Comparison of Targeted Lower Extremity Strengthening and Usual Care Progressive Ambulation in Subjects Post-Liver Transplant: A Randomized Controlled Trial

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COMPARISON OF TARGETED LOWER EXTREMITY STRENGTHENING AND USUAL CARE PROGRESSIVE AMBULATION IN SUBJECTS POST-LIVER TRANSPLANT: A RANDOMIZED CONTROLLED TRIAL

By

David Walter Mandel

A DISSERTATION

Submitted to the Faculty of the University of Miami in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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COMPARISON OF TARGETED LOWER EXTREMITY STRENGTHENING AND USUAL CARE PROGRESSIVE AMBULATION IN SUBJECTS POST-LIVER TRANSPLANT: A RANDOMIZED CONTROLLED TRIAL

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Individuals with chronic liver disease experience progressive muscle wasting, weakness, fatigue, and decreased quality of life. Liver transplantation is the only treatment for end-stage liver disease with cirrhosis; however, muscle wasting, strength impairments, activity limitations, and health related quality of life do not return to the level of healthy adults. Currently there is no plan of care for rehabilitation of individuals post-liver transplantation. These individuals are only instructed to gradually increase walking and activity. Walking may increase lower extremity muscle strength; however, walking at a self-selected pace is less effective than resistance exercise. The purpose of this dissertation was to compare the benefits of a home exercise program of targeted lower extremity resistance exercise with benefits of progressive walking in individuals who have undergone liver transplantation.

In Chapter 2 we performed a study to validate the ability of several outcome measures to detect changes in strength and activity performance in the population with liver disease and post-liver transplantation. The strength impairment measures of Grip Strength, Heel Rising, and Bridging along with activity limitation measures 30 Second Chair Stand and Six Minute Walk Test (6MWT) were able to differentiate strength and
activity performance across levels of liver disease severity including post liver transplantation. Liver disease severity was moderately correlated with the strength impairment measures Bridging and Heel Rising but was not correlated with Grip strength. Liver disease severity was moderately correlated with 6MWT and 30-Second Chair-Stand but was not correlated with the SF-36 physical function scale. Strength impairment measures were strongly correlated with the activity limitation measures. Heel Rising and Bridging were strongly correlated with 30-Second Chair-Standing and 6MWT. Grip strength was moderately correlated with 30-Second Chair-Standing.

In Chapter 3 we conducted a randomized controlled trial to assess the benefits of resistance exercise to progressive walking as a treatment plan for improving strength and activity performance in individuals post liver transplantation. We also examined the relationships of the change in muscle strength to the change in activity performance. Both the exercise and walking groups improved in strength and activity performance; however, the group performing the resistance exercise improved more. Bridging, 30 Second Chair Standing, Heel Rising, and 6MWT increased more for the exercise group than the walking group. Additionally, changes in strength were related to the changes in activity performance and health related quality of life. Bridging was correlated with Heel Rising, 30 Second Chair Standing, 6MWT, and the Chronic Liver Disease Questionnaire.

In Chapter 4 we discuss the clinical relevance of the results of the studies described in the above chapters. We conclude Bridging, Heel Rising, 30 Second Chair Standing, and 6MWT are valid outcome measures to measure changes in strength and activity performance in the population with liver disease. Individuals post liver transplantation improve in strength and activity performance through progressive
walking; however, the addition of resistance exercise to the current treatment plan is necessary for greater improvement. Additionally it is clinically relevant that this population was adherent to a home exercise program. Subjects adherent to the exercise program increased in strength and activity performance greater than subjects who were non-adherent.
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Your love and support through the years are very much appreciated. Thank you for always pushing me to achieve my goals and be the best I can be in all aspects of life. “Just Keep Plugging Away”.

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Daddy loves you so much. You are always there with a smile for me. Thanks for your love no matter how crazy and distracted I had become. I dedicate this degree to you.
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The liver is the largest gland in the body, weighing about 1.5 kilograms and is considered an exocrine gland because it secretes bile into ducts. The liver can produce one pint of bile a day.\(^1\) The liver has more than five hundred functions. Some of these include: removal of toxins entering the blood through the digestive system; elimination of byproducts from the cycling of red blood cells; conversion of bilirubin to bile; production of clotting factors; storage of vitamins and minerals; metabolism of carbohydrates, fats, cholesterol, proteins, drugs, and steroid hormones; and production of albumin and plasma proteins.\(^1,2\) The liver also plays a critical role in fuel management, nitrogen excretion, regulation of water distribution, and detoxification of foreign substances. Failure of the liver’s multiple functions negatively impacts body function leading to activity limitations and participation restrictions.

**Liver Disease**

Liver failure can result from cirrhosis, liver cancer, viral infection, or inflammation. Hepatic failure is a broad term encompassing encephalopathy, renal failure, endocrine changes, and jaundice.\(^2\) In 1999, five million Americans suffered from chronic infection from Hepatitis and other liver disorders.\(^3\) Five hundred thousand Americans each year are infected with Hepatitis A, B, C, or D resulting in fifteen thousand deaths annually.\(^2\) Hepatitis C virus (HCV) is the most common cause of chronic liver disease in the United States. Annual deaths from HCV are predicted to will double to 30,000 within the next year.\(^4\) Hepatitis results from five major viruses: A, B,
C, D, and E along with Epstein Barr, Herpes Simplex, Cytomegalovirus, Varicella Zoster, and Measles. After contracting the Hepatitis virus, many individuals do not present with symptoms of liver disease for a prolonged period of time. Progression from initial infection to cirrhosis can take up to thirty years. Undamaged surviving hepatocytes have a great ability to compensate for other lost liver cells resulting in the lack of presentation of signs and symptoms despite significant cirrhosis and liver failure.

Greater than fifty percent of new cases of HCV infection are due to IV drug abuse, while sexual transmission accounts for five percent. Other common sources of infection include: blood transfusions (prior to the early nineties), needle sticks in healthcare workers, and patients on hemodialysis. Barbers, manicurists, tattoo artists, body piercers, and traditional folk medicine practitioners all pose risk of virus transmission.

Liver disease is most commonly seen in males between the ages 20-45. Other forms of chronic liver diseases resulting in liver cirrhosis include: Laennec’s cirrhosis (Alcohol induced cirrhosis), primary biliary sclerosis, primary sclerosing cholangitis, cryptogenic cirrhosis, Budd Chiari syndrome, biliary atresia, autoimmune chronic active hepatitis, and metabolic related diseases including: Wilson’s disease, hemochromatosis, and Alpha- 1 anti-trypsin deficiency.

Fibrous tissue replaces damaged and necrosed hepatocytes leading to scarring (fibrosis) of the liver. Damaged hepatocytes regenerate in an abnormal pattern resulting in fibrous tissue that impairs blood flow through the liver. Decreased blood supply to liver tissues results in chronic inflammation, and congestive damage. The scarred hepatic tissue forms bands that constrict and partition the liver into irregular nodules. This
pathological change interferes with production of clotting factors, alters or obstructs biliary channels, and distorts the vascular bed decreasing blood flow through the liver. The obstruction of blood flow leads to portal hypertension interfering with regulation of fluid and electrolyte balance.\(^2\) Portal vein hypertension exerts retrograde pressure on the mesenteric vascular system responsible for returning venous blood from the visceral organs to the liver, resulting in leakage of fluid through the capillary beds. Ascites, the fluid that accumulates in the abdomen and legs from the portal vein hypertension, masks the significant muscle wasting resulting from end stage liver disease.\(^2\) Cirrhosis also interferes with metabolism of nutrients and detoxification of toxins absorbed from the intestines which frequently lead to encephalopathy, and renal failure.\(^2\) To date, there is no treatment for liver cirrhosis other than transplantation.

Individuals with liver disease endure progressive muscle wasting, ascites and fluid imbalances, fatigue, muscle weakness, deterioration of health, and decreased quality of life.\(^2,5,8,9\) Individuals with liver disease will rarely complain of pain from the damaged liver tissue and resultant fibrosis because the liver parenchyma is absent of nerve innervations.\(^2\)

Liver disease frequently leads to pulmonary impairment. Ascites increases intra-abdominal pressure, impeding descent of the diaphragm into the abdominal cavity. This restricts ventilation and decreases functional residual capacity.\(^6,10\) Individuals with ascites appear short of breath, especially when supine.

Liver disease frequently leads to cardiovascular impairments. Low peripheral resistance due to peripheral vasodilation causes chronic hypotension.\(^11,12\) Decreased afterload, decreased stroke volume, impaired circulatory reserve results from the cirrhotic
cardiomyopathy and worsen with ascites and physical stress. These cardiac alterations along with other energy metabolism impairments directly limit exercise capacity.

Endstage liver disease commonly leads to renal failure resulting in metabolic alkalosis. Chronic diuretic treatments for treatment of ascites lead to electrolyte imbalances which impact cognition and physical fitness. Ammonia is a byproduct from the breakdown of ATP during catabolic use of muscle protein. Increased ammonia levels result in encephalopathy in as many as eighty-four percent of individuals with liver disease. Patients with increased liver disease severity demonstrate greater cognitive deficits than those with lesser disease severity. Overt encephalopathy statistically has only a forty percent survival rate of one year. The impaired cognition resulting from electrolyte imbalances and increased ammonia levels results in significant activity limitations.

