Effects of eight weeks of aerobic exercise training versus usual care on peak oxygen consumption, muscle mass, distance walked in six minutes and health related quality of life in Child Pugh class A and B patients with cirrhosis

by

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Abstract

Patients with cirrhosis have reduced peak exercise oxygen uptake (peak VO_2) that is associated with decreased survival. The effect of aerobic exercise training (AET) on peak VO_2 has not been well studied in cirrhosis. The purpose of this investigation was to evaluate the safety and efficacy of eight weeks of supervised AET or usual care (UC) on peak VO_2, quadriceps muscle thickness, distance walked in six minutes (6MWD), and health related quality of life in this population.

Nineteen clinically stable patients between 18 and 70 years of age with Child Pugh class A and B cirrhosis were randomly assigned to AET or UC. Seventy-nine percent of patients were male with a mean age of 57.6 ± 6.7 years and mean Model for End-Stage Liver Disease (MELD) score of 10 ± 2.2. Supervised AET was performed on a cycle ergometer three days per week for eight weeks at 60 to 80% of baseline peak VO_2. Peak VO_2, quadriceps muscle thickness (measured by ultrasound), thigh circumference, Chronic Liver Disease Questionnaire (CLDQ), EuroQol-Visual Analogue Scale (EQ-VAS), 6MWD, and MELD score were evaluated at baseline and eight weeks. Statistical analysis was performed using analysis of covariance.

Compared to UC, peak VO_2 improved by 5.3 mL/kg/min (95% CI: 2.9 to 7.8,p=0.001) after eight weeks of AET. Thigh circumference (p=0.001), thigh muscle thickness (p=0.01), EQ-VAS determined self-perceived health status (p=0.01) and the fatigue sub-score of the CLDQ (p=0.01) improved with AET. No adverse events occurred during cardiopulmonary exercise testing or training.

In conclusion, eight weeks of supervised AET is an effective therapy to improve peak VO_2, muscle mass and symptoms of fatigue in compensated patients with cirrhosis. No relevant adverse effects were observed. These promising data support the performance of larger trials in this population.

Preface

This thesis is an original work by Laura Zenith. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Aerobic training in patients with cirrhosis," No. Pro00033449, November 8, 2012.

Chapters 1, and 3-6 of this thesis were the basis for the published manuscript "Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis," *Clinical Gastroenterology and Hepatology,* (in press) co-authored by N. Meena, A. Ramadi, M. Yavari, A. Harvey, M. Carbonneau, M. Ma, J.G. Abraldes, I. Paterson, M. J. Haykowsky, and P. Tandon. LZ, PT, and MM contributed to study concept and design, study conduct, data acquisition, data analysis and interpretation and drafting of the manuscript. MC, AH, AR, NM, MY, and IP contributed to study conduct, data acquisition, data interpretation, and drafting of the manuscript. JGA contributed to data interpretation and drafting of the manuscript.

Dedication

This thesis is dedicated to my parents for their encouragement and unconditional support.

"It is not the critic who counts; not the man who points out how the strong man stumbles, or where the doer of deeds could have done them better. The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strives valiantly; who errs, who comes short again and again, because there is no effort without error and shortcoming; but who does actually strive to do the deeds; who knows great enthusiasms, the great devotions; who spends himself in a worthy cause; who at the best knows in the end the triumph of high achievement, and who at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those cold and timid souls who neither know victory nor defeat."

Theodore Roosevelt, (1858-1919)

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List of Abbreviations

6MWD:	Six minute walk distance
ALT:	Alanine aminotransferase
ANCOVA:	Analysis of covariance
AST:	Aspartate aminotransferase
AET:	Aerobic exercise training
BMI:	Body mass index
CBC:	Complete blood count
CP A:	Child Pugh class A
CP B:	Child Pugh class B
CLDQ:	Chronic Liver Disease Questionnaire
EQ-VAS:	EuroQol-Visual Analogue Scale
ESPEN:	European Society of Enteral and Parenteral Nutrition
Hb:	Hemoglobin
HCC:	Hepatocellular carcinoma
HR:	Heart rate
INR:	International normalized ratio
UC:	Usual care group
RD:	Registered dietitian
RPE:	Rating of perceived exertion
Peak VO_2:	Peak exercise oxygen consumption
TIPS:	Transjugular intrahepatic portosystemic shunt
W:	Watts

Chapter One: Introduction to the Thesis

1.1 Brief Introduction

Cirrhosis is the final common pathway of a wide range of chronic hepatic insults. Cirrhosis is characterized by diffuse nodular hepatic fibrosis and progressive hepatic dysfunction and is associated with significant morbidity and mortality (1). In addition to the dysfunction of the involved organ, patients also have decreased exercise tolerance measured objectively as decreased peak exercise oxygen uptake (peak VO_2) (2, 3). Although the decline in peak VO_2 is most marked in patients with the most severe hepatic dysfunction (2-4), even in patients with early stage cirrhosis, it is up to 40% lower than in healthy controls (5-7). The postulated mechanisms of this impairment include cardiovascular and skeletal muscle dysfunction resulting in decreased oxygen delivery to and/or impaired oxygen extraction by the active muscles (2). The reduction in exercise tolerance is not only common but also clinically significant. Indeed, several recent studies have demonstrated an independent association of this parameter with pre and post liver transplantation mortality and duration of stay in hospital post-transplantation (8-10). Currently, it is unknown whether exercise tolerance can be safely modified in patients with cirrhosis.

In healthy and clinical populations, peak VO_2 is modifiable with aerobic exercise training (AET) (11-14). The exercise mediated increase in peak VO_2 has been associated with decreased morbidity and mortality (15) and concurrent improvements in relevant secondary outcomes including muscle mass (16), fatigue (17), depression (18), anxiety (19) and quality of life (17, 20). To date, the impact of

AET on peak VO_2 and relevant secondary outcomes in patients with cirrhosis remains unclear. Available data is based on two uncontrolled series including five (21) and four (5) patients studied over 20 years ago. This paucity of data may in part be related to concerns about the safety of an exercise intervention in the setting of cirrhosis. In 1996, Garcia-Pagan et al. (22) demonstrated that moderate exercise was associated with significant reductions in hepatic perfusion and increases in portal pressure. Importantly, however, this study was followed by data from the same authors showing that the use of a non-selective beta-blocker effectively prevented the exercise induced rise in portal pressure (23).

Therefore, provided adequate prophylaxis against variceal hemorrhage is in place, based on successful results in a wide range of clinical and healthy populations, exercise interventions that can attenuate the decline in peak VO_2 may play important roles in improving survival and quality of life for cirrhosis patients in the pre-transplant period.

1.2 Statement of the Problem and Purpose of the Thesis

The current proposal aims to build upon the work done by previous authors (5, 21). Existing studies evaluating the effect of AET on peak VO_2 in patients with cirrhosis have limitations. First, the AET group has not been compared to a control group. Secondly, the generalizability of the safety and efficacy of aerobic training on liver function is limited by the small sample sizes (n=5 (21) and n=4 (5)) and exclusion of patients with a history of liver-related complications including variceal

bleeding, ascites, and hepatic encephalopathy (21). Due to the limited number of studies it is currently unknown whether aerobic capacity can be safely modified in this population. To date, no studies have examined the effect of AET on quality of life in cirrhosis. Therefore, the purpose of this investigation is to evaluate the safety and efficacy of eight weeks of supervised AET on peak VO_2, muscle mass, and quality of life in patients with Child Pugh (CP) class A and B cirrhosis.

1.3 Specific Objectives

The primary objectives of the study are:

1) To determine the effect of eight weeks of AET on exercise capacity, measured as the change in peak VO_2.
2) To establish the safety of AET as determined by the presence or absence of adverse events including variceal bleeding, significant cardiac or pulmonary event, or alteration in liver enzymes.

The secondary objectives are:

1) To determine the effect of AET on muscle mass, as measured by cross sectional quadriceps muscle thickness using ultrasound (Mindray©, Shenzhen, China).
2) To determine the effect of AET on health related quality of life, as measured by the Chronic Liver Disease Questionnaire.
3) To determine the effect of AET on anxiety and depression, as measured by the Hospital Anxiety and Depression Scale.

4) To determine the effect of AET on global physical function as measured by six minute walk distance.

1.4 Hypotheses

The primary hypothesis is that there will be significant improvements in peak VO_2 in the AET group compared to the usual care (UC) group after eight weeks of AET in the absence of adverse events. Secondary hypotheses include that eight weeks of AET will be associated with improvements in thigh muscle mass, 6MWD, and overall health related quality of life.

1.5 Delimitations

1) The sample consisted of nineteen male and female Child Pugh class A or B patients (mean age: 57.6 ± 6.7 years) referred to the Cirrhosis Care Clinic.
2) Cardiopulmonary testing was performed on a Monark cycle ergometer.
3) The AET program was performed three times per week for eight weeks for a total of twenty-four training sessions.
4) Muscle mass was evaluated using a bedside ultrasonography machine (Mindray©, Shenzhen, China).
5) Health related quality of life was evaluated using the Chronic Liver Disease Questionnaire and the Hospital Anxiety and Depression Scale.

1.6 Limitations

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

1.7 Significance of the Study

This study will be the first randomized controlled trial to determine the safety and efficacy of AET on exercise capacity, muscle mass, and health related quality of life in pre-transplant cirrhosis patients with a history of complications including gastroesophageal varices, ascites, and hepatic encephalopathy. The findings of this pilot investigation will help to determine if AET is a potential therapeutic option to modify clinical outcomes in this population.

Chapter Two: Review of the Literature

This chapter begins with a brief introduction to the underlying pathophysiology and complications of cirrhosis, followed by an overview of the models used to assess liver disease severity. The remainder of this section reviews the literature related to the reduced aerobic capacity observed in cirrhosis, the underlying mechanisms responsible for the decline, and the effects of aerobic exercise to counteract the decline in aerobic capacity, muscle mass, and quality of life.

2.1 Introduction to Cirrhosis

Cirrhosis is the end-stage consequence of a wide range of chronic hepatic insults (1), most commonly including excessive alcohol consumption, chronic hepatitis C infection, and non-alcoholic fatty liver disease (24). Cirrhosis is characterized by the replacement of normally functioning liver tissue with diffuse fibrosis and regenerative nodules resulting in progressive liver dysfunction (25). As a result of the altered hepatic structure and function, resistance to portal blood flow through the liver increases, resulting in the development of portal hypertension: high pressure within the portal vein system (26). The disease progresses from an asymptomatic or compensated state, to one of decompensation marked by complications of portal hypertension including ascites, hepatic encephalopathy, variceal bleeding and jaundice (1, 27, 28). Disease progression is associated with significant morbidity and mortality (1). In Canada, chronic liver disease and cirrhosis represent the fifth leading cause of death in individuals between 55 and 64

years of age (29) with over 5,000 liver related deaths occurring each year (30). No therapies currently exist to reverse the fibrosis or hepatocellular dysfunction observed in cirrhosis and management is focused on treating the underlying etiology of liver disease and preventing complications. The only treatment for advanced stages is liver transplantation (31), however, this option is not available for the majority of cirrhosis patients (32). Long liver transplantation wait-list times increases the risk for further decompensation, reduced quality of life, and mortality (32). Therefore, non-transplant therapeutic options that can potentially extend survival and improve quality of life, such as aerobic exercise, are important to investigate.

2.2 Complications of Cirrhosis

Portal hypertension underlies most of the clinical complications seen in cirrhosis (33). These complications may impair patients' ability to exercise because of safety concerns, discomfort, and practicality. Increased portal pressures contribute to the formation of collateral blood vessels in the gastrointestinal system and shunting of blood from the portal vessels to blood vessels with lower pressures, commonly including the esophagus (34). Thin walled varices may form in this region that are subject to rupture and possible fatal hemorrhage when portal pressures raise significantly. The formation of varices and variceal bleeding are directly related to the presence and degree of portal hypertension (35).

Another common complication is hepatic encephalopathy: a spectrum of neural disturbances ranging from lack of mental alertness, to confusion,

convulsions, and coma as a result of hepatic insufficiency (36). Collateral vessels result in shunting of portal blood to the systemic circulation without first passing through the liver. Consequently, neurotoxic substances, drugs, bacteria and ammonia normally metabolized by the liver accumulate in high concentrations in the systemic circulation resulting in neuropsychiatric manifestations (26).

The most common complication of cirrhosis is ascites: the accumulation of fluid in the peritoneal cavity (35). Increased fluid retention may cause intra-abdominal pressure, dyspnea, and abdominal pain (36), making physical activities uncomfortable. However, it can usually be managed effectively with a combination of diuretics and salt restriction (37).

2.3 Models Used to Assess the Severity and Prognosis of Cirrhosis

Two prognostic models commonly utilized to predict morbidity and mortality in cirrhosis patients include the Child Pugh (CP) classification (38) (Table 1) and the Model for end-stage liver disease (MELD) score (39). These models will be used throughout this thesis to classify disease severity.

2.3.1 The Child Pugh Classification System

The CP classification is the most largely used model in both clinical research and practice (1) and is derived from five clinical variables: total bilirubin, serum albumin, international normalized ratio (INR), ascites, and hepatic encephalopathy.

Each variable is scored from 1 to 3, and the total score between 5 and 15 is used to determine the CP class: A, B, or C, with C indicating the most severe disease state (38). One and two year median survival times according to CP class are shown in Table 2.

Table 1. The Child Pugh Classification System (40).

Parameter	**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	Mild	Moderate or Severe
Encephalopathy	Absent	Grade 1-2	Grade 3-4

Table 2. One and two year median survival times according to Child Pugh class (1).

Child-Pugh Grade	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 Score

The MELD score is a logarithmic formula based on three objective laboratory variables; serum creatinine, total bilirubin, and INR. The score ranges from 6-40, with higher values indicating worsening liver disease (39). The MELD system was

developed to overcome the subjective nature of determining the degree of ascites and encephalopathy in the CP system and is used to determine organ allocation for liver transplantation (41). One and two year predicted survival rates according to MELD score are shown in Table 3.

Table 3. One and two year predicted survival according to MELD score (42).

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 Cirrhosis: Prevalence, Association with Morbidity and Mortality, and Effect of Aerobic Exercise Training

2.4.1 Reduced Aerobic Capacity in Patients with Cirrhosis: Prevalence and Mechanisms

In addition to liver dysfunction and its related complications, patients with cirrhosis also demonstrate reductions in aerobic capacity, or peak VO_2 (2, 3). Peak VO_2 is the greatest amount of oxygen that an individual can transport and utilize by the working muscles during maximal or peak exercise (43) and it is the gold standard measure of cardiorespiratory fitness and aerobic capacity (44). Measurement of peak VO_2 most commonly occurs during incremental

cardiopulmonary exercise testing on either a cycle ergometer or treadmill, which provides an assessment of the integrative response of the pulmonary, cardiovascular, hematopoietic, and skeletal muscle systems used during exercise (45). Any physiological factor limiting these systems will result in reduced oxygen consumption and lower peak VO_2 values (46).

