EQ-VAS	63.0 ± 16.9	62.6 ± 16.4	0.91	70.4 ± 24.8	72.9 ± 18.5	0.58	7.01 (-16.6 to 2.6)	0.15
MELD	9.05 ± 2.61	9.57 ± 2.51	0.47	9.71 ± 3.16	10.3 ± 3.65	0.59	0.35 (-2.02 to 2.73)	0.76
Child-Pugh score	6.35 ± 1.46	6.53 ± 1.46	0.85	6.26 ± 1.24	6.42 ± 1.46	0.72	0.44 (-0.21 to 1.09)	0.18
Lab values								
ALT (units/L)	46.8 ± 38.27	47.19 ± 50.53	0.98	44.69 ± 37.2	40.1 ±33.3	0.67	-4.3 (-14.2 to 5.6)	0.001
Bilirubin (µmol/L)	23.53 ± 16.3	27.2 ± 20.4	0.65	37.3 ± 51.3	34 ± 40.5	0.83	-3.9 (-18.6 to 10.8)	0.59
Albumin (g/L)	38.1 ± 4.50	37.1 ± 5.27	0.72	37.8 ± 4.44	37.9 ± 4.92	0.95	-0.69 (-3.4 to 2.05)	0.61

Data presented as mean ± S.D. Abbreviations: BMI: Body Mass Index, CLDQ: Chronic Liver Disease Questionnaire, EQ-VAS: EuroQol Visual-Analog Scale, ALT: Alanine aminotransferase

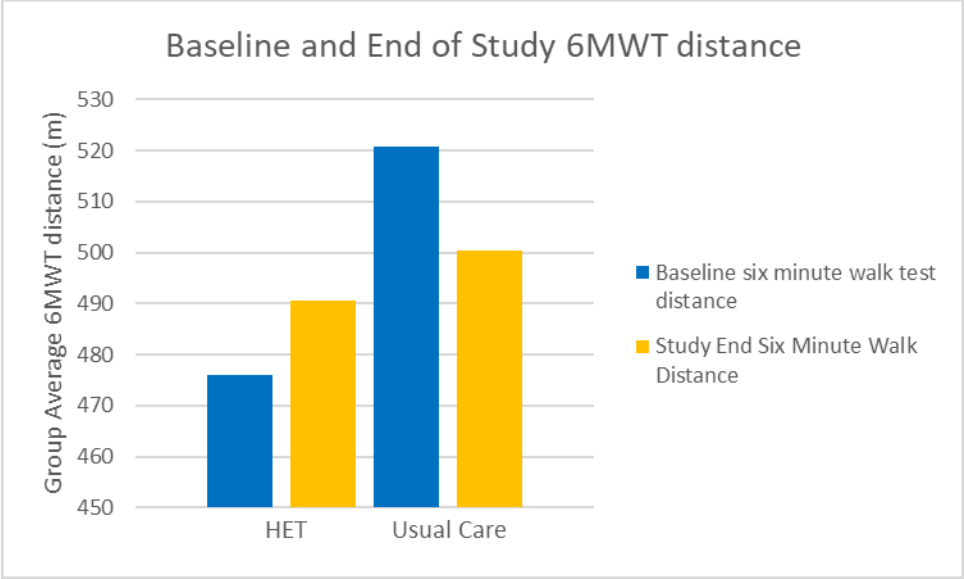


Figure 3. Baseline and End Study Six Minute Walk Test distance

Data presented as means.

4.5 Adherence

Only 30% of exercise participants completed the full prescribed exercise program. Even considering just the number of sessions completed, only 50% of exercise group patients completed ≥ 80% of their sessions, 10% completed 50-79% of their sessions, and 40% completed < 50% of their sessions. While not an ‘a priori’ outcome, exploratory analysis based on adherence was possible. Examination of this data was performed to inform findings and future research.

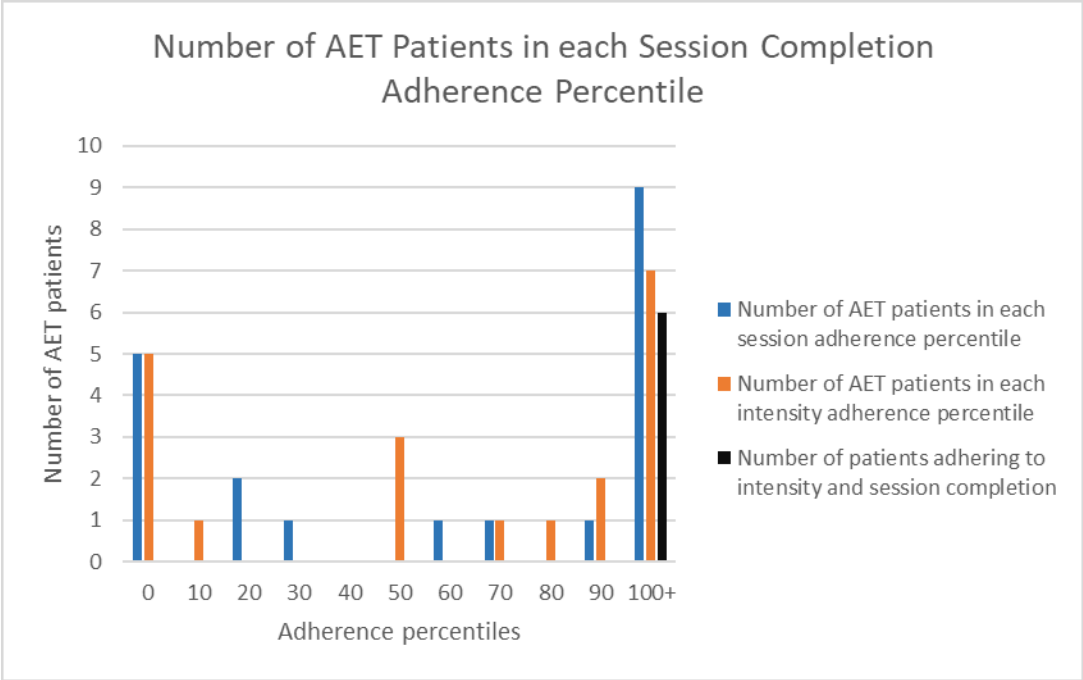


Figure 4. Adherence to number of sessions, intensity of sessions, and both number and intensity

4.6 Exploratory analyses

In an exploratory analysis of participants with a session completion adherence rate above 80% (n=11), male gender was found to be a significant predictor of adherence in this study (9/11, 82%), with being of a younger age resulting in a trend to significance (p = 0.06).

4.7 Adverse events

No adverse events occurred during cardiopulmonary exercise testing or during aerobic training. As well, no complications occurred related or unrelated to exercise, such as gastroesophageal varices. There were also no significant changes in AST, Child-Pugh or MELD scores between groups from baseline to study end. There was however a statistically significant change in ALT between groups from baseline to study end (-4.3 units/L, CI: -14.2 to 5.6, p = 0.001) in favour of the exercise group.

CHAPTER FIVE: DISCUSSION

5.1 Introduction and Major Findings

As far as is known, this study is the first randomized controlled trial of Child Pugh class A and B liver cirrhosis patients evaluating the effect of home based exercise training (HET) on VO_{2peak}, six-minute walk test distance, thigh muscle thickness and mass, and health related quality of life. Only one other study has previously evaluated these outcomes in a similar population, however that study was a supervised, hospital based exercise training study.