Esophageal varices, irregularly dilated veins located directly below the mucosa in the lower third of the esophagus due to portal hypertension, and coagulopathy, are observed in 60 percent of patients with cirrhosis. Individuals with large esophageal varices have a 45 percent risk of bleeding. Risk of death is as high as 50 percent with each incidence of bleeding. Patients are placed on nonselective beta blockers such as Propanolol and Nadolol to decrease the risk of bleeding down to 22 percent. Beta blockers for treatment of the esophageal varies can result in blunted heart rates and decreased activity tolerance.
Liver Transplantation

As there is no cure for cirrhosis, liver transplantation has become a major modality to prolong survival and improve quality of life. Transplantation is performed for patients with primary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia, alpha-1-antitrypsin disease, Laennec’s (Alcohol Related) cirrhosis, hepatitis B virus (HBV) and hepatitis C virus (HCV) cirrhosis, cryptogenic cirrhosis, and fulminant hepatic failure. Advanced cirrhosis secondary to HCV is the most common indication for liver transplantation in the United States. Life expectancy of an individual with Child-Pugh Class C cirrhosis, the most severe level of liver disease, is as low as 20 to 30 percent at one year post-diagnosis and five percent at five years when not undergoing liver transplantation. Transplantation significantly increases chances of survival. Based on data as of August 2009 from the Organ Procurement and Transplantation Network, a branch of the United States Department of Health and Human Services, the one-year survival rate after liver transplantation is 81% for hepatitis related necrosis, 89% for cholestatic liver disease, 86% for biliary cirrhosis.

The surgical procedure for liver transplantation stimulates the inflammatory process and increases cytokine production resulting in further depletion of body cell mass. Serum albumin and serum protein levels also decline post-operatively. Gupta et al. observed total body fat loss of 200g during the first seven days after hepatic surgery. Plank et al. reported that during the first two weeks after liver transplant individuals lose an additional ten percent of their body protein stores. At six months post-transplant, resting energy expenditure remains higher than in normal healthy individuals. Elevated resting energy expenditure and increased metabolism result in incomplete protein storage
twelve months post transplant. Hussani et al. also observed loss of lean body mass up to nine months post-transplant. Therefore, due to the continued loss and limited restoration of muscle mass, individuals have prolonged impairments in strength, activity performance, and quality of life after receiving their new liver. These limitations in strength and activity performance result in participation restrictions and prevention of return to previous employment.

Recipients of liver transplant initially exhibit impaired exercise capacity in a similar range to that observed after lung, cardiac, and renal transplantation. Torregrossa reported that improvement in heart function parameters begins between six to twelve months post-liver transplant. As basal systolic function normalizes and ventricular wall hypertrophy regresses, diastolic function improves at rest and during exercise. Overall response to exercise improves due to increased heart rate response, normalized left ventricular ejection fraction and diastolic function. Furthermore, abnormal shunting of blood by the liver as a result of hepatopulmonary syndrome is fully corrected after liver transplantation.

The majority of patients with chronic liver disease are malnourished and underweight prior to transplant. However, obesity can become a common problem post-transplant as food restrictions are lifted and physical activity remains low. Everhart observed an average weight gain of 5.5kg one year post-transplant. Some patients are on a high calorie diet pre-transplantation due to the hypermetabolism and fail to adapt their diet post-transplantation. Denervation of the afferent and efferent pathways between the transplanted liver and the hypothalamus affect satiety and influence overeating. On average, individuals gain 5 to 6 kg after the first year post-transplant
and 9 to 10 kg the second year.\textsuperscript{22,23} Individuals who were overweight pre-
transplantation tend to gain more weight than individuals who were not.\textsuperscript{22} There are no
differences in weight gain between genders; however, older patients gain more weight.\textsuperscript{23} Patients who become obese frequently are unable to return to work and have more
difficulty with locomotion, which are typical of a less physically active lifestyle.\textsuperscript{22}

Post- transplantation patients are on high doses of many different medications,
which individually or in combination can affect muscle and cardiovascular function. The
pharmacopoeia post-liver transplantation may include: immunosuppressants, antifungals,
antivirals, antibiotics, antihypertensives, glucose regulators, antidepressants, and/or anti-
osteoporotics.\textsuperscript{21} Corticosteroids have been linked with muscle weakness.\textsuperscript{24} The
immunosuppressant Cyclosporine can affect the sympathetic system resulting in a
reduction of heart rate and decreased mitochondrial skeletal muscle respiration.\textsuperscript{25}
Therefore, the medications taken by individuals post liver transplantation can impair
strength and function during the recovery process and healthcare providers need to
recognize that these medications can limit tolerance to exercise during rehabilitation. In
addition, because of the muscular and cardiovascular effects, post-operative medications
complicate exercise testing results as they can blunt heart rate response to exercise and
impair muscle respiration.\textsuperscript{11,21}

Liver Disease Muscle Wasting

As previously mentioned, liver cirrhosis is a catabolic disease leading to
profound muscle wasting.\textsuperscript{26} Muscle wasting is defined as the unintentional loss of five to
ten percent of body weight as a result of accelerated muscle proteolysis.\textsuperscript{27} The
prevalence of severe muscle wasting (cachexia) or protein-energy malnutrition approaches 80 percent of individuals with cirrhosis. However, patient perception of muscle wasting is much lower, as the loss of lean tissue is masked by ascitic fluid weight gain due to the inability of the impaired liver to regulate fluid balance. Peng et al. observed that protein depletion increased as Child-Pugh liver disease severity increased. The main proteolytic pathway to muscle wasting is the ATP-ubiquitine-dependent proteolytic system through which contactile proteins are degraded. The pathway is activated by cytokines, glucocorticoids, acidosis, low insulin levels, and/or physical inactivity. Additional factors that contribute to protein-energy malnutrition include: decreased dietary protein intake, malabsorption, decreased activity, and increased resting energy expenditure.

The pathogenesis of elevated resting energy expenditure has not been clearly determined, but evidence suggests an impaired relationship of the effects of insulin on glucose metabolism. Verboeket-van de Venne et al. observed sleeping metabolic rate per kilogram of body mass or fat free mass was significantly increased in individuals with cirrhosis. The breakdown of amino acids to form glucose for energy metabolism (gluconeogenesis) occurs primarily at night and results in depletion of muscle tissue. This is thought to be due to inadequate liver glycogen stores in individuals with cirrhosis. Swart et al. observed a small late evening meal appeared to help decrease the nocturnal amino acid breakdown.

A major factor contributing to muscle wasting associated with liver disease is glucose intolerance, occurring in up to 80% of individuals with cirrhosis. Insulin’s normal effect on muscle is to inhibit protein degradation, but this process is not effective
in individuals with liver cirrhosis due to insulin resistance and glucose intolerance. \cite{31,40}

Kruszynska et al. reported glucose intolerance in individuals with cirrhosis was due to decreased initial uptake of ingested glucose by the liver due to insensitivity of the peripheral tissues to insulin. \cite{41}

Greco et al. reports that lipids are the preferred fuel in patients with cirrhosis. \cite{31}

Basal lipid oxidation rates were higher in individuals with cirrhosis who have a lower rate of carbohydrate oxidation. \cite{41} However, during maximal exercise testing, Campillo et al. determined carbohydrates to be the primary source of fuel for “muscular work” in subjects with cirrhosis. \cite{40} Campillo also observed that there was minimal use of lipids for energy during exercise, reporting an inhibition of lipolysis due to the increased levels of insulin resulting in greater use of carbohydrates. \cite{40} There were no significant differences in skin fold thickness among the classes of liver disease severity, showing a pattern of malnutrition favoring muscle wasting with preservation of fat stores. \cite{42}

Clinically, the loss of muscle tissue is more important than the loss of body fat in individuals with liver cirrhosis and is associated with poorer prognosis. \cite{28,43} Skeletal muscle alterations in chronic liver disease are preferential to Type II fibers. \cite{44,45} Type II (phasic fast-twitch) muscle fibers generate high tensile strength in a very short period of time, fatigue quickly, and are used in anaerobic metabolism. \cite{44} This pathological muscle wasting may continue as long as nine months post-transplant. \cite{8} Alcoholic myopathy results in selective atrophy of type II fibers, but not due to catabolism. Liver disease is frequently brought on by alcohol abuse, however, skeletal myopathy as a result of alcohol occurs independent of liver disease. \cite{46} Alcohol decreases skeletal muscle formation by inhibiting protein synthesis. \cite{46} Myopathy, either due to catabolic loss of type II high
tensile strength muscle fibers or due to alcohol impacts the ability of individuals to perform basic everyday activities and affects their quality of life.

**Muscle Wasting Related Increased Energy Expenditure**

One of the functions of liver is fuel metabolism. Liver pathology results in a hypermetabolic state that rapidly devours the body’s carbohydrate stores. In glycolysis, anaerobic carbohydrate metabolism, glucose is phosphorylated into Fructose 1,6 diphosphate which is then converted into to two moles of pyruvic acid. The breaking of the chemical bonds holding together the glucose molecules during glycolysis releases hydrogen atoms that are sent to the respiratory chain to produce energy. In the cellular cytoplasm of the muscle, the energy from breaking apart glucose molecules is transferred to high energy bonds of adenosine triphosphate (ATP) molecules. 1,47

As the body’s carbohydrate and fat stores become depleted, skeletal muscles, large reservoirs of protein, are catabolically degraded into amino acids to produce energy and maintain protein synthesis.48 Insulin resistance results in breakdown of skeletal muscle protein and release of amino acids into the circulation.48 The amino acids alanine, glutamine, and aspartate are transaminated for energy production. Alanine is transported to the liver and converted into pyruvic acid to be used to form glucose for energy production in glycolysis. Glutamine is converted to alpha ketoglutaric acid and aspartate is converted to oxalocetic acid which enter aerobic metabolism. The process of converting amino acids into glucose is called gluconeogenesis. Insulin resistance inhibits the normal pathway of gluconeogenesis via pyruvate conversion from lactate in the liver, thus pulling amino acids from skeletal muscle for gluconeogenesis, further adding to the
vicious catabolic cycle. Swart et al. and others observed this form of protein oxidation to occur nocturnally. The process is very costly from an energy standpoint considering Glycolysis produces only a net two moles of ATP and Gluconeogenesis consumes a net six moles of ATP.