In the past twenty years, several studies (3, 5, 7, 47-49) have reported reduced peak VO_2 values in cirrhosis patients compared to either predicted values or healthy controls (Table 4), with over two thirds of these patients demonstrating a significant reduction in peak VO_2 (2, 4). The observed decline is most marked in patients with the most severe hepatic dysfunction (2-4), however, even amongst compensated patients, peak VO_2 values remain 22-40% lower than matched, healthy controls (6, 7, 47, 48). The postulated mechanisms of this impairment include cardiovascular, pulmonary, and skeletal muscle dysfunction resulting in decreased oxygen delivery to and/or impaired oxygen extraction by the active muscles (2) and are outlined in Figure 1. Indeed, cirrhosis is accompanied by several complications that may affect the oxygen transport and utilization process (2). Normally, during maximal exercise, cardiac output increases significantly and is mediated by an increase in heart rate and stroke volume (46). One cardiac condition related to cirrhosis that may impair cardiovascular function is cirrhotic cardiomyopathy: a cardiac dysfunction characterized by impaired contractile responsiveness to stress, electrophysiological abnormalities, and altered diastolic relaxation (50). Chronotropic incompetence, which represents an inability of the cirrhotic heart to adapt the heart rate to physiological demand (51), is one

electrophysiologic consequence limiting exercise capacity in previous studies (4, 49, 52). For example, Grose et al. (52) found a reduced exercise capacity in 16 of 20 cirrhotic patients (mean age=55 years). These patients demonstrated chronotropic incompetence and submaximal heart rates (reaching only 74% of age predicted maximal heart rate) regardless of disease etiology. Pulmonary abnormalities commonly seen in cirrhosis that may impair gas exchange and limit oxygen transport include ventilation-perfusion mismatch, intrapulmonary shunts, and diffusion-perfusion defect (2). While rare, cirrhosis-associated hepatopulmonary syndrome (HPS) impairs oxygenation of venous blood as it passes through the lung due to intrapulmonary vasculature dilations (53). Epstein et al. (54) have shown that the reduction in aerobic capacity is significantly reduced in patients with HPS, beyond that found in both hypoxemic and normoxemic cirrhotic controls. In addition, non-cardiopulmonary factors that may play a role in the decline in peak VO_2 in cirrhosis include anemia, beta-blocker therapy, and muscle wasting (2) (Figure 1).

Table 4. Studies reporting reduced peak VO_2 in pre-transplant cirrhosis patients.

Author, Year	**Participants**	**Cirrhosis Peak $V0_2$**	**Control/Predicted peak$V0_2$**	**% Control/ Predicted Value**	**p-value**
Campillo et al., 1990a (5)	24 Cirrhosis (24M, ave CP score=7.2)	19.6mL/kg/min	37.9 mL/kg/min (PV)	51.7% of PV	<0.001
Campillo et al., 1990b (48)	10 Cirrhosis (10M, ave CP score=6.8) 6 Controls (6M)	19.6mL/kg/min	32.7 ml/kg/min (CV)	60.0% of CV	<0.001
DeLissio et al., 1991 (7)	4 Cirrhosis (3M) 4 Controls (3M)	29.9 mL/kg/min	49.5 ml/kg/min (CV)	60.4% of CV	0.066
Epstein et al., 1998 (4)	19 Cirrhosis (12M) 12 Controls (6M)	1.64 L/min	2.17 L/min (CV)	75.6% of CV	<0.05
Wong et al., 2001 (49)	39 Cirrhosis (37M) 12 Controls (10M)	•13 L/min (patients with ascites) •24.5 L/min (patients with no ascites)	28.5 L/min (CV)	•45.6% of CV (patients with ascites) •85.9% of CV (patients with no ascites)	np np
Terziyski et al., 2008 (47)	19 Cirrhosis (19M) 19 Controls (19M)	23.9mL/min/kg	30.6 mL/min/kg (CV)	78.1% of CV	<0.001
Dharancy et al., 2008 (3)	135 Cirrhosis (103M)	17.2 mL/kg/min	np	61.2% of PV	np

Abbreviations: M= male, np=not provided, BMI=Body mass index, CP=Child Pugh, CV=Control value, PV=Predicted value, Ave=average.

Cardiovascular System

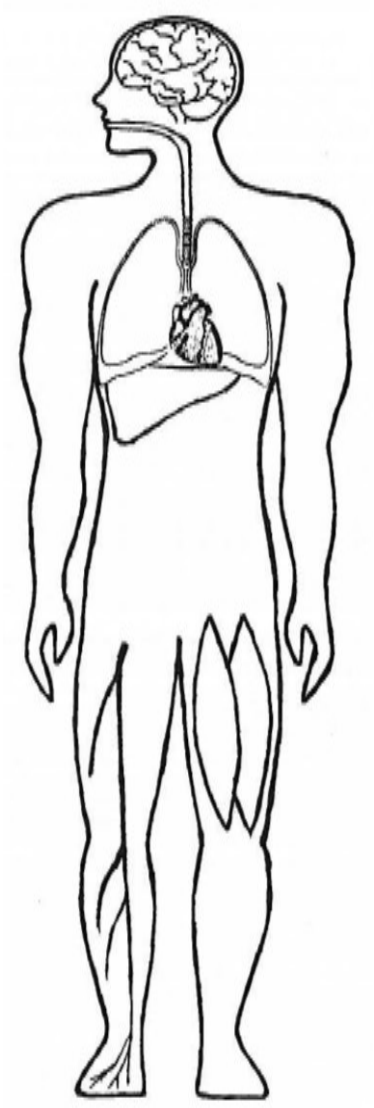
• Cirrhotic cardiomyopathy: characterized by increased baseline cardiac output with blunted ventricular response to stimuli, systolic and diastolic dysfunction, and electrophysiological abnormalities.

• Chronotropic incompetence: Inability of cirrhotic heart to adapt to physiologic demand.

Circulatory/Nervous System

• Autonomic reflex impairment: Redistribution of peripheral blood during exercise is partly under control of autonomic nervous system. Vasodilated state in cirrhosis may interfere with arteriolar vasoconstriction limiting shunting of blood from non-active tissues to exercising muscles, limiting oxygen extraction.

• Anemia: reduced hemoglobin levels as a result of malnutrition and gastrointestinal hemorrhage.



Skeletal Muscle

• Malnutrition, muscle wasting and deconditioning: decreased muscle mass, mitochondria, oxidative enzymes and capillary density reduce oxygen consumption

• Muscular Symptoms: painful muscle cramps may result in early cessation of exercise

Pulmonary System

• Hepatopulmonary Syndrome: intrapulmonary vasculature dilations impair oxygenation of blood as it passes through the lungs resulting in hypoxemia

Complications of Cirrhosis

• Hepatic encephalopathy: altered level of consciousness.

• Gastroesophageal varices: subject to rupture when portal pressure is increased, such as during exercise

• Ascites: increased fluid retention causing dyspnea and abdominal pain

Medications

• Beta-blocker treatment: reduces portal hypertension, heart rate and cardiac output.

Figure 1. Factors influencing exercise capacity in patients with cirrhosis (2).

2.4.2 Peak VO_2 as a Predictor of Clinical Outcomes and Mortality

The reduction in peak VO_2 observed in cirrhosis patients is not only common, but also clinically significant (6). In both healthy and clinical populations, large-scale epidemiological investigations have consistently indicated that reduced peak VO_2 is the most important predictor of mortality (55, 56). Myers et al. (55) reported that a reduction in peak VO_2 of 3.5mL/kg/min (equal to 1 metabolic equivalent (MET)) was associated with a 12% increase in the risk of mortality in 6213 men with or without cardiovascular disease. In addition, peak VO_2 is an independent predictor of all cause mortality among women after adjusting for cardiovascular risk factors. Amongst a cohort of 5,271 asymptomatic women followed for eight years after initial exercise testing, Gulati et al. (56) found that a 1-MET increase in peak VO_2 was associated with a 17% increase in survival.
These findings extend to patients with cirrhosis. Indeed, several studies have demonstrated an independent association of aerobic capacity with pre and post liver transplantation mortality and post-transplantation hospitalization (3, 8-10, 57, 58). Epstein et al. (57) first reported that reduced aerobic capacity (<50% predicted peak VO_2) was independently associated with 100-day mortality following liver transplantation. Similarly, Dharancy et al. (3) found an independent association between pre-transplant peak VO_2 and 1-year survival after transplantation. Among 135 patients undergoing cardiopulmonary exercise testing during preliminary liver transplantation examinations, those with lower peak VO_2 values (< 60% of the

predicted value) had lower 1-year survival (p=0.0003) than patients with greater peak VO_2 values (> 60% of the predicted value). Among those who underwent transplantation, those with peak VO_2 less than 60% of the predicted value trended towards longer lengths of hospitalization after transplant (22.8 vs. 17.7 days, p=0.06) and had significantly longer need for oxygen support.

More recently, Bernal et al. (10) examined the relationship between aerobic capacity and 1-year survival among patients with and without liver transplantation. Cardiopulmonary exercise testing was performed on 399 cirrhosis patients during first elective liver transplant assessment. In patients who did not receive a transplant, 1-year mortality was 34.6%. Peak VO_2 was significantly lower in those who died compared to survivors (13.8 mL/kg/min vs. 17.4 mL/kg/min, p<0.0001). Aerobic capacity remained independently associated with mortality on multivariate analysis. Among patients who received a transplant, those with the lowest quartile peak VO_2 values (<13.4 mL/kg/min, n=54) had significantly longer intensive care unit (ICU) stays post-transplantation (p<0.005). Accordingly, peak VO_2 is an important clinical outcome measure and therapies to improve this parameter are warranted in patients with cirrhosis.

2.4.3 The Effect of Aerobic Exercise Training on peak VO_2 in Cirrhosis

It is well established that peak VO_2 is modifiable through aerobic exercise training (AET) in both healthy and clinical populations (11-14). In healthy, sedentary individuals, this parameter can be improved by as much as 40% with AET

(6, 44). The effect of AET on peak VO_2 in cirrhosis patients, however, is limited to two uncontrolled trials conducted over 20 years ago (5, 21). In 1983, Ritland et al. (21) found that regular aerobic training resulted in improvements in predicted peak VO_2 with no harmful effects on patients' clinical condition or liver function. At baseline, nine patients with chronic active hepatitis, including five patients with histologically-proven cirrhosis, underwent a submaximal exercise test to predict peak VO_2. Patients were given written instructions for a home-based interval aerobic training program and asked to train for 30 minutes, 3-4 times per week, performing an activity of their choice including running, swimming and biking. After 4-6 weeks and 10-12 weeks, calculated peak VO_2 had increased by 19% ($p<0.05$) and 29% ($p<0.01$) from baseline, respectively. Training had no detrimental effect on liver function as assessed by bilirubin or the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). However, those included in the study had no history of variceal bleeding or signs of decompensation such as ascites or hepatic encephalopathy.

Seven years later, Campillo et al. (5) investigated the effects of 4-5 weeks of AET on peak VO_2 in four cirrhosis patients, yielding discordant results. Patients included in the study had been hospitalized for at least one complication of cirrhosis including ascites, variceal bleeding or sepsis, but had recovered to good clinical condition before exercise testing. The aerobic training intervention consisted of bicycle or treadmill exercise as preferred, 45-60 minutes per day, 5 days per week at 50-60% of peak VO_2. After 5 weeks of training, aerobic capacity increased in two

of four patients by 21.2% and 27.5%. In the other two patients, however, peak VO_2 remained unchanged.

2.5 The 6 Minute Walk Distance as a Predictor of Mortality in Patients with Cirrhosis

The six-minute walk distance (6MWD) may be a useful alternative to cardiopulmonary testing that provides clinicians with a more accessible way to obtain an estimation of aerobic capacity. Both Carey et al. (59) and Alameri et al. (60) have established the 6MWD as an independent predictor of mortality in cirrhosis patients. Among 121 patients with cirrhosis awaiting liver transplantation, Carey et al. (59) reported that the optimal 6MWD cut-point for mortality prediction was <250 meters with every 100 meter increase in walk distance being associated with a 52% reduction in mortality. Similarly, in a 1-year prospective follow up study, Alameri et al. (60) found that the 6MWD for surviving cirrhosis patients was longer than non-survivors (317 m vs. 245 m, p=0.021; 95% CI 11-132). In addition to cardiopulmonary exercise testing, the 6MWD may offer additional information regarding aerobic capacity among cirrhosis patients.

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

Skeletal muscle wasting, also termed sarcopenia, is frequent among patients with cirrhosis, occurring among 40% of those undergoing evaluation for liver transplantation (61). A variety of factors contribute to this loss of muscle mass including malnutrition, decreased hepatic protein synthesis, hypermetabolism, and loss of appetite related to metabolic and hormonal alterations, medications, and inflammatory cytokines (62). The prognostic significance of muscle wasting in cirrhosis has been established by several studies that have identified low muscle mass as an independent predictor of survival and both pre and post-transplant outcomes (61, 63-65). For example, Alberino et al. (65) identified low muscle mass defined by mid-arm muscle circumference to be an independent predictor of survival in 212 hospitalized cirrhosis patients. Montano-Loza et al. (61) further reported that muscle wasting as measured centrally at the 3rd lumbar vertebral level was strongly associated with death from sepsis and an independent predictor of pre-transplant mortality. Among 112 consecutive patients undergoing initial listing for liver transplantation, sarcopenia was present in 50% of cirrhotic men and 18% of cirrhotic women. Compared to cirrhotics with normal muscle mass, those with sarcopenia had significantly shorter transplant-free survival (19 months vs. 34 months, p=0.005). Using the same lumbar vertebrae index of muscle mass, Tandon et al. (63) found that sarcopenia in cirrhosis was associated with a 2.5-fold increase in transplant waiting list mortality.

In addition to reduced survival, sarcopenia contributes to the aggravation of encephalopathy, ascites, and portal hypertension (66-71), and is a major contributor to the decreased quality of life in cirrhosis patients (31, 72-74).

Unfortunately, very limited data are available on the mechanisms responsible for sarcopenia and few treatment options exist (31). Only limited success has been achieved in reversing the low level of muscle mass in cirrhosis with nutritional and hormonal interventions (75). Exercise may be one potential therapeutic approach to improve muscle mass and outcomes for these patients, however, the transient increases in portal pressure that occur with exercise, particularly resistance training, may result in variceal bleeding and possible fatal hemorrhage (22, 31). This inherent risk may be one reason for the very limited data on the effect of exercise training in cirrhosis patients. In four patients, Campillo et al. (5) investigated the effect of aerobic training on muscle mass in cirrhosis. Two of the four patients had resultant improvements in muscle mass by 20% and 15% as measured by mid arm muscle area following 4-5 weeks of cycle or treadmill exercise, 45-60 minutes per day, 5 days per week at 50-60% of peak VO_2. Muscle mass in the other two patients remained the same. To date, no studies have evaluated the effect of strength or resistance training on muscle mass in cirrhosis. Clearly, more studies are needed to determine the relationship between muscle mass, strength and exercise in these patients. Given the limited available data, extrapolation of the effect of aerobic training on muscle mass from other populations is useful.