The main findings of this study relate to safety and adherence. First, the lack of adverse events in testing and with HET sessions was a significant finding. Although there are concerns regarding the safety and tolerance of exercise in patients with liver cirrhosis, no complications or adverse events occurred during the study period despite the lack of supervision. The results suggest that with appropriate screening, fitness testing and primary prophylaxis in place, HET is potentially safe and feasible in this population.

Second, when examining the logbooks of participants, it was found that adherence to the prescribed exercise protocol outlined to patients was not achieved, as less than half of patients abided by prescribed exercise guidelines. When probed during follow-up phone calls and home visits, reasons provided for lack of adherence included fatigue, general malaise and lack of time. On home visits, some exercise was attempted but, as the participant had not been regularly exercising,

adjustments to the prescription had to be made. Thus, the given participant exercised but not at intensity or duration originally prescribed. Despite biweekly phone calls, low adhering participants did not change their behaviour for self-directed sessions. More supervision at the start of the study may have helped participants to transition to self-directed exercise and to overcome these barriers. Adding a method of patient-reported responses to exercise may have assisted the investigative team by identifying symptoms early on in the study. Evaluating reasons for the lack of adherence may have helped to ensure at least partial adherence for low adhering participants and would ensure that participants participate in at least some exercise, rather than none. Moreover, we did not include a behaviour change component such as goal setting and strategies to address poor adherence. Encouraging patient-reported responses to exercise and a method for early identification of issues may assist the investigative team in creating solutions to these issues before the issues impacted overall adherence. [94]

Hypothesis related findings:

Hypothesis 1: The primary hypothesis is that a home exercise-training (HET) program will prove safe and feasible in patients with cirrhosis of the liver.

In regard to our primary hypothesis, HET was found to be safe; however, feasibility as defined by exercise adherence of >80% of completed sessions and >80% at prescribed intensity and duration was not achieved.

Hypothesis 2: A significant improvement in peak VO_2 will be observed in participants in the eight-week HET group when compared to the usual care group (UC).

In regard to the second hypothesis, eight weeks of HET did not significantly improve peak VO_2, although improvements were observed suggesting trends to significance. There was however, a statistically significant within group improvement in peak VO_2 the exercise training group.

Hypothesis 3: Eight weeks of HET will result in significant improvements in cross sectional measures of thigh muscle mass, quality of life measures, six-minute walk distance.

- HET did not result in statistically significant between group differences thigh muscle mass between groups although, again, a significant within group improvement was seen in HET group.
- HET did not result in statistically significant differences either between or within groups in thigh muscle circumference.
- HET did not result in statistically significant differences in quality of life. There was however, significant within group improvement in the CLDQ emotional function domain in the HET group.
- A statistically significant between group difference was found in ALT measurement favouring the HET group.
- HET was found to significantly improve 6MWT distance.

5.2 The Effect of HET on Peak VO_2

This study showed an impairment in aerobic capacity among early stage liver cirrhosis patients when compared to age predicted values, as is consistent with current available literature. Patients in this current trial had a baseline mean peak VO_2 of 19.2 ml/kg/min. Limitations in peak VO_2 in cirrhosis patients are commonly attributed to muscle wasting and deconditioning, fatigue, and cardiorespiratory changes including cirrhotic cardiomyopathy and hepatopulmonary syndrome. [2] Baseline values in VO_2 in the present study were only slightly higher than reported in the literature. In a systematic review of 1107 cirrhotic patients being prepared for liver transplantation, the mean peak VO_2 was only 17.4 mL/kg/min. [95] This corresponds to the expected peak VO_2 level of a healthy sedentary female in her eighth decade of life [96] and is just below the threshold for independent living of 18 mL/kg/min. Thus, our sample was likely representative of the CP Class A and B Cirrhosis population.

Eight weeks of HET did not significantly improve peak VO_2 between groups; however, there was a statistically significant improvement within the HET group alone. This finding runs counter to previous exercise training studies in a liver cirrhosis population and other populations. [5] Ritland *et al.* in a non-randomized trial (n = 9) reported an increase in estimated peak VO_2 by 6 ml/kg/min and 9 mL/kg/min following four to six weeks of aerobic exercise training, and 10 to 12 weeks of aerobic exercise training in a population comprised of young females (mean age of 31 years) without a history or signs of decompensation, and with

liver cirrhosis being confirmed in only 55% participants. [52] Besides differences in patient population, Ritland *et al.* used a method of peak VO_2 estimation by use of a submaximal test to obtain values, a method that may have resulted in an overestimation of VO_2.

Several possibilities exist for why statistical significance was not achieved. The lack of adherence to the exercise program is no doubt the primary reason for a lack of significant change in peak VO_2. Notably, adherence in this study was significantly lower than in a previous study in a similar population using a hospital based supervised training program, a study which did show significant improvement in peak VO_2. [5] When explored further it was found that participants with high adherence were found to have an improvement in peak VO_2 exceeding the 2.8 ml/kg/min mean improvement seen in the exercise group, approaching the 3.5 ml/kg/min improvement associated with improved survival in patients referred for cardiac testing. This finding suggests the potential need for more exercise supervision to attain better adherence among patients with cirrhosis.

In addition, HET group participants had a significantly lower baseline peak VO_2 when compared to the UC group. The mean VO_2 of 17.3 in the HET group was below the threshold for independent living, suggesting that these participants would be challenged to complete even activities of daily living let alone exercise.

The exercise training program itself included steady state exercise only. Steady state aerobic exercise training that takes place below the anaerobic threshold does not train the anaerobic energy system to become stronger. While steady state

aerobic exercise training can be effective in increasing peak VO_2, more dedicated training with a higher adherence rate than this study realized would be required to achieve improvement. For example, Foster *et al.* investigated the effects of an eight-week steady state exercise protocol on peak VO_2 in 65 participants and found there was a significant improvement in peak VO_2; however, participants in the steady state exercise group had excellent adherence (100%) when compared to the current study. [97] Thus, it is possible to bring about significant change in an eight-week steady state exercise training protocol if adherence is optimal. No adverse events were seen with HET in this trial, thus it may be safe to consider incorporating interval training into future study protocols to help improve peak VO_2. The results of the present study suggest that a larger trial is needed to obtain a more definitive conclusion regarding the benefit of HET for peak VO_2 in patients with liver cirrhosis.

5.3 The effect of HET on Six-minute walk distance

Despite suboptimal adherence, the exercise protocol did lend itself to the improvement of aerobic endurance between the exercise and usual care groups. Steady state aerobic exercise as prescribed in the HET group increases endurance, perhaps contributing to the significant benefit observed in the six-minute walk test distance. The finding is in agreement with existing literature which shows that the six-minute walk distance significantly improves after exercise training in both clinical populations as well as a Child Pugh class A and B liver cirrhosis population. [54, 55] Importantly, the improvement seen in the current study is both statistically and clinically significant. Results showed mean difference

in favour of the HET group of 33.7 meters (7%) exceeds the clinically significant level of a 5% mean increase or an improvement of 20-50 meters. In addition to this, it was found that those in the high adherence subgroup had a higher 6MWD than when compared to the exercise group as a whole. While the exercise six-minute walk test distance showed significant change between groups when comparing exercise and control groups, the improvement shown when isolating the high adherence exercisers serves to further illustrate the dose response needed for exercise to be a successful intervention.

As VO_2 peak testing is not commonly or easily available to many clinics, the six-minute walk test can be easily administered in the clinic or hospital setting as a test of aerobic endurance.