The majority of energy production occurs in aerobic metabolism. Pyruvic acid from glycolysis is converted to Acetyl-CoA which then enters the citric acid cycle in the cell’s mitochondria. Acetyl-CoA is degraded to carbon dioxide and hydrogen ions that are used to synthesize ATP from adenosine diphosphate (ADP) through oxidative phosphorylation. As the hydrogen protons combine with available oxygen molecules to form water, ADP becomes phosphorylated, forming ATP. The breakdown of the resulting ATP provides energy for cells to work bodily functions.

Myopathy resulting from the catabolism of skeletal muscle impairs the ability of the muscle to extract oxygen from the blood. Oxygen is the terminal electron acceptor in aerobic metabolism, and without oxygen, energy in the form of ATP cannot be produced from hydrogen electrons generated by the citric acid cycle. As a result, the energy available for muscular work and activity performance is limited primarily to anaerobic glycolysis. The absence of oxygen turns off the citric acid cycle. As a result the two moles of pyruvic acid produced in glycolysis do not enter the citric acid cycle as Acetyl-CoA and are converted to lactic acid. The impaired fuel metabolism results in limited energy production leading to decreased exercise capacity, decreased ability to perform muscular work and therefore limitations in activity performance.

Lactic acid during light exercise is temporarily stored in skeletal muscle and then converted back to pyruvic acid to for further anaerobic energy production. However
during heavier exercise lactic acid stores build up as removal from skeletal muscle is impaired in individuals with liver disease.\textsuperscript{40,50,51} Lactic acid results in muscle fatigue through two mechanisms: inhibiting release of calcium from the sarcoplasmic reticulum impairing muscle fiber contraction and relaxation; and by causing pain. The resulting muscle pain and fatigue due to retention of lactic acid further limits exercise capacity, muscular work and limits activity performance.

Additionally, there are pharmacological impairments affecting fuel metabolism. An adverse complication of immunosuppressant medication to prevent organ rejection is impairment of mitochondrial oxygen consumption. The lack of oxygen available for use in the electron transport chain impairs the ability to produce the ATP from the citric acid cycle.\textsuperscript{19} The lack of energy production, and the accumulation of lactic acid, leads to impaired muscle function, resulting in limitation in activity and reduced quality of life.

**Impaired Gas Exchange in Liver Disease**

Pulmonary function impairment in individuals with liver disease primarily occurs due to development of ascites and vascular changes. Fluid retention frequently occurs producing interstitial and airway edema, this reducing alveolar ventilation. Ascites increases intra-abdominal pressure limiting descent of the diaphragm and displacing both hemidiaphragms upward.\textsuperscript{6} The resulting restrictive pattern of ventilation decreases functional residual capacity, the volume of gas remaining at the end of a normal exhalation.\textsuperscript{6} The greater the volume of abdominal ascites, the greater the reduction in functional residual capacity, leading to increased shortness of breath and further reduction of exercise capacity.\textsuperscript{6} The abnormal gradient between the intaperitoneal and
intrapleural pressure allows ascitic fluid to enter the pleural cavity through defects in the diaphragm. Pleural effusions develop further restricting ventilation. Pleural effusions have been documented in as many as 61 percent of patients with liver cirrhosis.

This decreased functional residual capacity interferes with alveolar function frequently resulting in pneumonia. The above ascitic complications create a low ventilation perfusion (VA/Q) ratio. A low VA/Q ratio is due to either decreased ventilation (VA) or increased perfusion (Q). The fluid accumulation impedement of the diaphragm leads to decreased ventilation. Additionally, individuals with cirrhosis at rest have a high cardiac output and a very low peripheral resistance leading to increased perfusion. Therefore, with the ventilation low and the perfusion high it creates a low ratio leading to impairments in endurance limiting exercise and functional activity. Complete recovery of ventilation perfusion ratio is observed after liver transplantation.

During exercise in individuals with liver disease, cardiac output further increases on an already reduced peripheral vascular resistance gradient. Hyperventilation at rest is typical in individuals with cirrhosis and therefore minute ventilation does not increase. As a result, arterial oxygenation does not increase and may even decrease with exercise. Arterial oxygenation is observed to be decreased in as many as fifty percent of individuals with liver disease. Exercise does not decrease pulmonary gas exchange. The ability of individuals to tolerate exercise and perform activity may be limited from impairment in arterial oxygenation.

Moreau et al. examined tissue oxygen extraction in patients with cirrhosis, finding that oxygen extraction was limited by arteriovenous shunting at the muscle capillary level. The muscles are not able to remove enough oxygen to meet their increased
demand during activity. The cause of this is not clear but proposed to be due to the increased linking of oxygen to hemoglobin or due to mixed venous oxyhemoglobin saturation, and arterial lactate concentrations. As a result, individuals with cirrhosis are more likely to fatigue more easily. A mechanism called hepatopulmonary syndrome common in individuals with cirrhosis consists of abnormal intrapulmonary vascular dilation with rapid movement of blood in the pulmonary vascular bed causing hypoxemia. In liver transplant recipients, total resting hepatic blood flow remains at a higher level than normal for at least six months after surgery suggesting liver blood flow may be under sympathetic control. This is important in terms of activity limitations and prescribing exercise because, due to sympathetic involvement, patients with liver disease may not be able to establish a training response and thus have poorer exercise tolerance.

**Impaired Lactate Clearance in Liver Disease**

Recovery from heavy exercise requires the body to clear lactic acid from muscle tissue and blood. Campillo et al. and Moreau et al. observed increased skeletal muscle lactate levels at rest in patients with cirrhosis. Casaburi et al. documented skeletal muscle lactate levels were higher in patients with cirrhosis after exercise. In the study by Casaburi et al., subjects exercised for seven minutes on a stationary cycle ergometer at moderate to heavy work. The time it took for lactate levels to decrease halfway to resting levels was observed. Compared to normal subjects, patients with liver disease took significantly longer to remove the lactic acid from muscle and blood. The half-life for the controls was 15 minutes. The half-life for individuals with liver disease was 46 minutes. Casaburi et al. report that the liver metabolizes most of the lactate generated
during heavy exercise during the rest period after exercise activity; whereas, skeletal muscle plays a more prominent role in lactate removal during the exercise.50 This is supported by their findings that levels of lactate were less elevated when low-level exercise was performed as a cool down. Low-level exercise as a cool down decreased the half-life time by 29 percent.50 Again, the detrimental effects of muscle wasting are seen with the resultant impairment in lactic acid removal.

**Pre / Post Liver Transplant Medication Related Muscle Wasting and Impairment**

Post-transplantation medications for prevention of organ rejection affect muscle tissue. High dose corticosteroid therapy pre and post transplantation is another source of muscle catabolism and replaces muscle tissue with adipose tissue, resulting in a decrease in lean mass.8,24 A strong correlation \( r = 0.57 \) was measured between decline in lean body mass and use of steroids for immunosuppression two to five months post-transplantation.8 Peripheral myopathy frequently results from treatment with Cyclosporine, a drug commonly used to prevent transplant rejection. This immunosuppressant impairs mitochondrial oxygen consumption and was observed to cause atrophy of the soleus muscle of rats, a 22% decrease in the rat muscle fiber cross sectional area, and impairment in the expression of the type I skeletal muscle phenotype impacting oxidative capacity. These findings were related to the symptoms experienced by transplantation patients who are administered Cyclosporine to prevent organ rejection.19,55 These symptoms include muscular pain, muscular atrophy, muscle weakness, and functional disability.55 These findings strengthen the evidence that individuals have the potential for continued impairments in strength, function, and quality of life many months to years after liver transplantation.
Impaired Pulmonary and Postural Effects on Energy Expenditure

Ascites, resulting from portal vein hypertension, also impacts energy from a pulmonary standpoint. The excess fluid increases intra-abdominal pressures which limit descent of the diaphragm, resulting in decreased functional residual capacity (FRC). Reduction in FRC results in shortness of breath and decreased energy capacity.

Movement in healthy individuals is designed to conserve energy. During walking, potential energy is converted to kinetic energy in a process frequently called “controlled falling”. Individuals with liver disease have altered postures due to large ascitic abdomens rotating the pelvis and moving the center of gravity forward. To improve stability and energy conservation, individuals are observed to flex their hips and knees and widen their base of support. These adjustments in posture lower the center of gravity, placing it closer to midline. Additionally, the posture shifts the emphasis of force to Type I muscles: quadriceps, gluteals, and soleus. Type I muscles are small units, that contract slowly, have low peak tension, and high endurance properties. The resultant posture gains stability through shifting to muscles that limit energy expenditure; however, restricts the mechanism of normal gait conversion of potential energy to kinetic energy. As a result, the body must rely on making even more energy at the cellular level.