In healthy and clinical populations, several studies have indicated that aerobic and strength-training programs are an effective intervention to increase muscle mass and attenuate muscle wasting (5, 16, 76, 77). For example, Kavanagh et al. (16) reported that long term aerobic training is associated with a 2-kg increase

in lean body mass in cardiac transplant patients. Sipila and Suominen (78) have further demonstrated that aerobic training is associated with increases in both total cross sectional area and lean tissue cross-sectional area of the quadriceps as measured by computed tomography. Although this parameter requires further study in cirrhosis, given the correlation of muscle mass depletion with mortality, the potential to increase muscle mass with exercise is of potential prognostic relevance.

2.7 The Effect of Aerobic Exercise on Portal Pressures

The safety and tolerance of exercise has remained a concern for cirrhosis patients and is likely the reason that such limited data is available in this population. One concern is the inherent risk of variceal bleeding with rising portal pressures that may occur during physical exercise. In a study of eight cirrhosis patients, Garcia-Pagan et al. (22) found that moderate intensity cycle exercise at 30% of peak work load, which corresponds to walking at roughly 3.5 mph (79), resulted in significant increases in portal pressure as measured by the hepatic venous pressure gradient (HVPG), and a significant reduction in portal blood flow. These measures were even more pronounced at 50% of the peak workload. The HVPG gradient correlates with bleeding status among cirrhotics with esophageal varices (80), thus, the increase in portal pressure that occurs during moderate exercise may increase the risk of variceal rupture among those with esophageal varices.

The exercise induced rise in portal pressure, however, can effectively be prevented by pretreatment with non-selective beta-blockade. A subsequent double blind study by Bandi et al. (23) characterized the effects of propranolol or placebo administration on the splanchnic hemodynamic response in twenty three patients with cirrhosis and portal hypertension at baseline and during moderate cycle exercise (40 Watts). In those receiving placebo, portal pressure as measured by HVPG significantly increased during exercise (from 16.7 ± 0.9 to 19.0 ± 1.0 mm Hg; $P < .01$) and decreased (from 16.3 ± 1.0 to 12.9 ± 1.1 mm Hg ($P < .01$)) in those receiving propranolol pretreatment.

2.8 Health Related Quality of Life in Cirrhosis and Potential Psychological Benefits of Exercise

Health related quality of life (HRQOL) is a multidimensional construct that refers to the impact of disease on a patient's physical health, mental health, social function, and general well being (81). It incorporates the patients' attributions, perceptions, and appraisal of their illness and its accompanying impairments (82). While traditional clinical outcomes are important endpoints for clinicians, including an assessment of HRQOL is a key component in evaluating therapeutic interventions because patients are frequently more concerned about quality than length of life and how disease affects their wellbeing (83). As a result of liver disease awareness and complications, patients with cirrhosis often suffer from anxiety, depression, fatigue, loss of self esteem, and inability to function at work which

profoundly decreases quality of life (84). Physical complications such as muscle cramps and wasting, ascites and hepatic encephalopathy also greatly influence patient's sense of wellbeing and life satisfaction (24, 85). Several studies have supported that HRQOL is substantially reduced in chronic liver disease compared to healthy controls and that this measure declines with disease severity (86-89).

While no studies currently exist evaluating the effect of AET on HRQOL in cirrhosis, a substantial amount of literature attests to the psychological benefits associated with habitual exercise (90-92). Such benefits include decreased anxiety (19) and depression (18), improved self-image and feelings of confidence, and perceived improvement in energy level and quality of life (17, 20, 90, 93). Fatigue is a common and difficult to treat symptom among chronic liver disease patients and is often associated with decreased activity levels (94). Physical activity, however, appears to mitigate this symptom. In a review of twelve large, epidemiological studies, there was an agreement among the studies suggesting a strong, consistent, dose-response relationship between physical activity levels and feelings of energy and reduced fatigue (95). More recently in a systematic review of twenty-five prospective studies, Mammen et al. (92) reported that even low levels of physical activity (ie walking <150 minutes per week) can prevent and treat depression.

2.9 Summary and Rational

Aerobic capacity, muscle mass, and quality of life diminish with the progression of liver disease. The influence of AET on patients with cirrhosis has only partially been explored and available data is not sufficient to conclude whether

physical training programs in this patient group are safe and effective to improve these parameters. A wide range of data from healthy and clinical populations suggest that AET programs can contribute to improvements in peak VO_2 and muscle mass, as well as improve common issues faced in liver disease such as anxiety, depression, and quality of life. Based on this information, the use of an exercise intervention to improve these outcomes seems justifiable in cirrhosis patients, so long as the necessary precautions to prevent raises in portal pressure and reduce risk of variceal bleeding are in place.

Chapter Three: Methods

3.1 Overview of Study Design

The *Effects of eight weeks of aerobic exercise training versus usual care on peak oxygen consumption, muscle mass, distance walked in six minutes and health related quality of life in Child Pugh class A and B patients with cirrhosis* was a prospective, randomized controlled trial conducted at University of Alberta Hospital in Edmonton, Alberta, Canada, from February to June 2013. Patients meeting eligibility requirements were randomized to receive supervised aerobic exercise training (AET) or usual care (UC) for eight weeks.

3.2 Ethics Approval

This investigation received approval from the Health Research Ethics Board at the University of Alberta (Study ID: Pro00033449) and the study was registered at ClinicalTrials.gov (Study ID: NCT01799785). Informed consent was obtained from all patients prior to participation.

3.3 Participants and Inclusion Criteria

All potentially eligible patients were consecutively screened and recruited during their clinic visits at the Cirrhosis Care Clinic. The participants included 19 male and female cirrhosis patients who met the following inclusion criteria:

1) Cirrhosis diagnosed on the basis of a liver biopsy demonstrating stage 4 fibrosis or a compatible radiological appearance to the liver, the latter in association with a history of portal hypertension related complications.
2) Child Pugh (CP) class A or B
3) Age ≥ 18 and ≤ 70 years
4) Guideline based primary prophylaxis in place for patients with high-risk gastroesophageal varices including either one of the following:
    a. Non-selective beta-blockade
    b. Endoscopic band ligation to the point of variceal eradication (96)

3.4 Exclusion Criteria

The exclusion criteria for this study included:

1) Post-liver transplantation
2) Significant cardiac disease (ejection fraction <60% or history of coronary artery disease, positive exercise stress test (≥1 mm ST segment depression)
3) Chronic renal failure on dialysis
4) Hemoglobin <110 g/L
5) Myopathy
6) Human Immunodeficiency virus infection

7) Hepatocellular carcinoma (HCC)
8) Active non-HCC related malignancy
9) Physical impairment or orthopedic abnormality preventing exercise training
10) Failure to consent

3.5 Baseline Evaluations

Participants meeting inclusion criteria were provided with an information sheet (Appendix A) outlining the purpose, procedures, benefits and risks involved in participation. After obtaining informed consent (Appendix B), the following baseline evaluations were performed on two separate days within a one-week period:

3.5.1 Day One: Clinic Baseline Evaluations:

Day one baseline evaluations occurred in the Cirrhosis Care Clinic at the University of Alberta Hospital. Information was recorded on the Baseline Data Collection Sheet (Appendix D).

1) Medical history and review of medications

Medications, complications of cirrhosis, etiology of liver disease, and patient co-morbidity information were obtained from each patient and confirmed either by the patient's attending hepatologist, information available through Netcare, or the Cirrhosis Care Clinic's Wolf patient database system.

2) Nutritional assessment and counseling by a registered dietitian (RD)

The Cirrhosis Care Clinic RD evaluated two-day diet records to estimate caloric and protein intake, and provided nutritional counseling and supplementary handouts (Appendix J) to all patients. Protein and calorie targets were based on the European Society of Enteral and Parenteral Nutrition (ESPEN) guidelines (97) and the *Nutrition Support Manual (Adult)* and *Daily Nutrient Recommendations for Liver Disease* provided by Alberta Health Services. For protein intake, 1.2-1.5g/kg protein was recommended in all patients daily. If the BMI was >30, protein was dosed based on an ideal body weight (BMI 24.9). Daily target calorie intake was BMI specific ranging from 25-30 kcal/kg for a BMI of 20-29.9, 21-25kcal/kg for a BMI of 30-34.9 and 14-17 kcal/kg for a BMI of 35-39.9. As cirrhotic patients have an impaired capacity to mobilize glucose during exercise (2) and in order to ensure that the calories burned with physical exertion were repleted, patients were asked to consume an additional 250-300 kcal/day on exercise days if they had been randomized to the AET group.

Anthropometric measurements of each patient were conducted by the same RD including height, weight and body mass index (BMI). BMI (kg/m^2) was calculated using the estimated dry weight divided by height squared. Estimated dry-weight is used by dietitians in the Cirrhosis Care Clinic to estimate a patient's weight in the absence of ascites or pedal edema. It was estimated by subtracting 5%, 10%, or 15% of the patient's weight in the presence of mild, moderate, and severe ascites, respectively (63). An additional 5% of body weight was subtracted for patients with bilateral pedal edema.

3) Measurements of muscle mass and thigh circumference

A portable ultrasound machine (Mindray©, Shenzhen, China) was used to measure the depth of the right quadriceps muscle (the rectus femoris and vastus intermedius). Based on published experience (98-100) as well as ongoing local studies in cirrhosis (101), points at one-third and one-half of the total distance from the top of the patella to the iliac crest were marked and measured. As the comparability and practicality of these measures are still under study, two readings were obtained at each point: a compression reading (Fig. 1a.) was taken by pressing the probe downwards until no further compression of the muscles was possible and a featherweight reading (Fig. 1b.) where the probe was held without pressure on the thigh. Measurements at both points on the thigh were averaged and corrected for stature by dividing by the patient's height squared to yield an average compression index and an average featherweight index.

Thigh circumference was evaluated at the 1/3 point using a tape-measure as a muscle mass correlate.

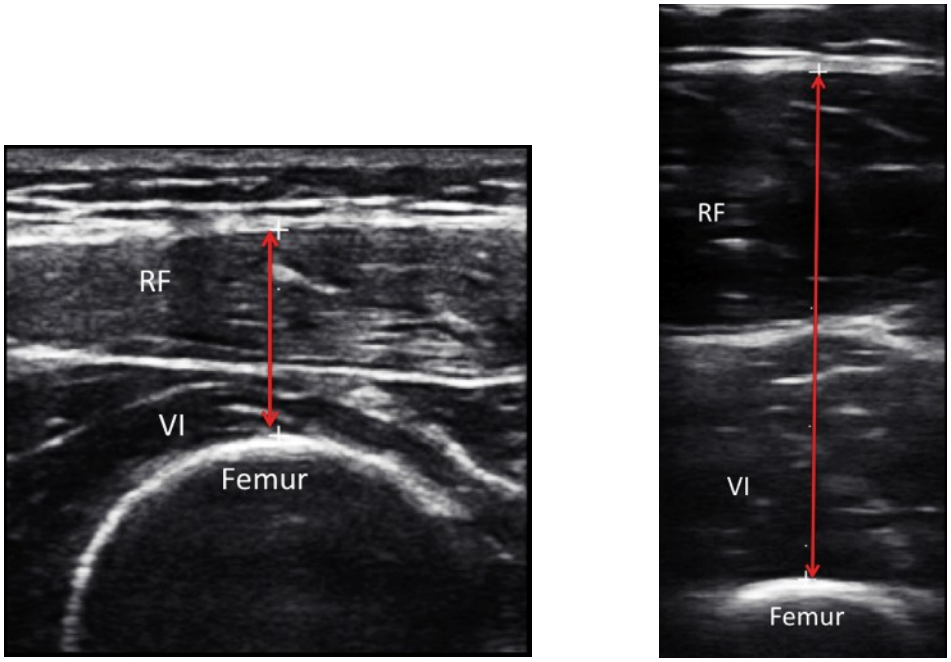


Figure 2. Ultrasonography images depicting thigh muscle thickness measurements. Muscle thickness illustrated by the arrow. VI=vastus intermedius. RF=rectus femoris.

Figure 2a. Compression Measurement Figure 2b. Feather Measurement

4) Assessments of Quality of Life

Patients completed the following quality of life questionnaires independently:

a) Chronic Liver Disease Questionnaire (CLDQ)

The CLDQ (Appendix G) is a 29-item self-administered HRQOL instrument developed for patients with all etiologies of liver disease and all cirrhosis stages (102). This questionnaire includes items in the domains of fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry, rated on a 7-point Likert scale. Higher summary and domain scores indicate minimal

symptom frequency and thus, a better health related quality of life (82). Means were computed for each domain subscale and for an overall score.

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 Likert scale (ranging from 0-3 points). Summed scores for each subscale range from 0-21 with higher scores indicating higher levels of depression and anxiety; case-ness defined by a score of 8 or above on both subscales yields an optimal balance between sensitivity and specificity (103).

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 patient's self-rated health state on a 100-point visual analogue scale (104). Patients were asked to rate their own health state along the scale with end-points labeled "Best imaginable health state" and "Worst imaginable health state." Higher scores indicate a more favorably perceived health status.

5) 6 Minute Walk Distance

A 6-minute walk test was performed according to American Thoracic Society Guidelines (105). Briefly, patients were instructed to cover as much distance as possible, without running or jogging, within the 6 minute period while walking from one end to the other of a straight, flat, 50m hallway marked at one-meter intervals. Participants were permitted to slow down and rest during the test if necessary, and instructed to resume walking once able. The total distance (m) walked during the six-minute period was recorded.

6) Requisition for bloodwork and assessment of liver disease severity

Each patient was provided with a bloodwork requisition to be completed at their laboratory of choice. The following bloodwork was collected to assess liver function, enzymes, and disease severity: 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 using both Child Pugh classification and MELD score.

3.5.2 Day Two: Cardiopulmonary Exercise Test

Cardiopulmonary exercise testing (Appendix K) took place in the Mazankowski Heart institute and was performed by an experienced exercise physiologist. As previously described (106), cardiopulmonary exercise testing was performed on an electrically braked cycle ergometer. The initial power output was set at 15 Watts and increased by 15 Watt increments every 1 to 2 minutes until volitional exhaustion. Participants ranked their rate of perceived exertion during

the last 30 seconds of each stage using the 15 point Borg Scale (107) during the test. Continuous expired gas analysis was performed with a metabolic measurement system (Innocor, Innovision). Blood pressure was acquired by cuff sphygmomanometer at the end of each exercise stage while heart rate was continuously measured by 12-lead ECG during exercise. The highest oxygen consumed over a one-minute period was used as the peak VO_2 score (106).