The mean distances in 6MWT in both the exercise (476 meters) and usual care groups (520 meters) were lower than values of healthy sedentary individuals of a similar age (659 ± 52 meters). [98] Improvement towards the higher baseline value of a healthy sedentary population would indicate a greater ability to live and complete daily activities in a way that reflects a stronger health status. Importantly, the six-minute walk test distance has been shown to be an independent predictor of mortality in cirrhosis. [54] In these studies, it was found that mortality predictions were optimal after a cut-off level of >250 meters achieved. Furthermore, Carey *et al.* reported that for each 100-meter increase in achieved walk distance was related to a 52% decrease in mortality.[55] Participants in the present study were far above

this cut off of 250 meters, reflecting better overall disease status consistent with CP A and B classification.

5.3.1 Potential Mechanisms

The exact mechanisms for the benefit have not been studied in this population, however it is known that improvement in aerobic capacity through exercise training in other populations such a heart failure population of similar age is produced by improvements in skeletal muscle oxygen uptake after exercise training.[99] In addition to this, it has been shown that those with end stage liver disease display a hyperdynamic cardiac state at rest, related to a decrease in pulmonary vascular resistance associated with increased cardiac frequency and cardiac index. [100] The current study also had low-moderate rate of Beta Blocker prescription, blunting an already elevated heart rate's response. Because of this, we may be able to speculate that the mechanism for the improvement in aerobic endurance is increased oxygen uptake by the musculature, and not any overt changes in cardiac behaviour. The increase in the exercise group's thigh muscle thickness and circumference may be able to account for any increased muscle tissue, which would in turn increase musculature oxygen uptake.

Regardless of the mechanism of improvement, the improvement itself is meaningful to clinicians, who can correlate change with life expectancy and ability to carry out tasks of daily living. The improvement is also significant to the patient population, demonstrating that exercise can produce positive effects in

submaximal exercise capacity and thereby enhancing their ability to carry out the tasks of daily living.

5.4 The Effect of HET on Thigh muscle thickness and circumference

In addition to the changes seen in six-minute walk distance, a significant increase in thigh muscle thickness was observed within the exercise group. Although there was no significant between group change, the increase in muscle thickness within the exercise group alone is similar to findings in many clinical populations where exercise training has resulted in an increase in muscle thickness [5, 36, 53] or lean body mass.[99]

Decreased muscle mass in liver cirrhosis populations has been linked to decreased survival, decreased quality of life, development of complications such as a decreased infection response, and decreased post-transplant survival. [68, 101] Studies have shown that decrease in muscle mass at the third lumbar vertebral level is independently related to a decreased life expectancy in cirrhosis populations awaiting liver transplantation.[59, 102] Besides thigh muscle circumference, ultrasound was used in this study to assess muscle thickness. Thigh muscle ultrasound has shown to correlate with measurement at the third lumbar vertebral level ($r=0.6$, $p=0.001$), has excellent inter-observer variability (correlation $r= 0.9$). Additionally, this method of muscle thickness and mass assessment does not make use of radiation.

Increases in lean muscle mass are dictated by several factors, as well as the interactions between these factors. Among these factors, protein intake as well as exercise intensity, frequency and duration are the biggest contributors to an increase in muscle protein metabolism and increases in lean muscle mass. [103]

In a six-month study of aerobic training in a population of chronic dialysis patients, Sakkas *et al.* found that there was a significant increase in lean muscle mass; however no significant between group changes in muscle fibre were found. [104, 105] It was found that changes to muscle fibre cross section thickness, as well as a decrease in the number of atrophic fibres were the result of the extended exercise program. In addition to this it was found that after the six months of training there was a higher capillarization of the muscle fibres, with the capillary contact per fibre having gone up a significant amount. It may be reasonable to extend these findings to the current study as the mechanism responsible for the increase in thigh muscle thickness, as the exercise training regimens were of similar intensity, and were carried out in a clinically similar population.

Benefits of these changes in muscle fibre morphology include increased oxidative enzyme capacity, increased mitochondrial density, and increased oxygen extraction and utilization due to the increased capillarization and possibly increased myoglobin content. [85] These morphological changes may result in the increased muscle thickness that is demonstrated, and may also have a part in the increased within group peak VO_2 value that is seen.

If these mechanisms are indeed involved in the changes observed to thigh muscle thickness and within group peak VO_2 improvement, it can be said that aerobic exercise, even when adherence is limited, such as occurred in the present study, can produce meaningful changes not only in thigh muscle thickness, but also in the underlying contributors to this effect – mainly the muscle fibres themselves. With an increased level of exercise training adherence, larger benefits may be realized in both thigh muscle thickness and peak VO_2.

5.5 The Effect of HET on Quality of life measures

Home based exercise training was not associated with beneficial effects in health-related quality of life, anxiety, depression or self-reported health status. As the CLDQ is the only questionnaire that is specifically designed for measuring HRQOL for all stages and causes of liver cirrhosis, it was chosen for use in this study. [76] The use of the CLDQ in the present study allowed comparisons across exercise intervention studies as well as to other medical and lifestyle interventions for liver cirrhosis. While the use of a more generic outcome measure may have better captured benefits associated with exercise, it also may have been less sensitive to specific improvements in this population. [76] To better assess impact, future studies should consider the use of both disease-specific and general HRQOL outcomes.

A significant benefit from exercise was found in the emotional role subdomain of the CLDQ, and there was a trend to significance in the systemic symptoms subdomain; however, no other significant changes were found in any subdomain

scores of the CLDQ. Similarly, Macías-Rodríguez *et al.* reported no significant change in CLDQ total score or any other subdomains aside from in a single domain (worry) in Child-Pugh class A or B patients after 14 weeks of exercise training in a supervised setting. [106] These findings however contrast with other studies that did find significant changes in total CLDQ and subdomain scores, measures in the fatigue and subdomains of the SF36 in a supervised hospital-based exercise training program in liver cirrhosis. [5, 36]

The significant change in the emotional role subdomain of the CLDQ may be attributed to the participant's feelings of taking charge of one's own health or a result of ongoing communication with the study team. This is speculation, however, as there are no similar findings in the literature to date and may represent a chance finding.

Anecdotally, participants reported to the exercise therapist on both home and clinical visits that fatigue was a major barrier to the HET. In previous studies, it has been shown that there is a positive relationship between physical activity and having of feeling of increased energy, or less fatigue. [107] This benefit is however both dose and intensity dependent. [107] While these changes cannot be explained by a single biological mechanism, there are several mechanisms at work when patients exercise, which have been shown to improve energy in both clinical and healthy patient populations. These changes include improvements to strength and muscle mass, improvements to physical fitness, an improvement to the ability to carry out basic tasks of living, improvement in cognition, as well as in patient mood. [36, 107-110]

As this beneficial relationship is dose and intensity dependent, it may be the case that significant improvement was seen in only one subdomain of the CLDQ measurement due to the low adherence rate of participants to the exercise prescription. With only 50% of the patients completing 80% or more of their prescribed sessions, it is possible that there were not enough participants gaining these stated benefits of exercise training to change the mean HRQOL values significantly either as a complete measure of the CLDQ, as one of the sub groups, or in the measurement of the EQVAS or HADS.

In addition to these findings, it is of importance to acknowledge that the participant baseline CLDQ scores for both the HET group and the control group were very similar to those of a healthy population, with the study group average 5.14 being very close to the healthy population average of 5.4-5.9. This is higher than previously reported average scores of the general cirrhosis population of 4.0 to 4.35. [76, 77] Thus, a ceiling effect may have occurred. Regarding HADS, while there was no significant difference between the groups, it is of note that the HADS score for the study population exceeded the cut-off value of 8, which is the clinical endpoint for defining anxiety and/or depression in a given case. [111]

5.6 Tolerance and safety of HET

In this study, the benefits seen after exercise took place without any significant adverse events occurring during testing or training, including no significant changes in MELD or Child-Pugh scores. The question of safety and tolerance of

exercise in a liver cirrhosis population is a concern, and likely plays a part in why there is limited data, to date, on exercise in this population.