Anaerobic metabolism, impaired oxygen extraction, lactic acid retention, and the inability to utilize available potential energy, collectively impact energy expenditure in this population. The fatigue leads to a sedentary lifestyle resulting in a cascade effect of increasing energy expenditure.
**Similar Disease Related Muscle Wasting as a Model of Wasting in Liver Disease**

*HIV Related Muscle Wasting*

Muscle wasting in human immunodeficiency virus (HIV) is strongly similar to muscle wasting in chronic liver disease. The primary causative factors of HIV muscle wasting include: increased energy expenditure, muscle proteolysis, and reduced protein synthesis stimulated by proinflammatory cytokines released locally in response to infection with HIV, all are equally involved in liver disease muscle wasting.\(^{59,60}\) Additional factors that contribute to wasting include: inadequate intake, malabsorptive disorders, metabolic alterations, and hypogonadism. These additional factors are strongly contributory in liver disease as well.

Similar to wasting associated with liver disease, weight loss of five percent or a body mass index less than twenty is associated with worse prognosis and increased mortality in HIV infection.\(^{27}\) Cross sectional muscle area is associated with function and muscle strength in men with HIV muscle wasting.\(^{27}\) Individuals with more wasting have decreased cross sectional muscle area and thus decreased strength and function.

Body cell mass (BCM) is comprised of muscle tissue, organ tissue, intracellular water, extracellular water, and bone; all the cellular elements in the body representing metabolically active tissue. BCM is an independent prognostic marker for survival in patients with HIV associated wasting. Individuals with a BCM less than 30 percent of their body weight have significantly decreased survival rates.\(^{61}\) Similar to HIV associated wasting, the loss of BCM in non-transplanted patients with liver cirrhosis is associated poorer prognosis.\(^{28}\) Wasting occurred in 20 percent of patients with HIV
before the advent of highly active retroviral therapy (HAART), but there is still a
reported loss of BCM in one third of individuals on therapy.27

The significance of wasting on survival, HIV disease progression, and functional
status, highlights the need for prevention of wasting and weight loss.59 Nutritional
counseling, appetite stimulants, progressive resistance training, and anabolic hormones
reverses weight loss and increases lean body mass in HIV infected patients.62 Inadequate
nutritional intake is a prominent cause of loss of BCM with HIV. Psychological factors
such as, loneliness, grief, anxiety, and depression affect appetite. Some individuals
become so weak they are physically unable to prepare meals. Physical ingestion
problems frequently occur with individuals with HIV. Similar to ingestion problems
associated with liver disease due to esophageal varices, individuals with HIV have
difficulty with oral and esophageal lesions, candidiasis, pharyngeal karposis sarcoma, and
Non-Hodgkins Lymphoma. As with liver disease and renal disease, medications
frequently alter sense of taste and smell, and cause diarrhea, nausea, and vomiting further
reducing appetite and intake.63

Altered metabolic function in HIV similar to liver disease results from decreased
sex hormones, decreased growth hormones, catabolic metabolism, and altered resting
energy expenditure. This abnormal metabolism leads to wasting and fatigue. Cytokines
stimulate lipogenesis by the liver, which increases plasma triglyceride levels. Tumor
necrosing factor stimulates peripheral lipolysis. The resulting fatty acids are re-esterified
to triglycerides in the liver and then excreted, eventually cleared by the bloodstream and
returned to adipose tissue. This “futile cycling” results in fatty acid passage between liver
and adipose tissue without utilization for production of energy.63
As HIV related liver disease is very similar to wasting observed in liver disease, many of the interventions used to improve strength and muscle mass in individuals with HIV can be performed in individuals with liver disease muscle wasting.

**End Stage Renal Disease Related Muscle Wasting**

Individuals with End-Stage Renal Disease (ESRD) have low peak oxygen uptake levels similar to those of persons with end-stage liver disease, CHF, and COPD. Abnormal exercise response in individuals with ESRD includes blunted heart rate and excessive increases in blood pressure. The primary reason for termination of exercise is leg fatigue. Limitations to exercise frequently include: reduced peak cardiac output caused by the blunted heart rate response; reduced oxygen carrying capacity from anemia; and impaired oxygen extraction due to structural and functional changes in muscle.

Similar to end-stage liver disease, measurement of cardiorespiratory fitness and maximal oxygen consumption in patients with renal disease is limited because many individuals cannot achieve maximal oxygen consumption due to symptoms of dyspnea and skeletal muscle weakness. These symptoms are identical to chronic liver disease, but are produced by different mechanisms. In renal disease these symptoms arise from low cardiac output due to blunted heart rate and hypertension. In contrast, in chronic liver disease, high cardiac output, ventricular hypertrophy, low blood pressure, and low peripheral vascular resistance limit ability to achieve maximal oxygen consumption.

Anemia, a limiting factor of peak oxygen uptake in renal disease, is not frequently seen in patients with liver disease. However anemia may not play a significant role in
oxygen uptake in renal disease. Painter reports the only treatment that increased peak oxygen uptake in patients with renal disease was exercise, not increasing hematocrit level. 7

Decreased functional performance and quality of life in ESRD is similar to that of chronic liver disease. Patients undergoing dialysis are frequently sedentary, with over half of the patients performing simple basic activities of daily living as their only source of physical activity. 65 Short-Form 36 scores for the physical function scale in patients undergoing dialysis were low with an average score of 44. Short-Form 36 scores for the physical component scale were reported at 35. The norm is 50. Patients who scored lower than the average on the physical component scale had increased mortality and were frequently hospitalized. 65

As with end-stage liver disease, many other chronic diseases result in secondary complications related to increased cardiovascular disease risk and overt cardiovascular disease. For example, the leading cause of death in individuals with ESRD is cardiovascular disease, not renal disease. Painter reports today’s healthcare focuses on high technology treatments of the primary disease and ignores secondary effects that significantly impair functional outcomes. These secondary problems can be easily addressed with low technology interventions such as exercise. 64

Chronic disease treatment frequently involves surgical and pharmacological intervention. Rehabilitation interventions following surgery or prolonged hospitalizations are usually minimal, resulting in improved medical condition but deterioration in physical function. Painter describes an example of kidney transplantation and reports peak oxygen uptake improved 28 percent within six weeks following kidney transplantation.
The initial improvement post-transplant did not increase further over time. After one year, individuals who remained sedentary had peak oxygen uptakes at 77 percent of age predicted values of normal sedentary individuals, whereas those that performed regular physical activity achieved 87 percent of age predicted oxygen uptake for sedentary normal individuals. Additionally, although kidney transplantation corrects the uremia and many complications associated with chronic dialysis, transplantation alone does not optimize physical functioning, which can only be achieved with exercise training. This scenario is equivalent to liver transplantation, with initial rehabilitation during the hospitalization post-operatively but no rehabilitation once discharged from the acute care setting.

The muscle wasting observed in end stage renal disease, like HIV related muscle wasting, is very similar to wasting observed in individuals with liver disease. Once again we can use the interventions for improvement in strength and function that are found to be beneficial in individuals with a similar chronic disease and apply them to individuals with liver disease with the thought that improvements will be similar.

COPD Related Muscle Wasting

Up to 40 percent of patients with chronic obstructive pulmonary disease (COPD) have been observed to have peripheral skeletal muscle wasting and weakness. Severity of airflow obstruction is correlated with reduced Fat Free Mass (FFM), the weight of muscle, skin, bone, and organs that is not fat. Low levels of fat free mass are associated with reduced exercise tolerance in persons with COPD. There is a reduction in type I muscle fibers and an increase in type muscle II fibers; the opposite pattern of fiber
type atrophy seen in chronic liver disease and HIV wasting which are preferential to loss of type II fibers. \(^{30,66}\) In advanced COPD, whole body protein synthesis, including skeletal muscle, is reduced. Hypoxia resulting from COPD, limits energy production suppressing muscle protein synthesis.\(^{30,66}\)

Similar extracellular factors associated with muscle wasting in individuals with end stage liver disease and HIV results in muscle wasting in individuals with COPD: insulin resistance, reduced growth hormone, reduced testosterone, reduced or altered contractile activity, increased energy expenditure, reduced dietary intake, hypoxemia, acidosis, steroid treatment, and increased pro-inflammatory cytokines lead to an imbalance between anabolic and catabolic activity.\(^{30,66}\)

Jagoe describes a model for muscle wasting in COPD. First there is loss of muscle mass in response to reduced physical activity and muscle load, exacerbated by a low-grade inflammatory response. Second, muscle loss is accelerated during acute exacerbations due to further restrictions on physical activity, increased circulating pro-inflammatory cytokines, hypoxemia and acidosis, and treatment with steroids. Third, the capacity to recover chronic and acute loss of muscle protein is impaired due to chronically raised levels of proteolysis and impaired protein synthesis from reduced circulating anabolic hormones. Finally, cytokines, tissue hypoxemia, and disuse result in loss of muscle satellite cells or impair their ability to differentiate and mature decreasing their ability to remodel or respond to injury.\(^{66}\) As seen in individuals with chronic liver disease and HIV, muscle wasting in individuals with COPD is associated with poorer prognosis.\(^{66}\)
The cachexia seen in all these chronic diseases has in common low plasma levels of anabolic hormones such as insulin like growth factors and testosterone; altered metabolism and food intake; and the presence of systemic and local inflammation as a result of increased circulating levels of cytokines (tumor necrosis factor, interleukins, and other proinflammatory molecules. Even though the muscle fiber type wasted is different in individuals with COPD, the method of wasting is similar. Therefore, the interventions used to reduce wasting and improve strength and function in individuals with COPD could be used with individuals with liver disease related muscle wasting.