3.6 Randomization

After completion of the baseline assessment, patients and investigators were informed of the study group assignment. Patients were randomized to the AET or UC group using an internet randomization plan obtained from http://www.randomization.com and placed into sealed numbered envelopes by a registered nurse external to the study team.

3.7 The Aerobic Exercise Training Program

Aerobic exercise training was performed in the exercise physiology laboratory (Corbett Hall, University of Alberta) and supervised by two physiotherapists. Training occurred three days per week, for eight weeks, on a Monark cycle ergometer at a heart rate equal to 60 to 80% of baseline peak VO_2. The training target heart rate ranges were calculated using the heart rate reserve method (Appendix M). After a brief warm-up of low-level cycling for 5 minutes, the exercise duration was initiated at 32.5 minutes per session and increased by 2.5

minutes each week until study completion. Each training session was followed by a 5 min cool-down period.

3.8 The Usual Care Group

Patients in the UC group were not given exercise guidelines and were asked to continue their normal lifestyle and activity patterns for the study duration.

3.9 Follow-Up Assessments During the Study Period

To assess liver function and hemodynamic stability during training, in the AET group the following bloodwork was collected bi-monthly for CP A or weekly for CP B patients: albumin, electrolytes, bilirubin, creatinine, ALT, AST, INR and a CBC. Patients in the AET group were seen three times per week by the trainers and questioned about any significant adverse events experienced during training. These included cardiovascular or pulmonary events, extreme fatigue or muscle weakness, variceal bleeding, paracentesis, infections, or hospitalizations.

At the study mid-point, two-day diet records were collected and follow-up phone calls were made by the Cirrhosis Care Clinic RD to all patients every two weeks to optimize adherence to dietary recommendations.

3.10 Post-Training Evaluations

The previously described baseline evaluations were repeated in all participants following eight weeks of AET or UC using the same staff and testing

procedures and recorded on the End of Study Data Collection Sheet (Appendix F). Patients in the AET group were counseled to adjust caloric intake in accordance with their current activity level.

3.11 Outcome Measures

The primary outcome measure was change in peak VO_2 from baseline assessment. Secondary outcome measures included changes in quadriceps muscle thickness as measured by bedside ultrasound, thigh circumference, 6 minute walk distance, health related quality of life and liver disease severity.

3.12 Sample Size

The sample size calculation was based on the primary outcome, peak VO_2. The expected improvement in peak VO_2 was 3.5 mL/kg/min greater after aerobic training compared to the UC group (106). If between group standard of deviation was 2 mL/kg/min, with a power of 80% and an alpha level of $p<0.05$, a total of eighteen patients would need to be recruited. To account for a 10% patient drop-out rate, the sample size was increased to 20 patients (n=10 exercise, and n=10 controls).

3.13 Statistical Analyses

Statistical analysis was performed using SPSS version 19 (SPSS Inc., Chicago, IL, USA). Variables were described using means and standard deviations, or

proportions. Depending on the variable distribution, Chi-squared, Fisher's exact or independent samples t-tests were used to determine if there were differences in the baseline characteristics between study groups. The analysis of covariance (ANCOVA) was used to assess for differences between groups. This accounts for the individual changes within patients, changes between groups and for baseline values and is robust to violations of normality assumptions (108). Statistical significance was established at a 2-tailed p value of less than 0.05.

Chapter Four: Results

4.1 Flow of Patients Through the Study

Figure 3 shows the flow of patients through the trail. Thirty-six consecutive patients were screened and approached between December 2012 and April 2013, of which 20 agreed to participate. One patient was excluded from the study following baseline evaluation as he met criteria for CP C cirrhosis. Therefore, data were available and analyzed for the nineteen remaining patients who completed the study (AET, n=9 and UC, n=10). In the AET group, 7 participants completed the study with full compliance. The remaining two patients had adherence rates of 12.5% and 79% due to conflicting schedules during training sessions.

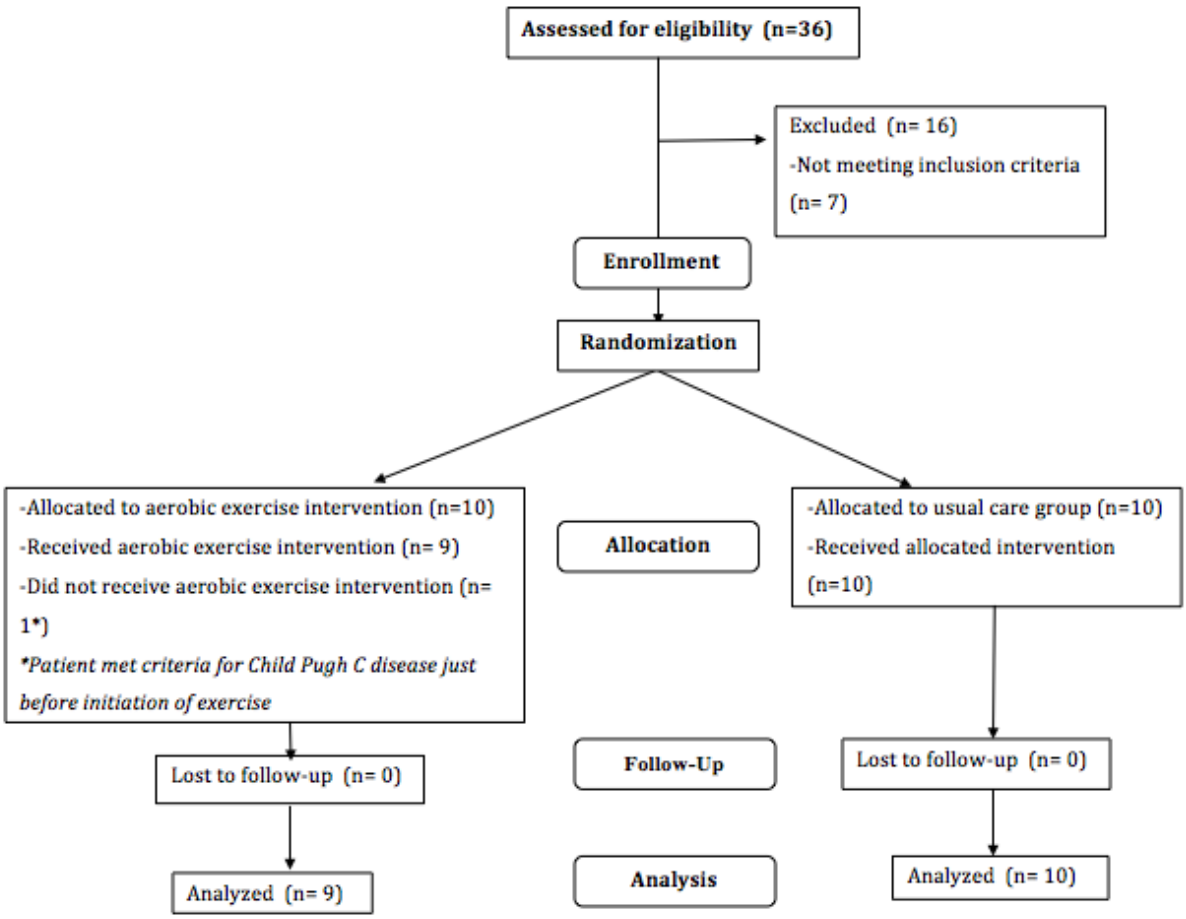


Figure 3. Flow of patients through the study.

4.2 Patient Characteristics

Baseline patient characteristics are shown in Table 5. Seventy-nine percent (n=15) of patients were male, 84% (n=16) were Caucasian and the mean age for all participants was 57.6 ± 6.7 years. Seventy-four percent (n=14) of patients were classified as CP A (mean CP score= 6.3 ± 1.4) and the mean MELD score was 10 ± 2.2. Fifty-three percent (n=10) of patients had either Hepatitis C and/or alcohol related liver disease. No patient had clinically detectable ascites or hepatic encephalopathy on baseline evaluation but a total of 26% (n=5) were on diuretic therapy. Eighteen patients had a history of varices, of which six had experienced previous variceal bleeding (1 in the AET group and 5 in the UC group). Six patients met criteria for primary variceal prophylaxis (2 in the AET group and 4 in the UC group) and 4 patients met criteria for secondary variceal prophylaxis (1 in the AET group and 3 in the UC group). One patient in the UC group had a well functioning transjugular intrahepatic portosystemic shunt (TIPS) in place and therefore was not counted as actively meeting criteria for variceal prophylaxis. One patient in each group was currently smoking. The baseline characteristics between the two groups were comparable (Table 5).

Table 5. Baseline Patient Characteristics.

Characteristic	**Exercise Training group (n=9)**	**Usual Care group (n=10)**
Age (years)	56.4 ± 7.7	58.6 ± 5.8
Male gender, n (%)	7 (78)	8 (80)
Caucasian Ethnicity, n (%)	8 (89)	8 (80)
Etiology of cirrhosis, n (%)		
Alcohol induced	3 (33.3)	3 (30.0)
Hepatitis B	1 (11.1)	1 (10.0)
Hepatitis C	1 (11.1)	3 (30.0)
Other*	4 (44.4)	3 (30.0)
Severity of liver disease		
MELD score	9.7 ± 2.4	10.2 ± 1.9
Child Pugh score	6.2 ± 1.4	6.0 ± 1.4
Use of diuretics, n (%)	3 (33.3)	2 (20.0)
History of varices n (%)	8 (89)	10 (100)
Variceal prophylaxis, n (%)		
Not required/TIPS in place**	6 (66.7)	3 (30.0)
Beta-blocker therapy alone	0 (0)	1 (10.0)
Band-ligation therapy alone	0 (0)	3 (30.0)
Combination Beta-blocker and Band-ligation	3 (33.3)	3 (30.0)
Medications, n (%)		
Beta-blocker	3 (33.3)	4 (40.0)
Diuretics	3 (33.3)	2 (20.0)
Labs		
Hemoglobin (g/L)	147.7 ± 18.4	141.1 ± 12.3
Platelet count	93.3 ± 31.0	90.6 ± 46.1
Albumin (g/L)	38.0 ± 5.2	36.8 ± 4.0
Creatinine (μmol/L)	77.0 ± 18.3	70.4 ± 16.3
Bilirubin (μmol/L)	20.7 ± 10.9	27.0 ± 13.7
INR	1.2 ± 0.2	1.2 ± 0.2
ALT (units/L)	36.2 ± 16.6	66.7 ± 75.9

BMI (kg/m^2)	27.7 ± 3.8	28.9 ± 4.2
Nutritional Intake		
Protein (g/day)	81.7 ± 20.3	102.1 ± 39.2
Calories (kcal/day)	1630 ± 475	2024 ± 612
Peak VO_2 absolute (L/min)	1.98 ± 0.65	2.21 ± 0.52
Peak VO_2 (mL/kg/min)	23.3 ± 7.7	25.2 ± 6.7

Values presented as mean ± S.D., with the exception of the categories of gender, ethnicity, etiology of cirrhosis and variceal prophylaxis where the values are frequency counts. For all baseline characteristic comparisons, p >0.05.

** The etiology of cirrhosis in the "Other" category included cryptogenic/Non-alcoholic fatty liver disease (n=3 in AET and n=2 in UC) and Primary biliary cirrhosis (n=1 in AET and n=1 in UC). ** TIPS was present in only one UC group patient and no AET group patients.*

Abbreviations: MELD=Model for End Stage Liver Disease, INR= International Normalized Ratio, TIPS= transjugular intrahepatic portosystemic shunt, ALT= Alanine Amino Transferase, µmol=micromole, BMI= Body Mass Index, m=meter, VO_2= oxygen uptake, n=number, L=liter, g= gram, kcal=kilocalories, min=minute, mL= milliliter, kg= kilogram.

4.3 Training Intensity

The mean aerobic training intensity for the AET group was 123 bpm, 84.5% of baseline peak heart rate.

4.4 Primary Outcome Measure: Effect of 8 weeks of AET or UC on peak VO_2

At baseline, the peak $V0_2$ was similar between groups. When compared to the UC group, peak VO_2 in the AET group improved by 5.3 mL/kg/min (95% CI: 2.9 to 7.8) when indexed to body mass (p=0.001) (Figure 4), or by 0.48L/min (95% CI: 0.30 to 0.65) in absolute terms (p=0.001) (Table 6).

Table 6. Baseline and study end measurements- cardiorespiratory measures.

	Exercise Training Group		**Usual Care Group**		**Difference between mean changes (95% CI)**	**ANCOVA p value**
	Baseline	**Study End**	**Baseline**	**Study End**		
Peak VO_2 (L/min)	1.98 ± 0.65	2.35 ± 0.79	2.21 ± 0.52	2.14 ± 0.62	0.48 (0.30 to 0.65)	0.001
Peak VO_2 (mL/kg/min)	23.3 ± 7.7	27.3 ± 6.2	25.2 ± 6.7	23.3 ± 4.8	5.3 (2.9 to 7.8)	0.001
Peak Power output (Watts)	147.8 ± 51.0	180.0 ± 60.6	157.0 ± 29.6	155.1 ± 36.6	35.1 (15.9 to 54.4)	0.001
Peak Heart rate (bpm)	145.0 ± 25.6	142.3 ± 24.9	134.9 ± 19.9	135.6 ± 21.1	-2.3 (-13.4 to 8.9)	0.67
Peak Systolic blood pressure (mmHg)	165.1 ± 21.6	165.1 ± 21.4	157.2 ± 15.0	153.7 ± 18.0	8.2 (-8.8 to 25.2)	0.07
Peak VO_2 (L/min)/Peak Heart Rate	13.6 ± 3.5	16.4 ± 4.3	16.4 ± 3.0	15.8 ± 4.0	3.8 (2.0 to 5.6)	0.001

Values presented as mean ± S.D. *Abbreviations*: *VO_2= oxygen uptake, L=liter, mL= milliliter, bpm=beats per minute, mmHg=milliliter of mercury, min= minutes.*

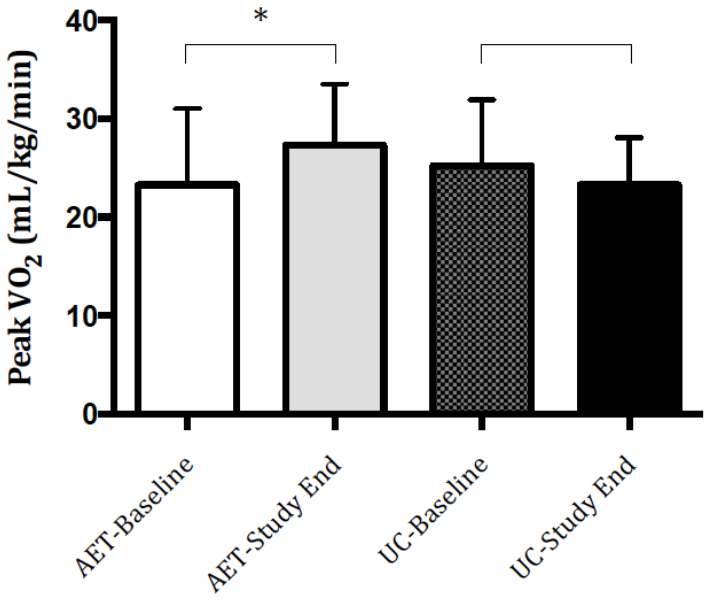


Figure 4. Effects of eight weeks of aerobic exercise training or usual care on peak VO_2. (Means ± S.D.; *Difference between group means, P=0.001).