Garcia-pagan *et al*. showed an acute increase in hepatic vein portal pressure after a bout of exercise in a compensated cirrhosis population. [88] In contrast to these findings, Rodriguez *et al.* in an RCT found that after 14 weeks of exercise training, those in the exercise group had a decrease in hepatic vein portal pressure. [106] For the purposes of this study, the protocol was declared as safe based on the criteria of: (1) there being no significant adverse events reported; as well as (2) there being no significant change in MELD or Child Pugh scores. The conclusion that HET is safe based on the absence of adverse events would not equate with 'no risk'. Despite safety measures administered in the screening process as well as safety procedures to minimize the risk of an event during testing and during the intervention phase, the lack of an adverse event may reflect chance.

The definition of an adverse event may also affect reporting. In a liver cirrhosis population where many patients may suffer from fatigue, muscle weakness and cramps, depression, anxiety, and general malaise, what may be considered a non-event for the investigative team may be considered a significant event for a given study participant. Their experience and level of participation in the study may directly related to how they feel, or how they perceived their response to HET. Expanding the definition may better reflect issues associated with HET, and allow for modifications and accommodations to the study protocol that may improve overall adherence.

5.7 Limitations

The present study was subject to several limitations in design, execution, and results. Firstly, the results may not be generalizable to all ethnicities or other liver cirrhosis populations, as 80% of participants identified as Caucasian, and 27 of 40 patients were designated as Child-Pugh class A cirrhosis patients. Given the limited data available prior to the present study, testing the HET protocol in a less severely afflicted cirrhosis population as a first step seemed prudent. Thus, data from this study cannot be generalized to more severe cirrhosis populations.

Another limitation of this study was that the exercise training program comprised aerobic exercise training alone. Aerobic exercise was chosen as even in the presence of appropriate variceal prophylaxis, there remain concerns over the safety of resistance or combination training in this population. Due to a lack of data in either aerobic or resistance training, this investigation chose to pursue an intervention similar to a previous study by our group that examined an aerobic exercise program in a supervised hospital-based program.

A further limitation to this study was the inclusion of patients on beta blocker therapy. Although stratification by beta blocker therapy use was not performed, there were close to equal number of participants randomized to both the exercise and control group. It has been found that beta blocker therapy can dull the VO_2 response, and thus blunt improvement in peak VO_2. [112] Although VO_2 may be blunted, significant training effects and prognostic information can yet be obtained

from a population undergoing beta blocker therapy. [112] This study did not show a significant change in peak VO_2 between groups, and while the beta blocker therapy may have been a contributing factor, given the small number of participants receiving this therapy (n =11) and low adherence rate to HET, we cannot completely or directly attribute this lack of change to beta blocker therapy.

Another limitation of this study was the small sample size, limiting the statistical power to detect small changes in peak VO_2. The sample size prediction was made based on an expected change of 3.5 ml/kg/min VO_2peak, which was previously surpassed in a similar population in a supervised group based exercise training program.[5] A change of that magnitude may have been overly optimistic for a home based unsupervised exercise training program. However, better adherence of participants to the exercise protocol would likely have resulted in improvements in peak VO_2 closer to the 'a priori' expected improvement of 3.5 ml/kg/min.

Finally, the assessor used to measure thigh thickness and ultrasound measurements was not blinded to participant group allocation. To address the issue with risk of bias, the assessor was blinded to prior thigh and ultrasound measurements, and a second assessor was used to evaluate the ultrasound images for accuracy. Together, the effect of this limitation was mitigated.

5.8 Future Directions

Given the results of this study, it is clear that there is much room to expand the scope of the research as well as to improve the methods used in this study. Figure 5 includes a summary of potential future research directions. Firstly, strategies are needed to increase adherence with a HET program. More supervision and incorporating behaviour change strategies such as goal setting, strategies for overcoming barriers and reminders may be helpful. There are several promising technologies emerging that may help to promote social interaction, one of them being a group teleconferencing technology that allows a group based training atmosphere in a home-based setting.

In regard to future changes and expansions, larger studies of HET in similar populations must be carried out in order to confirm or improve on our findings as well as to possible expand investigation to more compromised populations. Additionally, this research would benefit from a more thorough assessment of fatigue. In speaking with patients, it was found that many of them suffered greatly from fatigue and lack of energy was frequently cited as the main reason that participants did not complete their exercise training. More in-depth analysis of fatigue at baseline testing may prove helpful in prescribing HET and allow for personalized protocols to mitigate the effect of fatigue on adherence in future studies. Yet another possible area of future research would be the examination of a resistance training program in patients with prophylaxis in place. Resistance exercise may address issues with muscle mass loss more effectively than aerobic exercise training, and may be better received by participants. [113, 114] Lastly,

another area for potential research would be to determine the mechanisms that most improve endurance in this population, in order to inform a therapeutic approach. Examining potential mechanisms may foster development of targeted protocols to address the needs of this patient population.

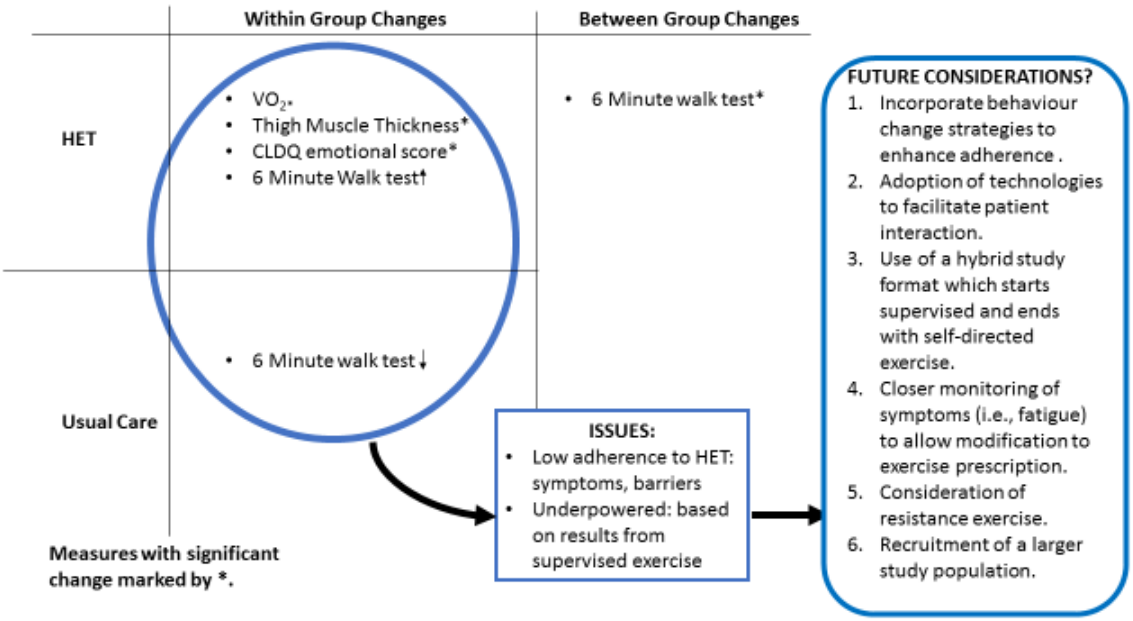


Figure 5. Changes seen within and between groups, issues, and potential future research considerations.