*Aging Related Muscle Wasting*

Along with chronic disease, age plays a role in strength deficits. Muscle strength reaches peak values at ages 25-35, is maintained or slowly declines in the forties, then rapidly declines (12 to 14 percent per decade) after age 50. Age associated strength levels decline earlier in the lower body compared to the upper body. As individuals age they lose type II muscle fibers. Atrophy of type II fibers associated with aging causes greater loss of strength at fast velocities than slow velocities, and loss of power. This is the same type of muscle wasting associated with chronic liver disease and human immunodeficiency virus which see a decline in type II fibers and an increase in type I fibers.

Age related concentric strength losses occur at the same time frame in both upper and lower extremities. Concentric strength losses develop a full decade earlier than eccentric strength losses. Eccentric losses however, arise earlier in the upper body. Leg
muscle mass significantly declines after age 60 in men and after 40 among women. Arm mass begins to decline at age 60 for both men and women. The control of muscle contraction is also affected by aging. Spinal cord motor neurons and functional motor units decrease with age. These neurologic changes result in further altered muscle fiber type and morphology. Older individuals have difficulty with maintaining steady muscle contraction due to slower motor unit discharge rates. Strength training in older men and women has been demonstrated to increase voluntary muscle activation, motor unit firing rates, and ability to sustain steady submaximal contractions.

Chronic liver disease, chronic obstructive pulmonary disease and HIV wasting all have decreased levels of growth hormone (GH) and insulin-like growth factor (IGF). These hormones also decline with age. These declines in hormones have been implicated in frailty in the elderly due to their effect on muscle mass and bone density. In men, aging is associated with decreases in available testosterone, estradiol, and dehydroepiandrosterone.

Decreases in the synthesis rates of many muscle proteins, specifically of myosin heavy chain and mitochondrial proteins occur with age. Muscle protein synthesis rates are reduced 40 percent in older persons. Besides muscle mass, the efficiency of muscle mass declines with age due to decreased muscle mitochondrial ATP production and reduced mitochondrial protein synthesis. As a result of reduced efficiency, muscle tissue of older persons fatigues faster than younger persons. Age is responsible for only 30 percent of the difference in strength in adults between the age range of 20-93. Multiple factors besides age affect sarcopenia. One factor
includes the same downward spiral seen with chronic disease where declining amounts of physical activity decreases strength which decreases ease of functional ability, and thus decreases participation in physical activity.\textsuperscript{71} Evidence of muscle fiber hypertrophy after resistance exercise in older adults suggests that sarcopenia is more a result of chronic physical inactivity than other physiological factors associated with aging.\textsuperscript{72}

Even though strength and muscle mass decline with age there is still potential to improve. Increased dietary protein intake increases muscle protein synthesis in older individuals. Short term and long term strength training in adults also increases the rate of muscle protein synthesis.\textsuperscript{67}

Frequently exercise interventions used for strengthening older adults are used for evidence to support exercise intervention for individuals with chronic disease due to the similarities between aging and chronic disease. There is a wealth of knowledge with resistance training and older adults. Many of the principles of exercise and strengthening with older adults can be applied to improving strength and function in individuals with chronic disease such as end stage liver disease.

**International Classification of Functioning, Disability, and Health (ICF)**

Verbrugge describes disablement as “the impact chronic conditions have on the functioning of specific body systems and on people’s abilities to act in necessary, usual, expected, and personally desired ways in their society”.\textsuperscript{73} Nagi in the 1960’s formulated the first model of disablement correlating pathology, impairment, functional limitation, and disability.\textsuperscript{74} In 1980 the World Health Organization (WHO) developed a similar classification system called the International Classification of Impairments, Disabilities, and Handicaps (ICIDH). Similar to Nagi the ICIDH classified impairments, disabilities,
Today there is a movement to use the International Classification of Functioning, Disability, and Health (ICF), a model of disablement developed in 2001 by the World Health Organization, to understand the positive and negative aspects of disease from a biological, personal and social perspective.

The ICF model links impairments in body structure, body function, with activity limitation, and participation restriction to discuss functioning and disability. The ICF describes impairments as “a significant deviation or loss in body structure (organs, limbs and components) and function (physiological and psychological)”. Activity limitations are defined as “difficulties an individual may have in executing activities”. Participation restrictions are “problems an individual may experience in involvement in life situations”.

The ICF model of disablement is easily applied to an individual with end stage liver disease. Liver organ (body structure) damage due to virus, cirrhosis, inflammation, or other process can result in body function impairments. Some of these include: decreased albumin synthesis; decreased production of clotting factors; altered metabolism of proteins, bilirubin, albumin, drugs, steroid hormones, and toxins; myopathy; abdominal fluid accumulation (ascites); impaired bone retention (osteoporosis); fatigue, malnutrition, decreased body mass, decreased strength, body pain, jaundice, and impaired cognition (encephalopathy). These impairments may lead to activity limitations. Some of these include: difficulty grasping or lifting objects, decreased ability to stand from a low surface, inability to ambulate household distances, inability to dress or bathe independently, and the inability to open jars or clean the house. The participation restrictions that result from the body function impairment and activity limitations may
include: decreased socialization, loss of employment, the inability to live alone and engage in recreational activity.

Traditionally physicians treating individuals for liver disease assess pathology and physiology through laboratory values, radiology, palpation, and auscultation. Few physicians actually assess activity limitations. Prevention of disability is a current area of interest in today's healthcare. Understanding the body function impairments, activity limitations and their impact on individual’s participation in the specific population with liver disease will help educate physical therapists and other healthcare providers on how to best address prevention of disability.

**Evidence for Relationship of Muscle Strength to Function**

Muscle strength is defined as “the ability to develop force against a resistance in a single contraction of restricted duration”. Functional strength is the ability to repeatedly produce smooth, coordinated, controlled force during functional activity. As described by the ICF, there is a significant relationship between muscle tissue (body structure) and muscle strength (body function) with activity limitations. Strength has been linked to activities such as walking, standing from a chair, and climbing stairs. Therefore, the lack of strength individuals with muscle wasting resulting from chronic liver disease leads to many activity limitations and participation restrictions.

Bassey et al. developed a flywheel rig to measure leg extensor power in elderly men and women. Power was determined multiplying the force of the leg pushing the flywheel by the maximal speed of the flywheel developed from that force. Bassey et al. correlated chair rising \( r=0.65 \), stair climbing \( r=0.81 \), and walking speed \( r=0.81 \) with
leg extensor power. Bohannon et al. studied the effect of lower extremity leg strength deficits on sit to stand performance in individuals with renal disease. Hand held dynamometric measurement of knee extension force was moderately correlated ($r=0.43$) with sit to stand performance. Hughes et al. compared young and elderly subjects performing chair rising. Among the variables tested such as chair height, balance, and rise strategy, only the lower extremity strength variable was related to the ability to rise from the chair. Elderly subjects with less lower extremity strength were unable to rise as well. Chandler provided elderly subjects with home exercises to strengthen their lower extremities. The strength gains assessed on the isokinetic dynamometer were significantly associated with improved chair rise ability, gait, stooping, and stair climbing. Jones et al. compared lower body strength, derived from one repetition maximum testing on a leg press machine, with 30-Second Chair-Stand performance in community residing older adults. The authors reported a moderate correlation between Chair-Stand performance and leg press strength. Bean et al. reported leg strength and leg power were predictors of performance. Strength derived from a one repetition maximum measure of seated knee extension and recumbent leg press along with power derived from the speed to perform the strength tests predicted stair climbing ($R^2=0.50$), chair stand time ($R^2=0.24$), and tandem gait ($R^2=0.29$). Furthermore, leg power and leg strength were strongly correlated ($r=0.89$). Finally, in a 2008 National Institutes of Health (NIH) study on mobility limited elders, Reid et al. observed total lean leg mass and reduced muscle strength were significant predictors of activity limitation. The evidence that functional performance is related to muscle strength, furthers the need for
research to assess the ability to increase strength in populations with muscle wasting in an effort to improve their functional performance and quality of life.

**Preliminary Study Evidence of Strength Relation to Function**

We performed a cross-sectional pilot study to validate several strength and functional performance measures, in individuals with muscle wasting resulting from liver disease. (See Chapter 2) Besides demonstrating good construct validity for several of the strength and functional performance measures, the study discovered that increased liver disease severity was associated with decreased muscle strength. See Chapter 2 for specifics on the Preliminary study. Bridging was moderately related to the 6 Min Walk distance ($r=0.78$) and 30 Sec Chair Stand ($r=0.59$). Heel Rise was moderately related to 6 Min Walk ($r=0.74$) and 30 Sec Chair Stand ($r=0.57$). Grip Strength was mildly related to 30 Sec Chair stand ($r=0.40$). Our study was able to demonstrate significant evidence for relationships between muscle strength in the hands, forearms, hips, thighs, and calves with functional activities in the population with varying levels of liver disease severity and post-liver transplant.

**Exercise for Strengthening**

Liver disease muscle wasting has the potential to normalize post-liver transplantation. However it is possible the length of recovery time may be shortened by the implementation of targeted muscle strengthening programs. “Usual care” of patients post-transplantation involves slow advancement of activity and progressive walking exercise. Aerobic exercises such as walking and jogging, used in previous studies, affect
the endurance component of muscle, but do little to increase the strength component. As described previously, liver disease leads to catabolic metabolism which degrades muscle mass, impairs muscle protein synthesis, impairs gas exchange within muscle tissue, and impairs muscle lactate clearance. Post-liver transplantation, these impairments remain for a prolonged period of time if not indefinitely. Additionally, post transplant medications affect muscle physiology for energy production and muscle contraction.