4.5 Secondary Outcomes measures: Effect of 8 weeks of AET or UC on muscle mass, thigh circumference, 6 minute walk distance, and quality of life

The changes in the secondary outcome measures are presented in Table 7 and Table 8, and Figures 5-9. Compared to the UC group, in the AET group, there was a statistically significant increase in thigh circumference by a mean of 1.1 cm (95% CI 0.5 to 1.6). The average compression index (the ultrasound measure of quadriceps thickness with the muscle compressed corrected for height squared) increased by 0.06 cm/m^2 (95% CI 0.01 to 0.11) and the increase in the average feather index trended to significance (p=0.10). As compared to the UC group, in the AET group, the 6MWD increased by a mean of 23.5 meters (95% CI -12.4 to 59.4, p=0.19). There was a statistically significant improvement in the activity (1.24 points (95% CI 0.34 to 2.14)) and fatigue (0.80 points (95% CI 0.22 to 1.38)) domains of the CLDQ. Moreover, the patient's self-perceived health status as measured by the EQ-VAS also significantly improved in the AET group when compared to the UC group, increasing by a mean of 20.4 points (95% CI: 5.1 to 35.8) on a 0 to 100 scale. There were no statistically significant differences in protein or total caloric intake, BMI, anxiety, depression, or other domains of the CLDQ in either group.

Table 7. Baseline and study end measurements- nutrition, anthropometric measures, and six minute walk distance.

	Exercise Training Group		**Usual Care Group**		**Difference between mean changes (95% CI)**	**ANCOVA p value**
	Baseline	**Study End**	**Baseline**	**Study End**		
Nutritional Intake						
Total protein (g/day)	81.7 ± 20.3	107.5 ± 32.0	102.1 ± 39.2	108.9 ± 31.6	10.4 (-17.1 to 37.9)	0.43
Total calories (kcal/day)	1630 ± 475	2112 ± 705	2024 ± 612	2356 ± 646	60 (-501 to 621)	0.82
Thigh Circumference (cm)	52.4 ± 4.7	53.6 ± 4.4	52.9 ± 4.7	53.1 ± 4.7	1.05 (0.54 to 1.56)	0.001
Average Feather Index (cm/m^2)*	1.27 ± 0.38	1.37 ± 0.33	1.10 ± 0.21	1.13 ± 0.19	0.11 (-0.02 to 0.25)	0.10
Average Compression Index (cm/m^2)*	0.58 ± 0.19	0.63 ± 0.18	0.53 ± 0.15	0.53 ± 0.11	0.06 (0.01 to 0.11)	0.01
Body Mass Index (kg/m^2)	27.7 ± 3.8	28.0 ± 3.6	28.9 ± 4.1	29.1 ± 4.0	-0.05 (-0.7 to 0.6)	0.86
Body Weight (kg)	83.7 ± 13.0	84.4 ± 12.3	89.7 ± 20.5	90.5 ± 20.2	-0.16 (-2.2 to 1.8)	0.87
6-Minute walk distance (m)	529.1 ± 131.8	570.5 ± 112.0	529.0 ± 84. 6	546.0 ± 97.7	23.5 (-12.4 to 59.4)	0.19

Values presented as mean ± S.D

** See Materials and Methods for definitions.*

Abbreviations: g=grams, kcal= kilocalorie, cm=centimeter, m=meter, kg= kilogram.

Table 8. Baseline and study end measurements- quality of life, liver function and liver enzymes.

	Exercise Training Group		**Usual Care Group**		**Difference between mean changes (95% CI)**	**ANCOVA p value**
	Baseline	**Study End**	**Baseline**	**Study End**		
CLDQ						
Total	5.72 ± 0.63	6.01 ± 0.63	5.42 ± 0.81	5.39 ± 0.96	0.35 (-0.14 to 0.84)	0.15
Abdominal Symptoms	6.44 ± 0.76	6.48 ± 1.03	6.16 ± 0.91	6.10 ± 1.00	0.10 (-0.47 to 0.67)	0.71
Systemic Symptoms	5.96 ± 0.91	6.00 ± 1.01	5.86 ± 0.53	5.60 ± 0.87	0.30 (-0.22 to 0.81)	0.24
Activity	5.52 ± 1.36	6.41 ± 0.62	6.07 ± 0.63	5.33 ± 1.12	1.24 (0.34 to 2.14)	0.01
Emotional Function	5.81 ± 0.50	5.89 ± 0.82	5.50 ± 1.04	5.47 ± 0.89	0.18 (-0.36 to 0.72)	0.50
Worry	6.16 ± 1.00	6.11 ± 1.44	5.48 ± 1.12	5.00 ± 1.74	0.47 (-0.85 to 1.78)	0.46
Fatigue	4.64 ± 1.52	5.62 ± 0.71	4.88 ± 1.12	4.93 ± 0.93	0.80 (0.22 to 1.38)	0.01
EQ-VAS	73.9 ± 9.2	83.6 ± 11.1	78.2 ± 13.3	66.2 ± 21.0	20.4 (5.1 to 35.8)	0.01
HADS						
Anxiety	3.9 ± 3.2	4.2 ± 3.6	5.6 ± 2.7	5.8 ± 3.0	-0.23 (-2.68 to 2.23)	0.85
Depression	2.8 ± 2.1	2.8 ± 2.4	4.9 ± 3.2	5.4 ± 3.4	-0.57 (-2.02 to 0.87)	0.41
MELD	9.7 ± 2.4	10.3 ± 2.60	10.2 ± 1.9	10.8 ± 2.70	0.08 (-1.36 to 1.52)	0.91
Child Pugh score	6.2 ± 1.4	6.3 ± 1.4	6.3 ± 1.4	6.3 ± 1.06	0.08 (-0.78 to 0.94)	0.84
ALT (units/L)	36.2 ± 16.6	40.4 ± 21.5	66.7 ± 75.9	68.0 ± 67.3	-0.92 (-9.8 to 8.0)	0.83
AST (units/L)	50.9 ± 33.6	54.1 ± 37.4	72.6 ± 62.2	66.7 ± 75.9	5.05 (-6.1 to 16.2)	0.35

Bilirubin (μmol/L)	20.7 ± 10.9	25.7 ± 8.8	27.0 ± 13.7	31.9 ± 11.8	-1.7 (-7.3 to 4.0)	0.54
Albumin (g/L)	38.0 ± 5.2	37.9 ± 5.1	36.8 ± 4.0	36.4 ± 3.3	0.48 (-1.4 to 2.4)	0.59

Values presented as mean ± S.D

Abbreviations: *CLDQ=Chronic Liver Disease Questionnaire, EQ-VAS=EQ-Visual Analogue Scale, MELD=Model for End Stage Liver Disease, ALT= Alanine Aminotransferase, AST= Aspartate Aminotransferase,* μmol=micromole, *L= Liter, g=gram.*

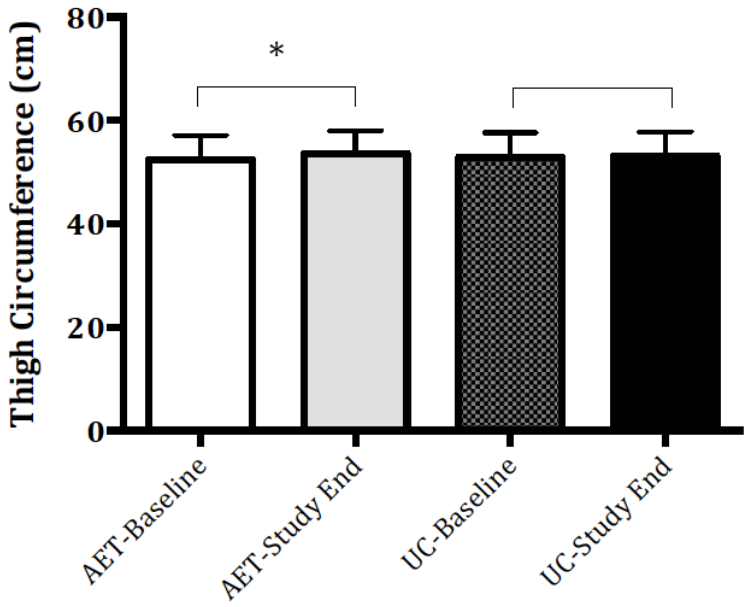


Figure 4. Effect of eight weeks of aerobic exercise training or usual care on thigh circumference. (Means ± S.D.; *Difference between group means, P=0.001).

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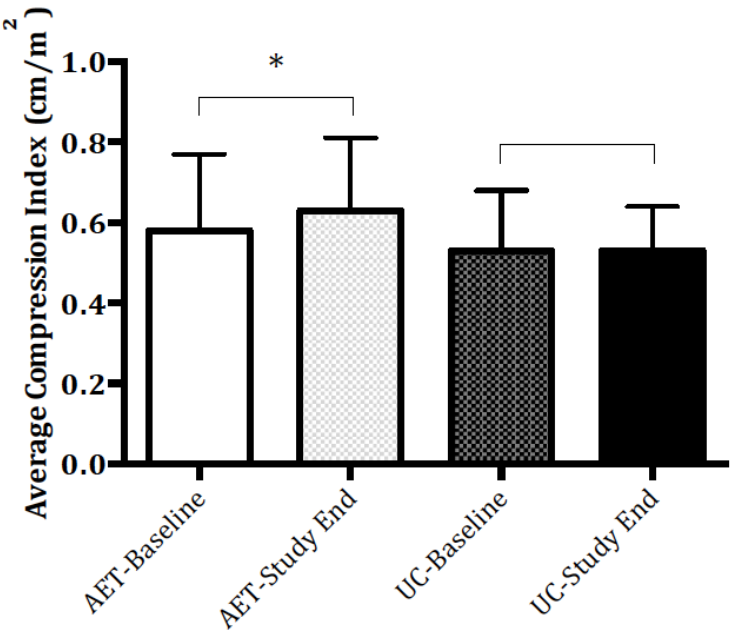


Figure 5. Effect of eight weeks of aerobic exercise training or usual care on muscle mass. (Means ± S.D.; *Difference between group means, P=0.01).

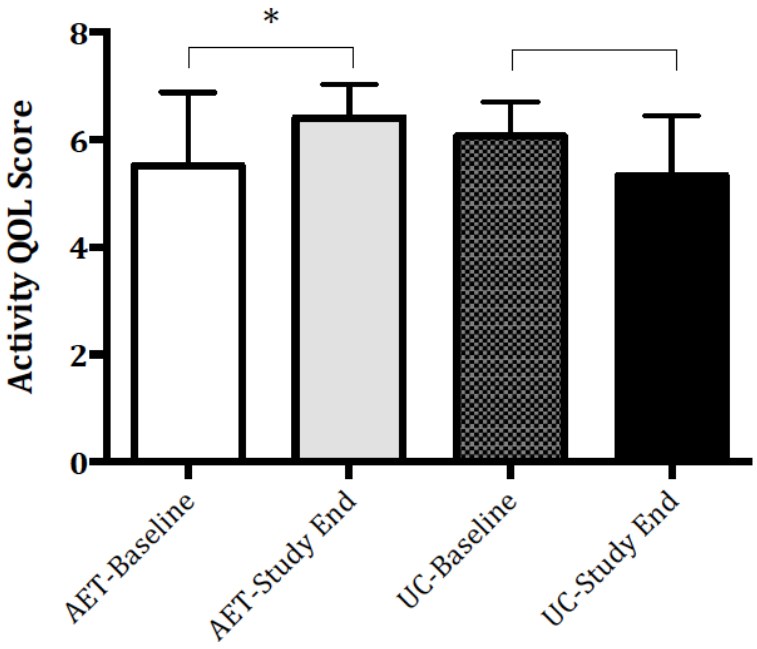


Figure 6. Effect of eight weeks of aerobic exercise training or usual care on the activity domain of the chronic liver disease questionnaire. (Means ± S.D.; *Difference between group means, P=0.01)

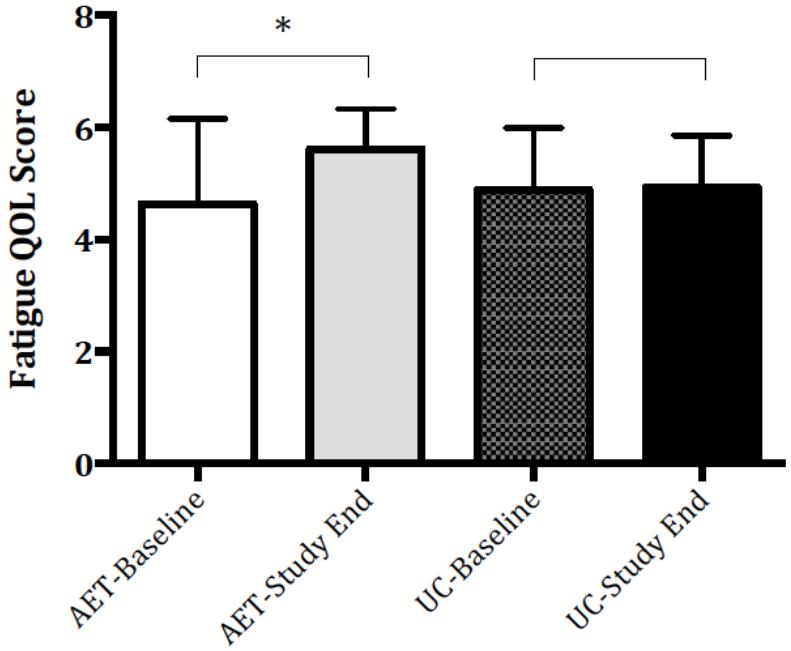


Figure 7. Effect of eight weeks of aerobic exercise training or usual care on the fatigue domain of the chronic liver disease questionnaire. (Means ± S.D.; *Difference between group means, P=0.01).