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APPENDIX A: INFORMATION SHEET

INFORMATION SHEET

AN 8 WEEK RANDOMIZED CONTROLLED TRIAL ASSESSING HOME EXERCISE THERAPY IN EARLY CIRRHOSIS

INVESTIGATORS:

P. Tandon, MD, FRCPC U of A, Division of Gastroenterology 492-9844 M. Haykowsky, PhD U of A, Dept. of Physical Therapy 492-5970 I. Paterson, MD, FRCPC U of A, Division of Cardiology 407-1857 R. Thompson, PhD U of A, Deparment of Biomed Engineering 492-8665
M. Ma, MD, FRCPC U of A, Division of Gastroenterology 492-8134
R.J. Bailey, MD, FRCPC RAH, Division of Gastroenterology 421-1029

BACKGROUND: Individuals with cirrhosis may have less muscle mass and may get tired easily when performing daily activities. Supervised aerobic training (walking or riding a bike) has been shown to be a safe and feasible therapy for individuals with early cirrhosis, improving exercise capacity, muscle mass and quality of life. This study will now evaluate the effects of a home exercise program in individuals with early cirrhosis.

PURPOSE: You are being asked to participate in a randomized controlled trial where half of the participants will receive 8 weeks of home-based aerobic exercise training and half will have no specific exercise training. This type of study design is important to determine whether the home-based exercise has a true effect on exercise capacity, muscle mass, and oxygen use, and quality of life. We aim to enroll 40 participants in this study.

DESCRIPTION OF THE STUDY: If you decide to participate in this study, the total time commitment will be 10 weeks. Participation in this study will not influence your treatments at the University of Alberta or Royal Alexandra Hospitals.

RESEARCH PROCEDURES

Randomization:

Once you decide to participate and your doctor agrees that you meet all of the necessary requirements, you will be randomized (assigned to a group by chance

like flipping a coin) to either the control group or the exercise training group. Baseline and end-of study testing will be done in both groups.

Baseline testing (First week).

You will do the following tests at the Mazankowski Alberta Hospital over a one-week period:

Test Day 1. Alberta Cardiovascular and Stroke Research Center (ABACUS), Mazankowski Alberta Heart Institute (Duration: 90 minutes).

Assessment of quality of life (5 minutes): We will ask you to fill out a questionnaire to assess your quality of life.

Assessment of physical function (12 minutes): We will perform a 5 minute test looking at how you walk, how good your balance is and how easily you can get up from a chair. We will also measure the distance you can walk in six minutes. This is called the six minute walk test.

Assessment of exercise capacity (60 minutes). ECG (electrocardiogram) leads (electrical contacts) will be placed on your chest to measure your heart rate. A blood pressure cuff will be placed on your arm to measure your blood pressure. You will start the test with easy pedalling that will become a little more difficult every two minutes. A special mouthpiece and nose clip will be used to measure your oxygen uptake. A number of electrodes (electrical contacts) will be placed on your chest and side of your neck, connected to a computer that will measure your heart rate and function. Throughout the test, your heart rate and blood pressure will be measured. The exercise test usually lasts 10 – 15 minutes and a specially trained health care worker (a qualified Physician or a qualified Nurse Practitioner) will supervise the test.

Assessment of muscle mass: We will use a bedside ultrasound machine to measure the thickness of your thigh muscle. A tape-measure will be used to measure the circumference of your thigh. This will take approximately 5 minutes.

Nutritional counselling: All patients enrolled in the study will be scheduled with a dietician who will provide expert advice on how many calories and how much protein and calories to target in your diet.

Test Day 2:

1) Incremental single leg-extension test (ABACUS, Mazankowski Alberta Heart Institute): Prior to the test, we will measure your height and weight. A number of electrodes (12-lead electrocardiogram) will be placed on your chest to monitor your heart rate and rhythm. A cuff will be placed on your arm to measure your blood pressure and your oxygen uptake. After resting measurements are obtained, you will perform knee kicking exercise with your dominant leg at comfortable speed and, every minute the workload will be made harder until you feel you are not able to exercise any longer at a constant pace. Your blood pressure will be assessed every two minutes during the exercise and recovery periods. Your heart rate, blood oxygen saturation (using a finger cuff) and oxygen uptake will be continuously measured during and after exercise. The exercise test usually lasts 8 to 12 minutes. You will be given a one hour break before performing the next test.

2) Leg blood flow, oxygen extraction and uptake at rest and during sub-maximal and maximal single leg extension exercise (Peter S. Allen MRI Research Centre, adjoining ABACUS in the Mazankowski Alberta Heart Institute): Prior to this test you will fill out and magnetic resonance imaging (MRI) safety screening form. As part of this test, you will be lie on your back in an MRI machine and your dominant leg will be positioned in the knee extensor device. Your heart rate and oxygen saturation (using a finger cuff) and will be continuously measured while your blood pressure will be measured every five to ten minutes. We will measure the size of your upper leg muscle, as well the blood flow and oxygen uptake of the quadriceps muscle (upper leg muscle) of your dominant leg. You will then perform sub-maximal (25%, 50% and 75% of maximal effort for three to five minutes with a five minute rest between each set) and maximal (one-minute of exercise) single leg knee extension.

Intervention Period (over the 8 weeks):

In all participants, the study dietician will contact you by phone every two weeks to see how you are doing with the dietary recommendations that were made and to answer any questions you may have. As per routine care, all participants will be asked to continue with once monthly bloodwork to ensure that the liver tests remain stable during the study.

For the patients randomized to the Intervention "Exercise" group, the exercise specialist associated with the study will come to your home to set up a stationary bike for you. He will teach you how to use both the bike and a heart rate monitor. The bike will be yours to keep after the trial is completed. The Physical Therapy Research Assistant will go over your personalized home-based aerobic training program with you in detail and make sure that you are comfortable with it. We will ask you to perform the home-based aerobic training program three times a week for 30 – 60 minutes each time. The

exercise specialist will be contacting you by phone on a weekly basis to assess your tolerance to the exercise that has been prescribed and to review your heart rate responses. The Physical Therapy Research Assistant will also set up a mutually convenient time with you every 2 weeks so that he can visit you to observe an exercise session.

All participants will be provided with our contact numbers and you can contact us with questions at anytime.

Follow-up testing (at week 8):

For participants in both the "Exercise" and the "Non-Exercise" groups, the same tests that were done at baseline will be repeated 8 weeks after enrolment. When you have your end of study testing done, in order to avoid biasing the people who are testing you, we would ask that you do not mention to the testers which group you were randomized to.

POSSIBLE BENEFITS: You may receive no health benefit from being in this study, however we hope that the information we get will help us understand whether a home based exercise program can benefit patients with cirrhosis.

POSSIBLE RISKS: The exercises that you will perform are generally regarded as very safe. All testing sessions will be performed under appropriate supervision. Data from individuals with or without heart disease suggests that the likelihood of having a heart attack or dying during a bicycle test is 1 in 10,000 tests. The mouthpiece that is used during the exercise test may make your mouth feel dry. You may also experience temporary muscle soreness after the initial exercise test and during the first weeks of exercise training. Exercise may reduce the bloodflow to the liver. This is unlikely to cause any significant problems, but to be safe, we will be checking your liver tests regularly. Your routine liver bloodwork will be done once a month. This is no more frequent than for the purposes of routine clinical care. It can be carried out at the laboratory of your choice. Bloodwork may cause bruising from the needle poke. The MRI is not associated with any significant risks. Lastly, there is a theoretical risk that exercise can cause pressures in the liver to increase. This is called portal hypertension. As part of your standard care, you will have had an endoscopy and if necessary, already been started on treatment for veins in the foodpipe. As this is important for your routine care, we will look to ensure this has been completed before we consider enrolling you in the study. It is not possible to know all of the risks that may happen in a study, but the researchers have taken all reasonable safeguards to minimize any known risks to a study participant.