Experts report the primary objective of a therapeutic exercise program is to maximize movement and function as activity becomes more complex. Increases in muscle strength and function require activation of larger motor units, changes in muscle fiber type, and increases in muscle mass through protein synthesis. These changes in muscle can only occur through targeted strengthening exercise.

Relative to skeletal muscle structure, strengthening exercise results in muscle fiber hypertrophy, and remodeling of fiber type composition. Neurologically, strengthening exercise increases motor unit recruitment, increases the rate of motor unit firing, and improves the synchronization of motor unit firing. Metabolically, however, strengthening exercise does not increase ATP or Phosphocreatine.

It is unknown if targeted strengthening exercise can improve the components of muscle responsible for increasing strength in this population. However, research by Horber et al. has shown that physical training can reverse corticosteroid induced muscle wasting and electron microscopy provides evidence that isokinetic training increased numbers of myofibrils, capillaries and mitochondria in thigh muscles of individuals on prednisone therapy post renal transplantation.
Strength training increases the muscles’ force as a result of neural adaptations and increase in muscle fiber recruitment. The muscle fiber hypertrophy resulting from strength training primarily occurs in Type II fibers. Therefore muscle strengthening exercises are ideal for individuals with liver disease related muscle wasting, as this population is reported to have atrophy of type II muscle fibers.

**Resistance Exercise for Strengthening**

The main goal of rehabilitation of individuals with wasting is to normalize lean body mass with the assumption that normalization of structure will lead to normalization of function. Resistance training is the main method for normalizing lean body mass and strength training in individuals with muscle wasting. The overload principle guides exercise prescription in resistance training. For muscle strength and function to improve, a load that exceeds the capacity of the muscle must be applied. The muscle must be consistently challenged to perform at a greater than normal level. In a resistance strengthening program the amount of resistance must be gradually and progressively increased to keep challenging the muscle.

Patients with muscle wasting conditions are capable of adhering to resistance and aerobic exercise training programs designed to increase their muscle mass and strength. Many of these individuals are weak and limited by endurance. However, even low to moderate intensity exercise is proven to be beneficial in these populations.

When designing a resistance program for individuals with wasting, much can be learned from the literature on exercise and resistance training in older adults. A primary focus of resistance exercise training prescription among the elderly is to stimulate muscle.
growth (hypertrophy) in an effort to counteract sarcopenia. Resistance training in older adults has been demonstrated to increase muscle mass, strength, and power, reduce the difficulty of performing daily tasks, enhances energy expenditure and body composition, and promotes spontaneous participation in physical activities. 71,94 Theses improvements are precisely the same goals necessary for individuals with chronic wasting diseases. Strength training is reported as the most effective way to restore lost muscle mass and strength in older people.68 Strength training improves bone health, insulin action, and increases overall level of physical activity. Low intensity strength training, as simple as using elastic bands, is beneficial for improving function. For example, resistance training with Theraband was demonstrated to increase gait velocity in healthy older adults.68

The literature on resistance training involving individuals with HIV and AIDS is can be utilized when designing a resistance program for individuals with muscle wasting and chronic disease. Short term, high intensity, progressive resistance training has been demonstrated to significantly increase lean body mass and strength in individuals with HIV muscle wasting.95

Research with pharmacological interventions and nutritional supplements have also demonstrated large increases in lean body mass with resultant increases in strength and function. Testosterone combined with resistance training is reported to synergistically increase strength and lean body mass in individuals with HIV related muscle wasting.27 Resistance exercise alone in individuals with HIV wasting increases lean body mass equal to administration of low doses of testosterone or anabolic steroids alone.62 Therefore, resistance training can be a substitute for pharmacological interventions that in some individuals may have significant unwanted side effects. Oral Testosterone would
not be appropriate in individuals with liver disease as the testosterone would need to be metabolized by the liver.

Agin et al. studied the effects of whey protein alone, resistance exercise alone, and whey protein and resistance exercise combined, on body cell mass, muscle strength, and quality of life in women with HIV. Whey protein alone promoted weight and fat gain with little effect on physical function and quality of life. Resistance training alone increased body cell mass, skeletal muscle, muscle strength, and quality of life leading to functional improvement. Coupling of whey protein and resistance exercise did not increase body cell mass greater than resistance exercise alone. However, because HIV wasting correlates with decreased food consumption, emphasis is placed on maintaining caloric intake. Resistance training results in loss of fat mass. Agin et al. report adding whey protein is essential to maintain energy dense fat mass stores to prevent catabolically consuming the newly acquired muscle mass for energy during the training.

Exercises that involve eccentric lengthening contractions elicit the most rapid and largest improvements in muscle strength and size. Eccentric strengthening is advantageous for protein synthesis and increasing lean body mass. Eccentric contractions produce microscopic tears in contractile protein muscle cells stimulating increased muscle protein turnover and prolonging the rate of protein degradation. Repeated eccentric contractions induce local accumulation of peptide growth factors, including insulin like growth factor, fibroblast growth factor, and platelet derived growth factor. These factors have been reported to increase satellite cell proliferation in vitro and increase whole body protein synthesis in vivo. These growth factors are released by macrophages and it is thought that the resultant muscle hypertrophy is related to the
inflammatory response to exercise induced muscle injury. Additionally, eccentric exercise decreases the body’s requirement of insulin for nearly two days. The increased amount of insulin in the blood results in increased muscle protein synthesis. In addition, insulin’s anabolic effect on skeletal muscle decreases the rate of muscle protein degradation, resulting in less muscle wasting.

Moore et al. observed an increased rate of myofibrillar protein synthesis after maximal eccentric lengthening contractions than shortening concentric contractions. Moore et al. found greater fuel use and increased oxygen consumption with maximal shortening contractions than lengthening contractions. This is important when prescribing strengthening exercise in chronic liver disease individuals with impaired fuel management.

Endurance exercise increases oxidation of essential amino acids and the requirement for dietary protein, however, resistance exercise results in a decrease in nitrogen excretion, and lowers dietary protein needs. Lowering the dietary protein needs through performance of resistance exercise, the loss of skeletal muscle mass decreases, further benefiting individuals with wasting diseases such as HIV infection, cancer, chronic renal failure, and especially sarcopenia in the elderly. Based on the evidence above, including eccentric strengthening and aerobic exercise into exercise prescription is necessary for individuals with protein catabolic wasting diseases.

There is no consensus on the optimal training program for individuals with muscle wasting. However, to maximize strength and muscle mass gains, endurance training should be limited to no more than three days a week. In a meta analysis on resistance training in older adults Hunter et al. reported that resistance load intensities should be 60
to 80 percent of an individual’s one repetition maximum; a volume of two to four sets of eight to fifteen repetitions per exercise is recommended; and each muscle group should be exercised two to three days per week along with low intensity high velocity contractions on one day to develop power. Galavo et al. report that low volume resistance training regimen is sufficient to significantly improve muscle function and physical performance in older persons. A single set of eight reps performed twice a week improves functional performance significantly. Overall, larger strength gains are observed with a higher volume (multi-set) training. However, individuals with chronic muscle wasting that cannot perform more than one set still have the potential for significant strength and functional improvements with a single set of resistance exercise per muscle group. Eventually progressing to a multi-set regimen will enhance physical reserve as strength improves. After endurance is improved, returning to a lower volume (single set) regimen for maintenance of muscle mass is recommended.

Both single set and multi-set exercise increases performance in activities requiring lower extremity strength and balance such as standing from a chair and stair climbing. Either regimen of resistance exercise is ideal for individuals with chronic liver disease because lower extremity strength is more affected than upper extremity strength in this population.

Research also supports the benefits of resistance exercise in the closely related wasting disease of end stage renal disease. Twelve weeks of resistance training increased peak quadriceps torque, six-minute walking distance, maximal walking speed, and performance on the sit to stand test. Physical therapists and other health professionals
can refer to the evidence on resistance exercise in other wasting diseases and develop an exercise prescription appropriate to the population with liver disease.