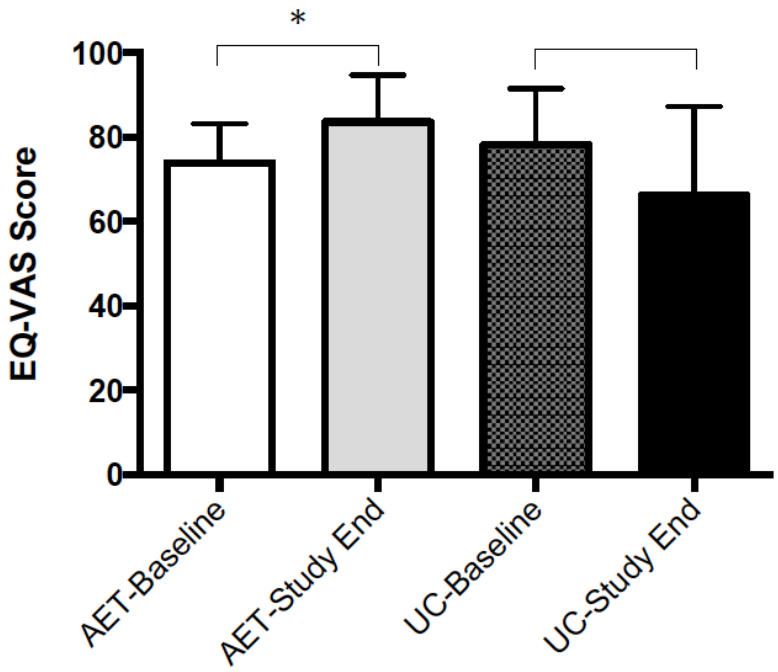


Figure 8. Effect of eight weeks of aerobic exercise training or usual care on self perceived health status as measured by the EuroQol-Visual Analogue Scale. (Means ± S.D.; *Difference between group means, P=0.01).

4.6 Adverse Events

Exercise training was well tolerated by all patients and no adverse events occurred during cardiopulmonary exercise testing or aerobic training. Similarly, there were no significant changes in ALT, AST, CP or MELD scores from baseline to study end.

Chapter Five: Discussion

5.1 Introduction and Major Findings

The safety and efficacy of aerobic exercise training (AET) in patients with cirrhosis has not been well studied. According to available literature, this is the first randomized control trial to evaluate the effect of supervised AET on peak exercise oxygen consumption (peak VO_2), muscle mass and health related quality of life (HRQOL) in patients with Child Pugh (CP) A and B cirrhosis. The main findings of this study are that eight weeks of AET significantly improves peak VO_2, quadriceps muscle thickness, thigh circumference and patient perceived health status compared to usual care (UC). Additionally, symptoms of fatigue were also significantly lower following AET. Although there have been concerns regarding the safety and tolerance of exercise in patients with cirrhosis, no complications or adverse events were encountered during the study period.

5.2 The Effect of AET on Peak VO_2

In accordance with the existing literature (2, 3), the current study confirmed an impairment of aerobic capacity in early-stage cirrhotic patients compared to age-predicted values. The mean baseline peak VO_2 of evaluated patients (mean age=57.6 years) was low at 24.3 mL/kg/min, a value comparable to healthy sedentary individuals who are approximately 75 years of age (109). Limitations in peak VO_2 among cirrhosis patients have been attributed to muscle wasting and deconditioning, fatigue, and cardiorespiratory alterations including cirrhotic cardiomyopathy and hepatopulmonary

syndrome (Figure 1) (2, 5, 6). While the mechanisms responsible for the observed impairment were not evaluated in this investigation, we found that eight weeks of aerobic training significantly improved peak VO_2 by 5.3 mL/min/kg in a group of patients with early cirrhosis. In the literature, AET has been shown to increase peak VO_2 in healthy and clinical populations (11-14) and in a limited number of cirrhosis patients studied in two uncontrolled series (Table 9) (5, 21). The improvement in peak VO_2 observed is in accordance with Ritland et al. (21) who reported increases in estimated peak VO_2 by 6 mL/kg/min (19%) and 9 mL/kg/min (29%) following 4-6 weeks and 10-12 weeks of AET, respectively. Limitations of the study by Ritland et al., however, included a predominantly young group of females (average age=31 years) without history or signs of decompensation and confirmed cirrhosis in only five of nine patients studied. The results of Campillo et al. (5) were discordant with only two of four male patients experiencing improvements in predicted peak $V0_2$ by 21.2% and 27.5% following 4-5 weeks of a home-based aerobic training program. We extend these findings by using a randomized controlled trial design, by including patients with a confirmed diagnosis of cirrhosis and by including patients with a history of portal hypertensive related complications (ie ascites, variceal bleeding, hepatic encephalopathy). In the current study, an 8-week supervised, controlled aerobic exercise intervention improved peak VO_2 among cirrhosis patients by a mean of 5.3 mL/kg/min (a 17% increase among the AET group). This is both a statistically significant and a clinically significant increase as an improvement of 3.5 mL/kg/min has been associated with a 12 to 18% increase in survival in healthy and clinical populations (56, 110). Furthermore, among cirrhosis patients not receiving liver transplantation, a

difference in peak VO_2 by 3.6 mL/kg/min was found to differentiate between those who died compared to survivors (13.8 mL/kg/min vs. 17.4 mL/kg/min, $p<0.0001$) (10). The increase in peak VO_2 following training may also have functional significance. For example, the VO_2 threshold required to perform activities of daily living has been suggested to be between 15-18 mL/kg/min (111). While the baseline peak VO_2 values in the current study were well above this range, the improvements after AET may have resulted in functional tasks or activities of daily living to be performed with less exertion. Consistent with this hypothesis, patients in the AET group reported significantly less fatigue following aerobic training.

The mechanisms underlying the exercise induced increase in peak VO_2 among cirrhosis patients were not evaluated in the current study and remain unclear. Peak oxygen consumption correlates with oxygen delivery and is dependent on cardiac output (heart rate x stroke volume) and peripheral oxygen utilization (49). In healthy and clinical populations, training adaptations include increases in maximal cardiac output, capillary density, and redistribution of blood flow to active tissues resulting in enhanced oxygen delivery to the exercising muscles (Figure 10) (46, 112-114). Other training adaptations include increases in the number of muscle mitochondria allowing for greater oxygen extraction and increased mitochondrial enzyme activities which improve performance by decreasing lactic acid accumulation at a given peak $V0_2$ (46). Whether these mechanisms also apply to cirrhosis, and to what extent, have not yet been evaluated and will require further investigation. Moreover, future studies will be needed to determine whether the improvement in peak VO_2 in this study also apply to patients with more advanced liver dysfunction and whether the improvements can be

further optimized with a longer training period, intensification of the aerobic training or the addition of resistance or interval training.

Table 9. Summary of studies that have examined the effects of aerobic exercise training on peak VO_2 in patients with cirrhosis.

Author, Year	Ritland et al. (21), 1983	Campillo et al. (5), 1990	Present Study
Participants	AET: n=9 (5 with biopsy-proven cirrhosis)	AET: n=4 (sub-group from a larger study of 24 patients)	AET: n=9 UC: n=10
Gender, Average Age	8 female, 31 yrs 1 male, 18 yrs	4 male, np (average age of larger study group=44.8 years)	15 male, 4 female, 57.6 yrs
CP/MELD Score	np	np (average CP score of larger study group=7.2, CP B)	6.1, CP A/10
Aerobic Activity	Home-based: Running, swimming, or biking	Home-based: Treadmill or bicycle	Supervised: Bicycle
Duration	4-6 and 10-12 wks	4-5 wks	8 wks
Frequency	30 min, 3-4 x/wk	45-60 min, 5 x/wk	32.5-47.5 min, 3x/wk*
Intensity	75% HR_{Max}	50-60% VO_{2Max}	60-80% VO_{2Peak}
Peak VO_2 Improvement	-6mL/kg/min (19%) after 4-6 wks -9 mL/kg/min (29%) after 10-12 wks	Improved by 21.2% and 27.5% in two patients. Baseline values np	5.3 mL/kg/min
Adverse Event	None; no change in ALT, AST, alkaline phosphatase or bilirubin	None	None
Limitations	-Select group; predominantly young females without signs of decompensation -Uncontrolled	-Select group; all males -Uncontrolled -peak VO_2 predicted using Bruce protocol and equations	-Predominantly CP A (74%) and male (79%)

	-peak VO_2 deduced from heart rate (Astrand formula)		

*AET was initiated at 32.5 minutes and increased 2.5 minutes per week until study completion.
Abbreviations: AET= Aerobic exercise training, UC=usual care, np= not provided, wk=week, CP= Child Pugh, ALT= Alanine amino transferase, AST= Alanine aminotransferase.

Cardiovascular System

•Increased cardiac output

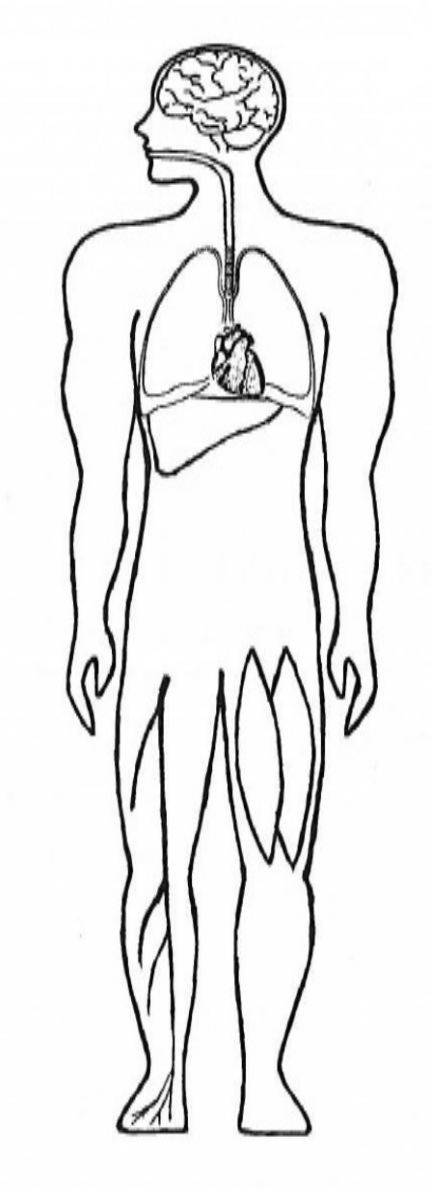
•Increased left ventricular wall thickness and mass; blood ejected with greater force

Circulatory System

•Increased number of capillaries per muscle fiber; enhanced delivery of oxygen/glucose to working muscles, removal of CO_2 and lactate

•Redistribution of blood flow

•Increased capacitance of arteries



Skeletal Muscle

•Increased intramuscular glycogen stores resulting in delayed muscle fatigue

•Increased intramuscular buffering ability

•Increased mitochondrial density; concomitant increase in aerobic enzyme concentration

•Increased myoglobin content enhancing transport of oxygen within muscle fibers

Metabolism

•Increased reliance on triglycerides/fatty acids, sparing liver and muscle glycogen and post-poning fatigue

Figure 9. Effects of aerobic exercise training (115).

5.3 The Effect of AET on 6 Minute Walk Distance

As peak VO_2 testing is not readily available at all centers, the 6MWD was also used to evaluate submaximal aerobic capacity and functional performance. Both Carey et al. (59) and Alameri et al. (60) have established the 6MWD as an independent predictor of mortality in patients with cirrhosis. In both studies the optimal 6MWD cut-point for mortality prediction was <250 meters. Carey et al. further reported that every 100-meter increase in walk distance was associated with a 52% reduction in mortality (59). Patients in the current investigation had less severe liver dysfunction than those in the study by Carey et al. (mean MELD score of 10 vs. 17) as well as high mean baseline walking distances (mean=529 meters for both AET and UC groups) that were only slightly lower than reference standards for healthy, active individuals in the same age category (558-588 m) (116). Due to these high baseline scores, the lower sensitivity of 6MWD compared to cardiopulmonary exercise testing, and use of a cycle based training program as opposed to one that was walking based, the lack of significant increase in the 6MWD was not unexpected. This information is, however, still useful to inform future exercise studies in patients with well-compensated disease, as relevant increases in aerobic capacity may be missed if the 6MWD is the only utilized measure.

5.4 The Effect of AET on Muscle Mass

In addition to the changes in aerobic capacity, supervised AET was associated with significant increases in thigh muscle thickness as measured by thigh ultrasound. Skeletal muscle wasting is a common complication of cirrhosis which adversely affects quality of life, response to infection, and survival (117). Recent investigations by both Tandon et al. (63) and Montano-Loza et al. (61) have identified skeletal muscle wasting as measured centrally at the 3rd lumbar vertebral level to be an independent predictor of mortality in patients with cirrhosis awaiting liver transplantation. For the current study, thigh muscle thickness adjusted by patient height was evaluated using bedside ultrasound. This measure correlates with muscle mass measured centrally at the 3rd lumbar vertebrae (correlation coefficient 0.6, p=0.001), has excellent inter-observer variability (correlation = 0.9), can be performed at the bedside and does not involve radiation (101). In Intensive Care Unit and chronic pulmonary disease patients, thigh ultrasound based muscle thickness correlates with lean-body mass detected by dual energy x-ray absorptiometry (DEXA) independent of edema (98-100), which is commonly encountered in cirrhosis patients (99). Moreover, as noted by one set of authors, the ultrasound measure of muscle thickness is potentially more sensitive to detecting exercise-induced changes in muscle than DEXA (98).

Prior to the current study, published data evaluating the impact of an exercise intervention on muscle mass in cirrhosis was limited to data from two of the four patients evaluated by Campillo et al. in 1990 (5). In those two patients, arm muscle area increased by 20% and 18% following 4-5 weeks of exercise training.

The current findings of a significant increase in muscle thickness are in keeping with prior work from heart transplant recipients showing that physical conditioning increases lean body mass (106). For example, long-term aerobic training has been associated with a 2-kg increase in lean body mass (16) and increases in both total cross sectional area and lean tissue cross-sectional area of the quadriceps as measured by computed tomography (78).

Muscle protein metabolism occurs as a response to exercise, nutrition, hormonal status, and the interactions among these factors. The exact response of exercise on muscle protein synthesis appears to be dictated by the training level of the individual, the type of exercise and the intensity at which exercise is performed (118). The present results suggest that the training intensity levels utilized were sufficient to induce a detectable difference in thigh muscle thickness/muscle hypertrophy. Based on available literature, it is likely that the improvements in the AET group were the result of increased percentage and/or area of type I and II muscle fibers. For example, Coggan et al. (119) reported an increase in the percentage of type IIa fibers and cross-sectional area of type I and type IIa fibers following long-term aerobic training in men and women. Favorable consequences of changes in skeletal muscle morphology include increased oxidative enzyme capacity, mitochondrial density and myoglobin content that may result in increased oxygen utilization and improvements in peak VO_2 (106). Consistent with this hypothesis was an improvement in peak VO_2 by 5.3 mL/min/kg following AET. Although these parameters require further study in cirrhosis, given the correlation of muscle mass depletion with mortality and the limited success in reversing the

low level of muscle mass with nutritional and hormonal interventions (75), the potential to increase muscle thickness with exercise is of potential prognostic relevance.