What happens if I am injured because of this research:

If you become ill or injured as a result of being in this study, you will receive necessary medical treatment, at no additional cost to you. By signing this consent form you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

COSTS:

You will not have to pay for the consultations that you receive by participating in this study. However, you may be coming to the University of Alberta/Royal Alexandra Hospital more often than if you were not participating in this study. As a result, there may be some extra costs for you such as gasoline, child care or meals. Parking passes will be provided for you for attending study related visits for this study.

CONTACTS: Please contact the following investigators listed below if you have any questions and concerns. P. Tandon, MD FRCP(C) (492-9844) or M. Haykowsky, PhD (492-5970).

CONFIDENTIALITY: During the study we will be collecting health data about you. We will do everything we can to make sure that this data is kept private. No data relating to this study that includes your name will be released outside of the study doctor's office or published by the researchers. Sometimes, by law, we may have to release your information with your name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your health information is kept private. The study doctor/study staff may need to look at your personal health records held at the study doctor's office, and/or kept by other health care providers that you may have seen in the past (i.e. your family doctors). Any personal health information that we get from these records will be only what is needed for the study. During research studies it is important that the data that we get is accurate. For this reason, your health data, including your name, may be looked at by the Health Research Ethics Board at the University of Alberta. By signing this consent form you are saying it is ok for the study doctor/staff to collect, use and disclose information about you from your personal health records as described above. After the study is done, we will still need to securely store your health data that was collected as part of the study. At the University of Alberta, we keep data stored for 5 years after the end of the study. If you leave the study, we will not collect new health information about you, but we will need to keep the data that we have already collected.

VOLUNTARY PARTICIPATION: You are free to withdraw from this study at any time without giving a reason. If knowledge gained from this study or any other study becomes available which could influence your decision to continue, you will be promptly informed.

If you have any questions or concerns about your rights as a research participant, or how this study is being conducted, you may contact the University of Alberta's Research Ethics Office at 780-492-2615. This office is independent of the study investigators.

APPENDIX B: CONSENT FORM

CONSENT FORM

AN 8 WEEK RANDOMIZED CONTROLLED TRIAL ASSESSING HOME EXERCISE THERAPY IN EARLY CIRRHOSIS

INVESTIGATORS:

P. Tandon, MD, FRCPC	U of A, Division of Gastroenterology	492-9844
M. Haykowsky, PhD	U of A, Dept. of Physical Therapy	492-5970
I. Paterson, MD, FRCPC	U of A, Division of Cardiology	407-1857
R. Thompson, PhD	U of A, Deparment of Biomed Engineering	492-8665
M. Ma, MD, FRCPC	U of A, Division of Gastroenterology	492-8134
R.J. Bailey, MD	RAH, Division of Gastroenterology	421-1029

1) Do you understand that you have been asked to be in a research study?
Yes No

2) Have you read and received a copy of the attached Information Sheet?
Yes No

3) Do you understand the benefits and risks involved in taking part in this
Yes No

research study?

4) Have you had an opportunity to ask questions and discuss this study?
Yes No

5) Do you understand that you are free to refuse to participate or withdraw

from the study at any time? You do not have to give a reason and it

will not affect your care.
Yes No

6) Has the issue of confidentiality been explained to you? Do you

understand who will have access to your health records including

personally identifiable health information?
Yes No

7) Do you want the investigator to inform your family doctor that you

are participating in this research study? If so, please provide your

doctor's name: _____
Yes No

This study was explained to me by _____

I agree to participate in this study. Yes No

_____ ……..
Signature of Research Participant Date of Signature

_____
Printed Name

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

_____

_____

Signature of Investigator or designee Date of Signature

APPENDIX C: SCREENING SHEET

An 8 week RCT assessing Home Exercise Therapy in CP A/B Cirrhotic Patients

Participant Inclusion/Exclusion Form

Name _____

Date _____

	Yes	No
Age 18-70	☐	☐
Diagnosis of cirrhosis Child Pugh A or B	☐	☐
Prophylaxis in place for esophageal varices	☐	☐
Absence of HCC outside of Edmonton transplant criteria	☐	☐
Absence of non-HCC related malignancy	☐	☐
Absence of EF <50%, past MI or positive stress test	☐	☐
Absence of a myopathy	☐	☐
Absence of Chronic renal failure on dialysis	☐	☐
Lacks a physical impairment that would make it impossible to ride bike	☐	☐
Absence of HIV infection	☐	☐
English-speaking	☐	☐

	Yes	No
ELIGIBLE FOR STUDY	☐	☐

Child Pugh Score: _____, list variables for MELD as well

Mailing Address: _____

_____

_____

Phone number:_____

Email Address: _____

APPENDIX D: BASELINE DATA COLLECTION SHEET

Aerobic Training in Cirrhosis:
Baseline Data Collection Sheet

Place
Patient Sticker

Patient General Information **Patient Study ID**_____

Patient Name	_____ First _____ Last _____ M.I.
Patient Contact	(__)_____ Home # (__)_____ Cell # (__)_____ Work #
Emergency Contact	_____ Name _____ Relationship _____ Contact #
Gender	[ ] Male [ ] Female
Date of Birth	_____/_____/_____ Year/Month/Day
Ethnicity	[ ] Asian [ ] Black/African American [ ] Hispanic [ ] Native American [ ] Caucasian/White [ ] Other _____
Date of Consent	_____/_____/_____ Year/Month/Day
Date of Baseline Visit	_____/_____/_____ Year/Month/Day

Patient Comorbidity Information:

Heart attack / MI	[ ] Yes [ ] No [ ] <7days [ ] <30days Date (if known):
Prior angioplasty or stent	[ ] Yes [ ] No
Prior cardiac surgery	[ ] Yes [ ] No Specify type(s):_____

Diabetes (type I or II)	[ ] Yes [ ] No [ ] End-organ damage [ ] Insulin-dep
Hypertension	[ ] Yes [ ] No
Dyslipidemia	[ ] Yes [ ] No
Peripheral vascular disease	[ ] Yes [ ] No
Stroke	[ ] Yes [ ] No [ ] Hemiplegia
Cerebrovascular disease (other than stroke):	[ ] Yes [ ] No Specify type(s): _____
Other neurologic disease (e.g. Parkinson's)	[ ] Yes [ ] No
Cirrhosis	[ ] Yes [ ] No
Gastro-intestinal disease (e.g. reflux, ulcer, hiatal hernia)	[ ] Yes [ ] No Prior GI bleed [ ] upper or [ ] lower
Pulmonary hypertension	[ ] Yes [ ] No PAPs (if known): _____mmHg
Emphysema / COPD (chronic obstructive lung disease)	[ ] Yes [ ] No [ ] Mild [ ] Moderate [ ] Severe FEV1 (if known): _____ [ ] HomeO2
Asthma	[ ] Yes [ ] No
Arthritis (rheumatoid or osteoarthritis)	[ ] Yes [ ] No
Congestive Heart Failure (CHF)	[ ] Yes [ ] No
Back disease (e.g. degenerative disc, spinal stenosis, severe chronic back pain)	[ ] Yes [ ] No
Visual impairment (e.g. cataracts, glaucoma, macular degeneration)	[ ] Yes [ ] No
Hearing impairment	[ ] Yes [ ] No
Dementia	[ ] Yes [ ] No
Depression	[ ] Yes [ ] No
Anxiety / Panic attacks	[ ] Yes [ ] No
Malignancy	[ ] Yes [ ] No
HIV/AIDS	[ ] Yes [ ] No
Falls (in past year)	[ ] Yes [ ] No