**Aerobic Walking versus Resistance Exercise**

Aerobic walking requires the use of musculature to move the legs and propel the body; however, there is minimal strengthening benefit from walking compared to resistance exercise.\(^\text{100,101}\) Individuals with liver disease that only perform aerobic walking show cardiovascular improvement, but strength and function are slow to return.\(^\text{9,11,25,102,103}\) In community dwelling older adults, Rooks et al. found resistance training significantly better than walking exercise for strength gain with results of a 65% increase in knee extension strength in the resistance trained subjects while there was a 6% loss of knee extension strength in those who only walked.\(^\text{100}\) Sarsan et al. examined aerobic exercise involving 15 minutes of brisk walking and additional stationary leg cycling exercise with resistance training of the quadriceps and gluteus medius leg muscles. Resistance exercise consisted of 10 repetitions at 40-60% of the subject’s maximum strength progressively over 12 weeks. Findings showed a statistically significant greater change in muscle strength for the resistance group.\(^\text{101}\) Additionally, Painter et al. performed a randomized trial of aerobic exercise training in individual’s status-post renal transplantation and found that muscle strength at 12 months of aerobic exercise remained lower than normal values, and they suggested that resistance training was needed to normalize muscle strength.\(^\text{104}\)
Response to Exercise in Liver Disease

Research by Weisinger et al. and Campillo et al. demonstrated that maximal exercise achieved by cirrhotic patients is lower than half that of healthy individuals.\(^9,^{40}\) The level of exercise individuals with cirrhosis can tolerate is unclear, however; maximal exercise has been demonstrated to be inversely related to liver disease severity.\(^{40}\) Individuals with less severe liver disease tolerate more activity, whereas, individuals with more severe liver disease tolerate only small amounts of activity.\(^{40}\)

Wong et al. observed that persons with cirrhosis, especially individuals with ascites, exercised for shorter periods and achieved lesser peak oxygen consumption compared to individuals without liver disease. Their decreased exercise capacity was thought to be a result of abnormal inotropic and chronotropic responses to exercise, due to abnormalities in the sympathetic activation of the myocardium.\(^{105}\) Impaired inotropy and chronotropy result in decreased stroke volume and submaximal heart rate response repectively. Ejection fraction is observed to remain unchanged from rest to exercise in individuals with liver disease.\(^{105}\) Grose believed the impairment in exercise capacity was primarily due to reduced oxygen delivery as a result of chronotropic dysfunction, based on observation of impaired chronotropy in 80 percent of the subjects with liver cirrhosis as they performed supine bicycling exercise.\(^{106}\)

Others believe that skeletal muscle dysfunction is the major limiting factor of exercise capacity, claiming skeletal muscle is unable to properly use the oxygen supplied.\(^7,^{49}\) Epstein found that two thirds of individuals with cirrhosis, without cardiopulmonary disease or other confounding factors, displayed significantly reduced aerobic capacity during exercise testing.\(^{49}\) The liver or other visceral organs do not limit
delivery of oxygen rich blood from reaching the contracting tissues. The splanchnic or visceral regions decrease their own blood flow nearly 80 percent during exercise to permit ample blood flow to contracting muscles.\textsuperscript{49} Therefore, if a myopathy exists, it involves abnormal peripheral oxygen utilization. Epstein found that ninety-five percent of subjects exercised beyond anaerobic threshold.\textsuperscript{49}

Peak oxygen consumption is more highly correlated with skeletal muscle mass than with hemoglobin in individuals with liver disease.\textsuperscript{7} If this is true, then interventions by physical therapists to improve skeletal muscle mass may increase an individual’s exercise capacity. Reduced exercise capacity is likely a result of both cardiac dysfunction and muscle dysfunction. Reduced oxygen delivery to exercising muscles resulting from abnormal stroke volume response and impaired skeletal muscle oxygen extraction, both contribute to exercise limitation.

**Post-Transplant Rehabilitation**

Rehabilitation for individuals post-liver transplant typically involves only the use of gradual progressive aerobic walking. There is no significant evidence to date of protocol directed performance of targeted muscle strengthening post-liver transplantation. The majority of individuals post-liver transplantation express a desire to do anything that would help them get back to their body function and activity levels prior to onset of their liver disease. Patients attending the post liver transplant clinic at the Miami Transplant Institute reported they would dedicate time for one walk a day if possible. However, most subjects reported they included their ambulation into their daily errands. No emphasis
was placed on distance or speed of their ambulation. For example one patient used the walk required from the time he exited the Jackson Memorial Hospital (JMH) Metrorail Station to the transplant clinic (approximately 300 meters) as his dedicated walk. He would come to clinic 1-2 days a week for blood work or to see a physician or nursing coordinator.

Barriers to Exercise to individuals with Liver Disease Pre and Post Transplant

A main barrier to improved activity performance in individuals with liver disease and other related muscle wasting diseases is that functional assessment is not routinely performed and physical activity recommendations are not provided as part of the routine care. Interventions such as physical therapy are implemented only after the patient becomes non-ambulatory, which is much too late. Another barrier to improvement is fear from the patient and family that physical exertion will make the condition worse, will make the individual tired and fatigued, or that physical activity is not appropriate for individuals with illness. Although patients are expected to increase their physical activity after transplantation, fear of damaging the new organ and the over protective attitude of family members and friends may discourage them from performing many activities.

Encouragement, along with proper education, is required to motivate patients with chronic disease to participate in physical activity and exercise. Painter reports that following organ transplantation, instructions from healthcare providers are frequently misinterpreted. Phrases such as, “Take it easy” and “Don’t over do it” are misinterpreted as a restriction to any strenuous activity. Individuals post-transplant do not know their
abilities and activity limitations. Once the individuals experience fatigue and general weakness they deem the activity as too strenuous. The healthcare provider often fails to addresses the concept of progressing activity rigor and as a result, physical activity is postponed. 64

Another barrier to functional improvement is the overall assumption by the health care providers and family that becoming physically inactive is unavoidable. The patients and families adopt low expectations for physical functioning. As a result, no attention is paid to body function, activity limitation, and participation restriction. No effort is provided to enroll patients in interventions to reverse the limitations and restrictions. 64 Individuals with cirrhosis should be encouraged to undertake a graduated exercise program. Walking, swimming, and biking have all demonstrated no deleterious effects.108,109 Subjects with chronic hepatitis demonstrated no abnormal change in liver function test values during and after a twelve week aerobic exercise program involving three to four 30 minute sessions of exercise per week; thus, no negative training effects on liver function were observed. 7,49,108,110 Ersoz measured hepatic portal vein blood flow in patients post-liver transplantation before starting and immediately after 40 minutes of treadmill running or walking for at least 20 minutes at 75% of maximal heart rate. As individuals exercise the blood flow normally shifts from the visceral organs to the peripheral muscles. However, the observed flow pattern of high inflow to the portal vein, due to arterial vasoconstriction in the visceral organs, combined with increased resistance in the new liver, not due to portal hypertension but due to the altered vascular system of the new liver organ, is thought to protect the liver from exercised induced low flow states. Based on these findings, Ersoz reports exercise and physical conditioning
should be recommended without hesitation for liver transplant recipients. In patients with hepatitis who performed 30 minutes of exercise weekly over a three month period, peak oxygen uptake increased and no negative effects on liver function were observed.

Exercise is considered safe to perform in patients with liver disease because circulation and oxygenation of vital tissues are maintained. During exercise in patients with liver cirrhosis, hepatosplanchnic blood flow reduces approximately 30 to 45 percent, allowing cerebral blood flow to increase maintaining cerebral oxygenation as well as muscle oxygenation as exercise intensity increased. Both cerebral and skeletal muscle oxygenation returned to pre exercise levels at rest.

Kujala summarized randomized controlled trials of exercise therapy in the treatment of chronic disease. He reported exercise capacity and muscle strength were consistently improved in patients with various chronic diseases without having any detrimental effects on disease progression. He reported complications were very rare and disease related symptoms were reduced in many chronic diseases such as osteoarthritis, asthma, and COPD. As previously mentioned, during exercise there is a shift in blood flow from the viscera to the exercising muscles due to splanchnic arterial vasoconstriction. Following liver transplantation, venous drainage problems and increased intrahepatic resistance may influence portal blood flow patterns; however, this flow pattern was unaffected protecting the liver from exercised induced low flow states. Ersoz reports exercise and physical conditioning should be recommended without hesitation for liver transplant recipients. Ritland et al. encouraged physical activity and training within tolerance and stated that prolonged bed rest should be avoided, reporting no deterioration occurred after moderate workloads in individuals with liver
cirrhosis.\textsuperscript{110} Strength training in other chronic diseases such as ESRD and HIV\textsuperscript{97} has also been documented to be safe. Evans et al. reports exercise increases nitrogen retention, and reduces the need for the kidneys to work hard, easily handling the nitrogen.\textsuperscript{97,113}

**Exercise Prescription and Recommendations**

Physical therapists must have an understanding of the cardiovascular, respiratory, and musculoskeletal changes associated with chronic liver disease before prescribing any form of exercise.\textsuperscript{6} Pre-transplantation exercise may slow the disease process, maintain functional capacity, and prevent loss of lean body mass, with the overall goal of sustaining independence until time of transplantation. Post-transplant exercise may counteract some of the pharmacological side effects, improve functional capacity, and reduce risk factors for secondary complications such as cardiovascular disease, and diabetes. Exercise prescription should begin as a generalized routine and be modified according to the individual’s impairments.\textsuperscript{21} Equally as important, before and after liver transplantation, exercise should not be implemented until nutrition is optimized to prevent further catabolism of muscle protein.

Patients with chronic liver disease are able to exercise at 60-70 percent of their heart rate maximum, 20-30 minutes, three times per week.\textsuperscript{6} Maximal training is inappropriate in patients with chronic liver disease with severe muscle wasting. It is recommended to work at 60 percent of the individual’s one repetition maximum to increase strength.\textsuperscript{6} Patients with chronic liver disease should avoid heavy weights and instead concentrate on low weight with high repetitions.\textsuperscript{7,64} The plan of care should
include stretching to maintain flexibility and a focus on functional specific activity exercises.  

Patients with alcoholic liver disease must be slowly progressed due to possible latent cardiomyopathy. However, all individuals with liver disease may have cardiovascular impairments as previously described. Blood pressure, heart rate, oxygen saturation, and physical exertion must be monitored before, during, and after exercise or physical activity for all individuals with or without alcoholic involvement. Also, patients should always perform an active cool down to improve lactate clearance. 

Individuals need to be educated to avoid performing a valsava maneuver, to prevent esophageal and gastric varices formation. Care must be taken when performing weightlifting and contact exercise due to increased risk of bleeding and bruising from coagulopathy.