5.5 The Effect of AET on Health Related Quality of Life, Anxiety, Depression, and Self Perceived Health Status

Supervised AET was associated with beneficial effects on fatigue and the patient's self perceived health status. Currently, no studies exist evaluating the effect of AET on HRQOL in cirrhosis. As generic instruments do not assess disease-specific symptoms and may be less responsive to small but clinically important improvements in HRQOL in patients with liver disease (88), we chose to evaluate HRQOL using the CLDQ in the present study. This questionnaire is the only disease-specific HRQOL instrument evaluated for all etiologies and stages of cirrhosis (102) and appears to be more responsive than generic measures. Using this questionnaire, a statistically significant improvement was observed in the fatigue domain following AET, indicating reduced fatigue symptom frequency. This finding is clinically relevant as fatigue is a common and difficult to treat symptom among chronic liver disease patients and is often associated with decreased activity levels (94). There appears to be, however, a dose-response relationship between physical activity and feelings of increased energy (95). No biological mechanism can currently explain the protective effect of exercise against fatigue, however, postulated mechanisms responsible for improvements in vitality among healthy and clinical populations include improvements in muscle strength and mass, aerobic

capacity, ability to perform daily tasks (120-123) and mood (124). The present findings of increased peak VO_2, muscle thickness, and mean change in self-perceived health status by an estimated 20% following AET are supported by these mechanisms and may in part explain why physical activity appears to mitigate the symptoms of fatigue in cirrhosis.

The lack of improvements in other measures of the CLDQ (abdominal and systemic symptoms, emotional function, and worry) and anxiety and depression as measured by the HADS in this study cannot be generalized to mean that exercise training has no benefit on these outcomes as patient baseline scores were quite good. For example, all patients at baseline had HADS scores well below 8, the cut-point considered clinically relevant for defining case-ness of anxiety and depression (103). Additionally, patients in the AET group had overall CLDQ domain scores comparable to that of normal healthy controls (AET group=5.72 vs. healthy controls=5.4-5.9) as opposed to reported scores in patients with chronic liver disease and cirrhosis (4.0-4.35) (86, 125). While it is possible that self-selection bias attributed to the high HRQOL observed in the present study, it is important to note that disease-specific scales such as the CLDQ may not be a comprehensive view of quality of life as it does not capture other factors influencing a patient's health (126). The use of a generic instrument in conjunction with a disease specific instrument may provide a better assessment of HRQOL for patients with cirrhosis in future investigations.

5.6 The Safety and Tolerance of AET

All of the above noted benefits were seen without an increase in adverse events, defined by variceal bleeding, infections, hospitalizations, and severe alterations in liver enzymes or worsening of disease severity. The safety and tolerance of exercise has remained a concern and is likely the reason that such limited data is available in cirrhosis patients. The original study by Garcia-Pagan et al. (22) found that moderate intensity cycle exercise at 30% of peak work load (40 ± 5 W; corresponds to walking at roughly 3.5 miles per hour) (79), resulted in significant increases in portal pressure and a significant reduction in portal blood flow. A subsequent double blind study by Bandi et al. (23) demonstrated that this rise in portal pressure was effectively prevented by pretreatment with non-selective beta-blockers. Currently, no adverse events have been reported in studies of cardiopulmonary exercise testing or exercise training in patients with cirrhosis (5, 6, 21). However, it is possible that the absence of adverse events is related to the exclusion of high-risk participants (6). For example, exclusion of patients with a history of variceal bleeding, ascites, or encephalopathy in the exercise intervention by Ritland et al. (21) may in part explain the absence of adverse events in this investigation. By including patients with varices and with a history of previous variceal hemorrhage, we attempted to extend these findings and make our study as generalizable as possible to routine clinical practice. As the intensity levels used in our study were well above 30% of peak workload, we were careful to ensure that all patients who met criteria for either primary or secondary variceal prophylaxis (96) had adequate beta-blockade and/or band-ligation therapy in place. Cycle exercise

was well tolerated among all participants and training had no harmful effect on liver function as assessed by MELD, CP or liver enzymes. Whether this lack of adverse events also extends to patients with more advanced hepatic dysfunction remains to be evaluated.

5.7 Limitations

There are several limitations to this investigation. First, the majority of patients were male (79%) and of Caucasian ethnicity (85%). In addition, the results are most generalizable to CP A cirrhotic patients, as they made up 74% of the enrolled patients. Given the limited safety and efficacy data in the literature, we considered it necessary to first evaluate exercise in these patients with early disease. Ongoing studies will determine whether these results can be generalized to patients with more advanced disease. Secondly, although this study was sufficiently powered to support exercise as an effective intervention in patients with early cirrhosis, it was not powered to assess safety. Further safety data are therefore required before this intervention can be routinely recommended. The lack of adverse outcomes in the current investigation is promising and supports the performance of these larger trials. Whether an exercise intervention will also translate into an improvement in clinical outcomes, such as delayed hepatic decompensation, retained functionality and reduced mortality are exciting possibilities that will require further investigation. A third limitation is that the exercise regimen consisted solely of aerobic exercise training. In the setting of

cirrhosis and adequate variceal prophylaxis, the efficacy and particularly safety of resistance training either alone or in combination with aerobic training remains unclear (127). Fourthly, as adequate nutritional intake is an essential building block for materializing any benefits associated with activity, although we consider the involvement of our dietitian to be a strength of the study, unfortunately we did not have the funding to provide all patients with identical standardized meals. Importantly, there were no significant differences between the changes in protein and calorie intake in each group and the mean end of study intakes were quite similar.

Another limitation is that the end of study thigh circumference and thigh ultrasound measurements were performed by an unblinded investigator. As this investigator did not access the baseline data at the time the measurement and as a second independent blinded investigator late evaluated the ultrasound images for accuracy, the potential impact of this limitation was reduced.

Lastly, another possible limitation is the inclusion of patients on beta-blocker therapy. Importantly, by randomization, a comparable number of patients were on beta-blockade in each group. Data from the cardiac rehabilitation literature suggests that although beta-blockers may blunt the improvement in the peak VO_2 (128), substantial training effects and prognostic information can still be achieved despite therapeutic doses (128, 129). Given the marked improvement in peak VO_2 (5.3 mL/kg/min) that we observed, it does not appear that beta-blockers had an effect on our primary outcome.

5.8 Future Directions

The positive results from this study illustrate the necessity for additional investigations similar to this to reinforce the success and impact of exercise on aerobic capacity, muscle mass, and fatigue in patients with cirrhosis. Based on the findings and limitations of this study, the following recommendations are provided in hope that future studies will be stimulated in this field:

1) Investigate the safety and efficacy of alternative forms of exercise training (AET alone, resistance training alone, or a combination of AET and strength training) to determine which form of exercise, frequency, duration, and intensity has the most beneficial effect on peak VO_2, 6MWD, muscle mass, and quality of life in patients with well compensated and advanced cirrhosis.
2) Utilize measurements of blood flow, oxygen delivery and oxygen utilization to determine the underlying mechanisms responsible for the improvement in peak VO_2 in this population, and the extent to which each factor contributes to the impairment. This will allow clinicians to more efficiently target factors that are contributing to this decline, perhaps at an earlier stage of disease.
3) Perform a long term follow up study to determine if the improvements in peak $V0_2$, muscle mass, quality of life and physical activity habits are maintained following a training program and if these improvements have beneficial effects on clinical outcomes such as hospitalizations and mortality.

Chapter Six: Conclusions

In conclusion, the present findings indicate that eight weeks of supervised AET is an effective therapy to improve peak VO_2, muscle mass, and symptoms of fatigue in a group of patients with clinically stable Child Pugh class A and B cirrhosis. Within our study limitations, these findings support the value of supervised AET as a clinical tool to modify these factors. Future studies with a higher number of patients are needed to confirm our findings of efficacy and importantly of safety in early stage patients with cirrhosis, to extend these evaluations to patients with more advanced disease and to determine the mechanisms responsible for the impaired aerobic capacity observed in cirrhosis.

References

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Appendix A: Information Sheet

UNIVERSITY OF ALBERTA

Division of Gastroenterology
Department of Medicine

Puneeta Tandon
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INFORMATION SHEET

EFFECTS OF AEROBIC TRAINING ON HEART FUNCTION AND EXERCISE CAPACITY IN OUTPATIENTS WITH 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
L. Zenith, BSC	U of A, Division of Gastroenterology	969-4245
M. Ma, MD, FRCPC	U of A, Division of Gastroenterology	492-8134

BACKGROUND: Individuals with cirrhosis may have less muscle mass, may find exercise difficult, and may get tired easily when performing daily activities. Aerobic training (walking or riding a bike) has been shown to be a safe and feasible therapy for healthy individuals and clinical populations and can improve exercise performance. The effects of aerobic training to improve blood vessel function, heart function, exercise capacity, muscle mass, and quality of life in cirrhosis has not been studied.

PURPOSE: You are being asked to participate in a randomized controlled trial where half of the participants will receive 8 weeks of aerobic exercise training and half will have no specific exercise training. This type of study design is important to determine whether the exercise has a true effect on blood vessel function, heart function, exercise capacity, muscle mass, and quality of life. We aim to enroll 20 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 affect/influence your treatments at the University of Alberta.

RESEARCH PROCEDURES

Randomization:

Once you decide to participate and your doctor agrees that you meet all of the necessary requirements, you will be randomized 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 and blood vessel function (30 minutes): We will ask you to fill out a questionnaire to assess your quality of life. We will test your blood vessel function with peripheral arterial tonometry (PAT). The PAT test involves measurements of the pulsations of blood flow in one of the fingers on your right or left hand. A sensor on your finger will inflate and deflate intermittently. Measurements are taken at rest, and again after blocking the circulation in your upper arm with a pressure cuff for 5 minutes. Another sensor is placed on a finger of the other hand to act as a control.

Assessment of heart function and exercise capacity (60 minutes). ECG 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. We will measure the heart's pumping ability by analyzing the air that you breathe at rest, during, and after exercise with a "rebreathing" test. This will be done through the mouthpiece or mask connected to a bag full of air and small concentrations of two inactive gases. 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 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.

Intervention Period (over the 8 weeks):

Supervised Aerobic Training (Therapeutic Exercise laboratory, 1-30 Corbett Hall, University of Alberta): Based on the results of the baseline tests, we will develop a personalized aerobic training program (riding a bicycle and walking on a treadmill) for you. You will perform the supervised aerobic training program three times a week for 30 – 60 minutes each time.

During study Follow-up: Depending on the condition of your liver, we will ask you to do bloodwork every 1-2 weeks. This is so that we can make sure your liver tests stay stable during the study. We will be contacting you by phone the day after the exercise testing is done (at baseline and at the end of 8 weeks). We will also see you in follow-up in the clinic one month after the study has started. You will be provided with our contact numbers and you can contact us with questions at anytime.

Follow-up testing (at week 8):

The same tests that were done at baseline will be scheduled for you after completion of the supervised aerobic training program.

POSSIBLE BENEFITS: This study will determine the effect that aerobic training has on vascular function and heart muscle function and exercise capacity in cirrhosis. You may not personally derive benefit by participating in this study.

POSSIBLE RISKS: The exercises that you will perform are generally regarded as very safe. All testing and exercise 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. During the blood vessel test, a blood pressure cuff will be inflated to block the blood flow to your hand for a continuous 5 minute period. At this time, the blood pressure cuff may cause mild discomfort or aching around your arm. However, this is not risky in any way. You may feel increasing numbness or tingling (pins and needles) in your hand which will rapidly dissipate when the cuff pressure is released. The ultrasound does not have any harmful effects. 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. Depending upon how severe your liver disease is, bloodwork will be done every 1-2 weeks. It can be carried out at the laboratory of your choice. Bloodwork may cause bruising from the needle poke. Lastly, exercise can cause pressures in the liver to increase. This is called portal hypertension. This can increase the chances of bleeding from veins in the foodpipe but can be controlled if the veins are treated before exercise is started. Therefore, before you are enrolled in the study, we will make sure that you have had a recent check of the veins in your foodpipe and that these are being controlled with either medication (beta-blocker) or elastic bands around the veins.

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 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 while you

participate in 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 people from 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 pariticpant, or how this study is being conducted, you may contact the University of Alberta's Research Ethics Office at 780-492-2615. This office has no affiliation with the study investigators.