	How many _____
Psychological stress or acute disease	[ ] Yes [ ] No

Etiology of Liver Disease:

-Hepatitis B ☐

-Hepatitis C ☐

-Alcohol induced ☐

-Primary biliary cirrhosis ☐

-Primary sclerosing cholangitis ☐

-Autoimmune hepatitis ☐

-Non-alcoholic fatty liver disease ☐

-Cryptogenic ☐

-Other:_____ ☐

History of Cirrhosis Complications

-Ascites: ☐ Y ☐ N

- ☐ Diuretics- ascites controlled
- ☐ Diuretics/ ascites
- ☐ Refractory ascites (requiring paracentesis)

-Variceal bleeding ☐ ever

-Spontaneous bacterial peritonitis ☐ ever

-Hepatic encephalopathy requiring admission to hospital ☐ ever

-TIPS or surgical shunt in place ☐ Y ☐ N

-Date of placement: _____

Current Medications (Prescriptions, Herbal, OTC, Supplements)		
Drug Name	Dosage (mg)	Frequency

Medical and Surgical History	

Average Alcohol Intake: (#drinks/week)

☐ None ☐ _____

Smoking History:

☐ Never ☐ Current_____ ☐ Ex-Smoker_____

Short Physical Performance Battery			
1) **Gait Speed**: (time taken to walk 4 m)	Trial 1 (s):		Was the test performed with a walking aid? Yes No
	Trial 2 (s)		
	Average (s):		
	Side-by-side	**Semi-Tandem**	**Tandem**

2) **Balance Tests** (record time (s))			
3) **Chair Stands**: (time to stand up from chair 5 times)		Was the patient able to stand up from chair 5 times without using armrests? Yes No	

General Assessment				
Height (cm)				
Weight (kg)				
Weight Loss:	Loss of >5lbs or 10% of body weight over the last 12 months? Yes No			
Pedal Edema				
Weight- estimated dry (kg)				
BMI (dry wt)				
Handgrip Strength (kg)	**Right Hand**		**Left Hand**	
	Trial 1:		Trial1:	
	Trial 2:		Trial 2:	
	Trial 3:		Trial 3:	
	Average:		Average:	
	Max:		Max:	

Nutrition Assessment- (Based on 2 day diet record)	
Protein Intake (g)	
Calorie Intake (kcal)	

General Assessment Con't				
Right thigh muscle circumference (cm) Distance measured from hip to top of patella:_____cm	**1/3**		**1/2**	
Right rectus femoris muscle thickness **1/3:_____cm** **½:_____cm**	**1/3**		**1/2**	
	F	**C**	**F**	**C**
6 Minute Walk Distance (m):				

Questionnaire Scores		
PASE		
Paffenbarger PAI (kcal/week)		
MMSE		
CES-D (2 questions)		
HADS		
CLDQ		
EQ-5D	EQ-5D:	EQ-VAS:

Baseline Laboratory Information Date of Lab Visit:	
WBC	
Platelets	
Hemoglobin	
Serum albumin	
Serum bilirubin	
Creatinine	
INR	
ALT	
AST	
Alkaline Phosphatase	
Urea	
Serum sodium	
Serum potassium	
CRP	
Fasting Glucose	
Fasting Insulin	
Testosterone (am)	

Randomization & Stratification

Control Group/Usual Care ☐ or Exercise Training Group ☐

Child Pugh Class A: 5-6 points ☐

Child Pugh Class B: 7-9 points ☐

	Score		
	1	**2**	**3**
Bilirubin (umol/L)	<34	34-50	>50
Albumin (g/L)	>35	28-35	<28
INR	<1.7	1.7-2.3	>2.3
Ascites	Absent	Diuretic controlled/TIPS in place	Paracentesis required
Encephalopathy	Absent	Lactulose/Rifaximin controlled	Not controlled/coma

Meld Score: _____

Labwork approved by:

Name: _____ Date: _____

☐ Patient may continue to participate in study

☐ Patient must refrain from study until lab-work is stable

Signature: _____

Baseline Follow-up Phone call by:

Name: _____ Date: _____

Patient Concerns:

APPENDIX E: END OF STUDY DATA COLLECTION SHEET

Aerobic Training in Advanced Cirrhosis:
End of Study Data Collection Sheet

Place Patient Sticker Here

Date of End of Study Data Collection: __ __/__ __ __/ __ __ __ __

Current Medications –changes since enrollment?		
Drug Name	Dosage (mg)	Frequency

Average Alcohol Intake: (#drinks/week)

☐ None ☐ _____

Smoking History:

☐ Never ☐ Current_____ ☐ Ex-Smoker_____

Short Physical Performance Battery			
1) **Gait Speed:** (time taken to walk 4 m)	Trial 1 (s):		Was the test performed with a walking aid? Yes No
	Trial 2 (s)		
	Average (s):		
2) **Balance Tests** (record time (s))	**Side-by-side**	**Semi-Tandem**	**Tandem**
3) **Chair Stands:** (time to stand up from chair 5 times)		Was the patient able to stand up from chair 5 times without using armrests? **Yes** No	

General Assessment Con't					
Circumference at 1/3 point:					
Right rectus femoris muscle thickness	**1/3**		**1/2**		
	F	**C**	**F**		**C**
1/3:_____cm					
½:_____cm					
6 Minute Walk Distance (m):				Pre	Post
			Dyspnea		
			Fatigue		

Randomization & Stratification

Control Group/Usual Care ☐ or Exercise Training Group ☐

Child Pugh Class B: 7-9 points ☐

Child Pugh Class C: 10+ points ☐

	Score		
	1	**2**	**3**
Bilirubin (umol/L)	<34	34-50	>50
Albumin (g/L)	>35	28-35	<28
INR	<1.7	1.7-2.3	>2.3
Ascites	Absent	Diuretic controlled/TIPS in place	Paracentesis required
Encephalopathy	Absent	Lactulose/Rifaximin controlled	Not controlled/coma

Meld Score: _____

End of Study Laboratory Information **Date of Lab Visit:**	
WBC	
Platelets	
Hemoglobin	
Serum albumin	
Pre-albumin	
Serum bilirubin	
Creatinine	
INR	
ALT	
AST	
Alkaline Phosphatase	
Urea	
Serum sodium	
Serum potassium	
CRP	
Fasting Glucose	
Fasting Insulin	
Testosterone (am)	

End of Study Follow-up Phone call by:

Name: _____ Date: _____

Patient Concerns/Comments:

Questionnaire Scores		
PASE		
Paffenbarger PAI (kcal/week)		
MMSE		
CES-D (2 questions)		
HADS		
CLDQ		
EQ-5D	EQ-5D:	EQ-VAS:

Reason for Termination of Study:

☐ Patient completed 8 weeks of aerobic training

☐ Patient performed baseline/follow-up session (control)

☐ Patient withdrew from study

-Date of withdrawal: _____

-Reason for withdrawal: _____

APPENDIX F: CARDIOPULMONARY EXERCISE TEST SHEET

Exercise WORKSHEET (Test Day 2)

DATE:_____ **ID #/INITIALS:**_____

HT/WT:_____

RESTING HR:_____**BEATS/MIN** **REST BP:**_____

Peak Power output (Test Day 1)_____

EXERCISE TEST DATA

TIME	% PPO	INTENSITY Watts	HR Beats/min	BP mmHg	RPE (0-10)
Rest	0	0			
1	25				
2	25				
3	25				
4	25				
5	25				
1	50				
2	50				
3	50				
4	50				
5	50				
1	75				
2	75				
3	75				
4	75				
5	75				
1	100				
2	100				
3	100				

APPENDIX G: THE CHRONIC LIVER DISEASE QUESTOINAIRE

THE CHRONIC LIVER DISEASE QUESTIONNAIRE (CLDQ)
QUALITY OF LIFE INDEX FOR PATIENTS WITH CHRONIC LIVER DISEASE

Name_____ **Date**_____

This questionnaire is designed to find out how you have been feeling during the last two weeks. You will be asked about your symptoms related to your liver disease, how you have been affected in doing activities, and how your mood has been. Please complete all of the questions and select only one response for each question.