Appendix B: Consent Form

UNIVERSITY OF ALBERTA

CONSENT FORM

EFFECTS OF AEROBIC TRAINING ON HEART FUNCTION AND EXERCISE CAPACITY IN OUTPATIENTS WITH 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
L. Zenith, BSC	U of A, Division of Gastroenterology	969-4245
M. Ma, MD, FRCPC	U of A, Division of Gastroenterology	492-8134

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 research study? Yes No

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

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

Aerobic Training in Cirrhosis:
Screening Sheet

Place Patient Sticker Here

Inclusion Criteria:

-Age ≥18 and ≤70	☐ Y ☐ N
-Cirrhosis (need at least one of the following):	☐ Y ☐ N
-History of portal hypertensive complications	☐ Y ☐ N
-Compatible laboratory data (albumin <35 g/L, bilirubin >20 micromoles/L, INR >1.2)	☐ Y ☐ N
-Biopsy proven cirrhosis	☐ Y ☐ N
-Radiologically diagnosed cirrhosis	☐ Y ☐ N
-Child Pugh class A or B (circle)	
-Appropriate variceal screening and prophylaxis in place:	☐ Y ☐ N

-Date of last gastroscopy_____
-Gastroscopy findings: ☐ low risk ☐ high risk
-If high risk:
- ☐ Band ligation performed
-Date of band ligation_____
Or
- ☐ Beta-blocker therapy
-Dosage_____
-Date of initiation_____
-Current heart rate_____

Exclusion Criteria (exclude if yes is answered to any question)

-Post-liver transplant	☐ Y ☐ N
-Hepatocellular carcinoma (HCC)	☐ Y ☐ N
-Active non-HCC malignancy	☐ Y ☐ N
-Significant cardiac disease-ejection fraction <60% or known coronary artery disease	☐ Y ☐ N
-O2 saturation at rest <95%	☐ Y ☐ N
-Known myopathy	☐ Y ☐ N
- Hb (<110 g/L)	☐ Y ☐ N
-Chronic renal failure on dialysis	☐ Y ☐ N
-Physical impairment making it impossible to ride an exercise bike or treadmill	☐ Y ☐ N
-Orthopedic abnormality preventing exercise training	☐ Y ☐ N
-HIV infection	☐ Y ☐ N
-Patient unwilling to consent to study	☐ Y ☐ N

Appendix D: Baseline Data Collection Sheet

Aerobic Training in Cirrhosis:
Baseline Data Collection Sheet

Place Patient Sticker Here

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_____

General Assessment				
Height (cm)				
Weight (kg)				
Pedal Edema				
Weight- estimated dry (kg)				
BMI				
Right thigh muscle circumference (cm)				
Right rectus femoris muscle thickness	**1/3**		**1/2**	
	F	**C**	**F**	**C**
1/3:_____cm **½:_____cm**				
6 Minute Walk Distance (m):				

Questionnaire Scores	
HADS	
CLDQ	
EQ-VAS	

Baseline Laboratory Information Date of Lab Visit:	
WBC	
Platelets	
Hemoglobin	
Serum albumin	
Serum bilirubin	
Creatinine	
INR	
ALT	
AST	
Serum sodium	
Serum potassium	

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

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: Follow-Up Data Collection and Clinical Events Sheet

Aerobic Training in Cirrhosis:
Follow-Up Data Collection Sheet

Place Patient Sticker Here

Training Information:

Week of Aerobic Training (/8): _____ Session # (/3): _____

Date of Follow-up Data Collection: __ __/__ __ __/ __ __ __ __

Patient Study ID: _____

Stratification

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

Aerobic Training Program:

Training Duration: _____

Training Intensity (% baseline peak V02): _____

Tolerance to Exercise:

☐ Training session completed
☐ Training session terminated early (reason): _____

Patient Comments/Concerns:

Aerobic Training in Cirrhosis:
Clinical Events Sheet

Record Each Event that Occurred Since (previous week/session)

☐ Cardiovascular or pulmonary event making it impossible to exercise (ie severe dyspnea, chest pain)
-Date(s): _____

-Reason: _____

☐ Extreme fatigue or muscle weakness
-Date(s): _____

-Reason: _____

☐ Significant alterations in blood-work
-Affected parameter: _____

☐ Variceal bleed
-Date(s): _____

☐ Paracentesis
-Number: _____

-Date(s): _____

☐ Infection
-Date(s): _____

-Cause (if known): _____

☐ Hospitalization
-Date(s): _____

-Reason: _____

☐ Death
-Date: _____

-Reason: _____

☐ Other outcome of interest: _____

Labs (To be completed q2weeks for CPA or qweek for CPB)	
WBC	
Platelets	
Hemoglobin	
Serum albumin	
Serum bilirubin	
Creatinine	
INR	
ALT	
AST	
Serum sodium	
Serum potassium	

Meld Score: _____

Labwork reviewed by:

Name: _____ Date: _____

☐ Patient may continue to participate in study

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

Signature: _____

Appendix F: End of Study Data Collection Sheet

Aerobic Training in Cirrhosis:
End of Study Data Collection Sheet

Place Patient Sticker Here

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

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

Average Alcohol Intake: (#drinks/week)

☐ None ☐ _____

Smoking History:

☐ Never ☐ Current_____ ☐ Ex-Smoker_____

General Assessment	
Height (cm)	
Weight (kg)	
Pedal Edema	
Weight- estimated dry (kg)	
BMI	
Right thigh muscle circumference (cm)	

Right rectus femoris muscle thickness 1/3:_____cm ½:_____cm	1/3		1/2	
	F	C	F	C
6 Minute Walk Distance (m):				

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: _____

End of Study Laboratory Information Date of Lab Visit:	
WBC	
Platelets	
Hemoglobin	
Serum albumin	

Serum bilirubin	
Creatinine	
INR	
ALT	
AST	
Serum sodium	
Serum potassium	

End of Study Follow-up Phone call by:

Name: _____ Date: _____

Patient Concerns/Comments:

Questionnaire Scores	
HADS	
CLDQ	
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 G: The Chronic Liver Disease Questionnaire

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

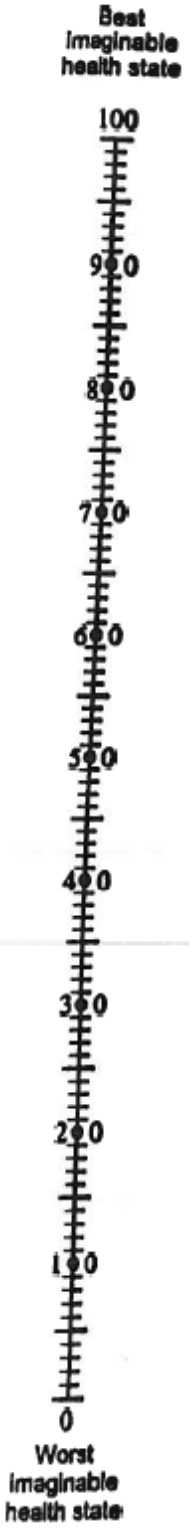
D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0
A	**I get a sort of frightened feeling like "butterflies" in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite often	2
	Very often	3
D	**I have lost interest in my appearance:**	
	Definitely	3
	I 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: Nutrition and Advanced Liver Disease Handout

Alberta Health Services
Capital Health

This resource has been developed by Registered Dietitians

Nutrition and Advanced Liver Disease

Your liver uses the food that you eat to produce the protein and energy that your body needs. Protein, energy, vitamins and minerals keep your muscles strong and help you to carry out your activities every day. If your liver is not working properly, you may become tired and weak.

Weight and muscle loss, fluid retention, nausea, vomiting and poor appetite are common problems for people with liver disease. If your liver is not working properly, you also may not be able to absorb some of the foods that you eat. This causes low levels of vitamins and minerals in your body.

A healthy diet can help to keep your muscles, bones, and body tissues stronger. It can also help your body to fight disease and control fluid retention and confusion.

If you need a liver transplant, strong muscles and good nutrition will help you recover better after surgery. Talk to a dietitian about your eating habits. Your dietitian will help you to prevent weakness and weight loss and to keep your body stronger while you wait for your transplant.

Weight and muscle loss

Weight and muscle loss are common results of liver disease. Liver disease can also cause nausea, vomiting, poor appetite, and diarrhea, resulting in weight loss. Use the following suggestions to prevent weakness or to build up your muscles.

- **Eat 3 meals and 2 or 3 snacks every day.** Eat every 2 to 3 hours during the day and have a snack before you go to bed. Include a grain product in your bedtime snack to prevent muscle loss. Here are some bedtime snack ideas:
  - 2 slices of toast with margarine
  - 1 cup (250 mL) of cereal with milk
  - 1 small muffin with a piece of fruit
  - 3 cups (750 mL) unsalted popcorn
- **Choose foods high in protein and calories.** Add extra calories and protein to the foods that you are eating. Choose protein foods like meat, fish, poultry or milk products at each meal and add higher fat and sugar condiments to boost your calorie intake. Avoid low calorie and low nutrient foods that fill you up without providing nutrition (i.e. soft drinks, coffee, or tea).
- **Have a nutrition supplement**. If you can't eat a full meal or if you miss a snack, you should have a nutritional supplement. You can choose drinks such as Ensure and Boost or high protein, high calorie bars and puddings.

Eat enough protein

People with liver disease need to have more protein in their diet in order to keep their muscles strong.

Foods that are good sources of protein are:
- Poultry – chicken, turkey, duck
- Fish, seafood and shellfish
- Meat – beef, pork, wild game, lamb
- Eggs
- Cheese
- Dried beans, peas, and lentils
- Tofu
- Nuts and peanut butter

If you have encephalopathy (confusion), you may need to follow a low protein diet for a short time. **Do not** follow a low protein diet for more than a few days as it will cause your muscles to become weaker. If you are following a low protein diet, ask your doctor to refer you to a dietitian to help you to slowly increase your protein intake and to choose protein foods that will not aggravate your confusion.

Follow your doctor's suggestions for treatment of confusion. Make sure that you take Lactulose® if prescribed by your doctor.

Tips for increasing protein in your diet:

✔ Include small amounts of protein foods in your meals and snacks over the day.

✓ Choose more vegetable proteins (dried beans, peas, and lentils, nuts or tofu) and less animal proteins (beef, pork, or chicken).

✓ Each person needs a different amount of protein based on their body weight. You should have ____ oz. or _____ g of protein foods every day

Limit sodium intake

People with liver disease and fluid retention should reduce the amount of sodium in their diet. Sodium makes it harder for your body to get rid of fluid. Sodium is found in all types of salt as well as in canned and processed foods, processed meat and cheese and convenience meals. Do not add salt to your foods when cooking or at the table and avoid canned or processed foods and high salt condiments.

Calcium and vitamin D

Osteoporosis is common in liver disease. Getting enough calcium and vitamin D in your diet will help to keep your bones strong.

Your goal is to get 1200 - 1500 mg of calcium every day. Milk products are the best source of calcium available and are also supplemented with vitamin D. You need 4 servings of milk products each day to get enough calcium.

One serving of milk products is equal to:
- 1 cup (250 mL) milk
- ¾ cup (175 mL) yogurt
- 1 to 2 oz (30 to 60 g) cheese
- 2 cups (500 mL) cottage cheese

If you are lactose intolerant, you can choose lactase treated milk or look for lactase drops or pills at your pharmacy. You may also choose calcium fortified soy or rice beverages as these contain similar amounts of calcium as milk products.

If you cannot eat this many servings of milk products, you should take calcium pills. For best results, choose a calcium supplement that includes vitamin D. Your dietitian will suggest the right amount and type of calcium for you.

Vitamin and mineral supplements

Vitamin and mineral pills are important for people with liver disease, especially if you have:

- Poor appetite and little variety in your diet
- Weight or muscle loss
- Liver disease caused by alcohol

Choose a multivitamin/mineral that contains a wide variety of vitamins and minerals but no herbs included. Make sure that your choice includes zinc as this mineral is often low in liver disease. Your multivitamin/mineral should also contain 400 IU vitamin D to keep your bones strong. If you have hepatitis or hemochromatosis, **avoid** any vitamin that contains iron.

Cholestatic liver disease affects the bile flow from your liver to your gut and decreases the absorption of vitamins A, D, E, and K from the food that you eat. Your doctor or dietitian can check the levels of these vitamins in your blood. If these vitamin levels in your blood are low, you may need a special vitamin pill that will be easier for your body to absorb. Your dietitian or doctor will help you to decide if this is necessary.

Herbs and liver disease

Discuss with your dietitian, doctor or pharmacist before you take any herbal product. The amount, strength, and quality of herbal ingredients may not be written on the label and may vary between bottles. They may also contain other herbs or ingredients that are not shown on the label. Not all herbal remedies have been tested for safety and the effects of herbs on your liver are often not known. They may harm your liver or put your health at risk.

If you have a liver transplant, you will not be able to take any herbal remedies after your transplant as they may interfere with your anti-rejection drugs.

Nutrition Plan:

Your individual nutrition plan is based on your specific requirements:

- ☐ Eat 3 meals every day with 2 to 3 snacks between your meals. Include a snack before bed.
- ☐ Choose foods high in protein and calories.
- ☐ Take a nutrition supplement if suggested by your doctor or dietitian:

  _____
- ☐ Eat ____ oz. or _____ g of protein foods every day.
- ☐ Follow a low sodium (salt) diet.
- ☐ Take a multivitamin/mineral pill everyday – choose one that contains zinc and vitamin D but no iron.
- ☐ Eat _____ servings of milk products every day and/or take the calcium supplement suggested by your dietitian.

  _____
- ☐ Contact your dietitian if you have any concerns with following your nutrition plan or if you lose weight or muscle strength.

Appendix K: Cardiopulmonary Exercise Test Form

EXERCISE (PEAK VO2) TEST

NAME:_____ **HT:**_____

DATE:_____ **WT:**_____

TIME:_____

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

MEDS:_____

EXERCISE TEST DATA

TIME	INTENSITY Watts	HR Beats/min	BP mmHg	RPE (0-10)	Other
0-2	0				
2-4	15				
4-6	30				
6-8	45				
8-10	60				
10-12	75				
12-14	90				
14-16	105				
16-18	120				
18-20	135				
20-22	150				
22-24	165				
24-26	180				
26-28	195				
28-30	210				

REASON FOR STOPPING:_____

PRE TEST 0_2: _____ % **PRE TEST CO_2:** _____ %

POST TEST: 0_2: _____ % **POST TEST CO_2:** _____ %

IS ADJUSTMENT NECESSARY? (CIRCLE) YES NO

Bar Press:_____ **Temp:**_____

DATE ADJUSMENT DONE_____ **NEW VALUE:**_____

PHYSIOLOGIST NAME:_____

Appendix L: Aerobic Exercise Training Form

AEROBIC TRAINING AND EXERCISE CAPACITY IN CIRRHOSIS STUDY

Study # _____ Initials:_____

Date_____(dy/mn/yr) Target HR:_____bpm

	Week	Time	HR	BP	Kp	Rpm	RPE
Rest							
Warm-up		0-5					
		5-10					
Aerobic		0-5					
		5-10					
		10-15					
		15-20					
		20-25					
	1	25-30					
	2	30-32.5					
	3	32.5-35					
	4	35-37.5					
	5	37.5-40					
	6	40-42.5					
	7	42.5-45					
	8	45-47.5					
Cool-down		0-5					

Comments_____

Appendix M: HEART RATE RESERVE & TARGET HEART RATE RANGE CALCULATION

The Heart Rate Reserve (HRR) method of determining exercise intensity is used to estimate the heart rate needed to exercise at a specific percentage of peak VO_2 consumption (115). The American College of Sports Medicine suggests most adults need to train from 40-50% (minimum threshold training intensity) up to 85% of peak VO_2 to elicit aerobic fitness gains (130). In the current investigation, the target heart rate range was equivalent to exercising at 60-80% of baseline peak VO_2 values. The target heart rate ranges were determined using the following equations:

HRR = Peak HR – Resting HR

Target Heart Rate = Resting HR + (% Peak VO_2 x HRR)

For example, Patient #1 had a resting heart rate of 90 beats/min and a peak heart rate of 153 beats/min during cardiopulmonary exercise testing. His HRR is 153 bpm-90bpm= 63 bpm.

His target heart rate at 60% peak VO2 = Resting HR + (60% Peak VO_2 x HRR)

= 90 bpm + (0.6 x 63)

= 128 bpm

His target heart rate at 80% peak VO2 = Resting HR + (80% Peak VO_2 x HRR)

= 90 bpm + (0.8 x 63)

= 140 bpm

A target heart rate range for patient #1 of 128-140 bpm would result in exercising at 60-80% of peak VO_2.