QUESTIONS	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
1. How much of the time during the last two weeks have you been troubled by a feeling of abdominal bloating?	1	2	3	4	5	6	7
2. How much of the time have you been tired or fatigued during the last two weeks?	1	2	3	4	5	6	7
3. How much of the time during the last two weeks have you experienced bodily pain?	1	2	3	4	5	6	7
4. How often during the last two weeks have you felt sleepy during the day?	1	2	3	4	5	6	7
5. How much of the time during the last two weeks have you experienced abdominal pain?	1	2	3	4	5	6	7
6. How much of the time during the last two weeks has shortness of breath been a problem for you in your daily activities?	1	2	3	4	5	6	7
7. How much of the time during the last two weeks have you not been able to eat as much as you would like?	1	2	3	4	5	6	7
8. How much of the time in the last two weeks have you been bothered by having decreased strength?	1	2	3	4	5	6	7
9. How often during the last two weeks have you had trouble lifting or carrying heavy objects?	1	2	3	4	5	6	7
10. How often during the last two weeks have you felt anxious?	1	2	3	4	5	6	7
11. How often in the last two weeks have you felt a decreased level of energy?	1	2	3	4	5	6	7
12. How much of the time during the last two weeks have you felt unhappy?	1	2	3	4	5	6	7

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
13. How often during the last two weeks have you felt drowsy?	1	2	3	4	5	6	7
14. How much of the time during the last two weeks have you been bothered by a limitation of your diet?	1	2	3	4	5	6	7
15. How often during the last two weeks have you been irritable?	1	2	3	4	5	6	7
16. How often during the last two weeks have you had difficulty sleeping at night?	1	2	3	4	5	6	7
17. How much of the time during the last two weeks have you been troubled by a feeling of abdominal discomfort?	1	2	3	4	5	6	7
18. How much of the time during the last two weeks have you been worried about the impact your liver disease has on you family?	1	2	3	4	5	6	7
19. How much of the time during the last two weeks have you had mood swings?	1	2	3	4	5	6	7
20. How much of the time in the last two weeks have you been unable to sleep at night?	1	2	3	4	5	6	7
21. How often during the last two weeks have you had muscle cramps?	1	2	3	4	5	6	7
22. How much of the time during the last two weeks have you been worried that your symptoms will develop into a major problem?	1	2	3	4	5	6	7
23. How much of the time during the last two weeks have you had a dry mouth?	1	2	3	4	5	6	7
24. How much of the time in the last two weeks have you felt depressed?	1	2	3	4	5	6	7
25. How much of the time in the last two weeks have you worried about your condition getting worse?	1	2	3	4	5	6	7
26. How much of the time in the last two weeks have you had problems concentrating?	1	2	3	4	5	6	7
27. How much of the time have you been troubled by itching during the last two weeks?	1	2	3	4	5	6	7
28. How much of the time during the last two weeks have you been worried about never feeling any better?	1	2	3	4	5	6	7
29. How much of the time during the last two weeks have you been concerned about the availability of a liver if you need a liver transplant?	1	2	3	4	5	6	7

APPENDIX H: THE HOSPITAL ANXIETY AND DEPRESSION SCORE

Hospital Anxiety and Depression Score (HADS)

This questionnaire helps your physician to know how you are feeling. Read every sentence. Place an "X" on the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important

A	I feel tense or 'wound up':	
	Most of the time	3
	A lot of the time	2
	From time to time (occ.)	1
	Not at all	0
D	I still enjoy the things I used to enjoy:	
	Definitely as much	0
	Not quite as much	1
	Only a little	2
	Hardly at all	3
A	I get a sort of frightened feeling as if something awful is about to happen:	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0
D	I can laugh and see the funny side of things:	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3
A	Worrying thoughts go through my mind:	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not often	1
	Only occasionally	0
D	I feel cheerful:	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0
A	I can sit at ease and feel relaxed:	
	Definitely	0
	Usually	1
	Not often	2
	Not at all	3

D	I feel as if I am slowed down:	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0
A	I get a sort of frightened feeling like "butterflies" in the stomach:	
	Not at all	0
	Occasionally	1
	Quite often	2
	Very often	3
D	I have lost interest in my appearance:	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care	0
A	I feel restless as I have to be on the move:	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0
D	I look forward with enjoyment to things:	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3
A	I get sudden feelings of panic:	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0
D	I can enjoy a good book or radio/TV program:	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

APPENDIX I: THE EQ-VISUAL ANALOGUE SCALE

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

APPENDIX J: AEROBIC EXERCISE TRAINING DIARY FORM

Home Exercise Study

Study 1D #:_____ Date:_____

Weight:_____kg Rest heart rate:_____.

Target Heart rate_____bpm. Target Rate of perceived exertion **14-15** out of 20

Time	Heart rate (bpm)	Rate of Perceived exertion (RPE)
Warm up (5 min)		
Aerobic Phase		
0-5 min		
5-10 min		
10-15 min		
15-20 min		
20-25 min		
25-30 min		
35-40 min		
45-50 min		
55-60 min		
Cool down		
5 (min)		

Comments (how was the training session today?

_____

_____

_____

_____

_____.

APPENDIX K: HEART RATE RESERVE AND TARGET HEART RATE RANGE CALCULATION

In the current investigation, the target heart rate range was to be equivalent to exercising at 60-80% of the heart rate at the patient's baseline VO_2 peak values. The equation used to determine this is as follows:

HRR: Heart Rate Reserve

HR: Heart Rate

HRR = Peak HR – Resting HR

Target HR = resting HR + (% Peak VO_2 x HRR)

For example: Patient A has a resting HR of 70 beats per minute, and a peak HR of 160 beats per minute. The HRR is 160 bpm – 70 bpm = 90 bpm.

Patient A target heart rate at 60% of peak VO_2:

Resting HR + (60% peak VO_2 x HRR)

70 bpm + (0.6 x 90 bpm) = 124 bpm

Patient A target heart rate at 80% of peak VO_2

Resting HR + (80% peak VO_2 x HRR)

70 bpm + (0.8 x 90 bpm) = 142 bpm

Therefore, to have Patient A exercise at an intensity between 60% and 80% of their VO_2 peak, exercise must be prescribed at an intensity of 124-142 bpm.

APPENDIX L: SAMPLE SIZE CALCULATION

Sample size was calculated assuming an expected 3.5 ml/kg/min improvement in peak VO_2, the primary outcome. Between group standard deviation was assumed to be 2 ml/kg/min. Power level was set at 80%, and alpha level was $p<0.05$.

Formula: interval independent variable

$$\frac{n}{\text{group}} = \frac{2\eth}{(U_2 - U_1)^2} \times f(\alpha, \beta)^1$$

Where ð = standard deviation U_1

U_1 = mean response on standard care

U_2 = mean response on experimental therapy

A = type I error

β = type II error