Patients with liver disease will frequently complain of low back pain. This pain results from several factors: trunk muscle atrophy from bed rest and disuse, weak abdominal muscles stretched from ascites, incisions in the abdominal musculature during liver transplantation surgery, and poor posture from stooping to protect the wound. During transplant surgery, the large abdominal wound is closed by primary intention using stitches. Patients with ascites have poor posture due to displacement of their center of gravity anteriorly resulting in a hyper-extended lumbar spine. This poor posture leads to back pain that limits activity and desire to participate in exercise. Individuals with chronic liver disease must be educated on proper posture during exercise to help decrease pain and improve compliance. Abdominal exercises may begin with isometrics
and progress to concentric isotonic contractions once strength is developed to maintain proper technique.  

Additionally, individuals prescribing exercise must monitor for steroid induced diabetes, which occurs in approximately 30 percent of individuals after transplantation. Besides being a significant health issue, diabetes impairs tolerance to activity and exercise.

The American College of Sports Medicine has provided the following goals for aerobic and strength training of individuals after abdominal organ transplantation: 1) Reverse muscle wasting and weakness; 2) increase the maximal number of repetitions; 3) increase aerobic capacity; 4) increase work capacity; 5) improve blood pressure; 6) assist with weight management; and 7) reduce risk of secondary cardiovascular disease. These goals should be incorporated into the individual’s exercise prescription.

Krasnoff recommends several modifications to exercise programs based on complications frequently seen among individuals with end stage liver disease: 1) For individuals with ascites, therapists should make the individual comfortable by limiting exercises and positions that require abdominal musculature strength; 2) For individuals with portal hypertension and esophageal/gastric varices, it is important to stress proper breathing technique to avoid valsalva maneuver with resistance exercises and calisthenics; 3) Individuals with encephalopathy must always exercise with a partner; 4) Individuals with electrolyte imbalances must reduce their intensity of exercise to avoid dehydration; 5) Individuals with coagulopathies must reduce the intensity of training to avoid tearing of tissue, bruising, and injury resulting in bleeding; 6) Individuals with
infection must reduce the intensity of training to allow the body to fight off the infection.\textsuperscript{21}

Additionally for improved adherence to exercise programs, patients need education on drug effects resulting in fatigue. Furthermore, education must be provided on the best time of day to exercise based on their drug schedules.\textsuperscript{21} Encephalopathy must be taken into account when prescribing an exercise program. Encephalopathy will limit the individual’s ability to perform the exercise programs independently and effectively. These individuals will require more supervision and verbal cueing during exercise.\textsuperscript{6} Therefore, it is important to provide well-marked instructions and encourage exercising with supervision.

Frequently it is difficult to integrate an exercise program into an already complex and intensive medical schedule; however, exercise training provides the only chance to increase or at least maintain functional capacity. Overall, there are no specific standardized guidelines for exercise in most chronic diseases. Therefore, exercise prescription should be a common sense approach to recommending activity that is individualized and considers many factors including: symptoms, clinical status, medications, and treatments. A gradual increase in physical activity, working up to 30-minute sessions at an exertion level that is easily tolerated (symptom limited), is recommended.\textsuperscript{64,114}

**Rationale for Home Exercise Program vs. Outpatient Rehabilitation Program**

Individuals with end stage liver disease present with weakness and fatigue.\textsuperscript{115-117} It is reported that even after transplantation a significant percentage of individuals still
present with mobility and endurance impairments. Additionally, the polypharmacy of anti-rejection medications, blood pressure medications, and antibiotics also leads to reduced activity tolerance. For these reasons, individuals post-transplantation may better tolerate performing a home exercise program that is initially instructed by a physical therapist in the outpatient surgical clinic and monitored regularly by telephone. A home exercise program eliminates the energy expenditure required to commute to and from an outpatient rehabilitation center. The patient’s full energy can be directed to the performing the home exercise program thus increasing the potential benefits from exercise. Academic medical centers are the main site for liver transplant surgery. For example, the Miami Transplant Institute accepts candidates from all over the southern portion of Florida. Individuals living in the area margins may commute large distances. Individuals begin their day very early, wait long periods of time in the clinic, and then commute back home. The fatigue that results from this process impacts performance of their regular daily activities. Due to risks of traumatic injury to the abdomen from the steering wheel or airbag and the poly-pharmacy affecting cognition, vision, and reaction times, individuals post-transplant are not permitted to drive a car limiting their ability to make outpatient rehabilitation visits three to four days a week. Additionally, it is more manageable for individuals to perform a home exercise program around medication schedule than to have to additionally factor in travel time and time spent with healthcare staff.

Individuals can schedule their home exercise program around their daily routines and medication schedules to provide the maximal potential benefit from their exercise program. There is no significant evidence to show that home exercise is better than clinic
based exercise in the population post liver transplantation. However there is literature from the population post-renal transplantation, a similar muscle wasting disease process, which provides evidence that home exercise improves strength and health related quality of life.  

Mikesky et al. reports a home based exercise program using elastic tubing was beneficial to increasing strength in individuals over the age of 65. A 90% adherence rate for exercising 3 days a week at home was observed in this study with elderly subjects. The physical therapists at outpatient rehabilitation centers provide encouragement for the patients to perform extra repetitions, however, family members can be instructed on how to assist and provide the same encouragement. Outpatient rehab clinics are designed to provide the optimum equipment for strengthening and exercise. However, the strengthening program these individuals can perform due to impaired mobility and fatigue is minimal post-transplantation and going to rehab gyms and lifting heavy weights is not appropriate for their strength levels and their abdominal incision lifting restrictions. There is no literature on lifting restrictions post liver transplantation and surgeons follow the abdominal surgery restrictions of no lifting greater than 20-25 lbs for six weeks. Strengthening exercises using gravity and elastic bands for resistance can easily be performed at home sitting in a chair, lying on the bed, couch or floor, and standing and leaning against a door, wall or counter top. Therefore, a home exercise program is ideal for this population with liver disease muscle wasting post transplant.
Nutrition

As described earlier, individuals with liver disease catabolically consume muscle protein stores as a result of complete depletion of carbohydrates. A study measuring oxidation of fuels during an overnight fast showed the calorie requirements of individuals with liver cirrhosis were the same as healthy individuals, but the fuels oxidized were similar to those of healthy subjects after three days of starvation. Thus, appropriate nutrition is important for individuals with liver disease to avoid this state of starvation. Some individuals will have diet issues due to protein or fat restrictions. Liver damage predisposes individuals to hypoglycemia and altered lipid metabolism limiting energy availability during exercise.

Frequently, patients with cirrhosis retain sodium often leading to formation of ascites. In early stages of cirrhosis urinary sodium excretion is good. Therefore a negative salt balance is achieved through restricting sodium intake. Many of the sports-exercise drinks are high in sodium. Avoiding these drinks is recommended. Decreasing ascites reduces pressure on the intestinal tract, which can result in desired weight gain and increased serum albumin.

Kondrup reports the main reason for malnutrition in patients with liver cirrhosis is decreased dietary intake, impaired post-prandial glycogen storage, and increased protein requirement. Negative nitrogen balance and tissue catabolism induced by inadequate protein intake may further promote encephalopathy by increasing the brain contents of aromatic amino acids. Kondrup reports adding protein to dietary intake may help improve low-grade encephalopathy, and restricting diets of protein is based on the assumption that encephalopathy is associated with protein intolerance although no studies
support the idea that protein restrictions improve mental state. Patients should be encouraged to eat a balanced diet. Based on the evidence, neither adding nor restricting proteins is recommended.

**Summary of Preceding Conceptual Review**

Besides cardiopulmonary impairment, cognitive impairment, and nutritional impairments, chronic liver disease results in significant impairment in metabolism. The damage liver organ is unable to control the elevated metabolism and it catabolizes the muscle protein reservoir for energy production. The resulting hypermetabolic catabolic state results in several body structure and body function impairments of muscle tissue. These impairments include: muscle degradation, muscle atrophy, impaired muscle tissue oxygen extraction, impaired muscle lactate clearance, muscle weakness, and increased energy expenditure. The resultant muscle impairments lead to activity limitations; for example, the inability to get out of bed, stand from chairs, walk short distances, ascend / descend stairs, and to perform activities of daily living such as dressing and bathing without assistance. These activity limitations lead to decreased socialization and the inability to return to their work resulting in loss of employment affecting their lifestyles and their families.

Liver transplantation serves as a modality to increase chances of survival and improve quality of life. However, research has demonstrated that muscle wasting continues, strength and quality of life remains impaired, and many individuals do not return to employment post transplantation. Current “usual care” post-liver transplant includes only gradual progressive aerobic walking, but does not include rehabilitation of
lost muscle strength. Currently, there are no protocols for targeted muscle strengthening post-liver transplantation. Aerobic walking has demonstrated cardiovascular improvements, without significant improvements in muscle strength and function in individuals post-liver transplantation. Targeted resistance strengthening has been demonstrated to have a significantly greater effect on muscle strength and function than gradual progressive walking in healthy individuals.

**Evidence Based Practice for Increasing Strength and Function in Liver Disease**

Studies measuring maximal oxygen consumption, muscle strength (grip strength and quadriceps strength), functional performance (Six Minute Walk, Timed Up and Go) and quality of life in individuals with liver disease have been performed.\(^7,9,25,40,49,51,105,106,112,122\) Most studies have assessed these strength and functional measures in individuals with various forms of liver disease pre and post-liver transplantation to understand the population’s overall impairments and limitations. There is a dearth in the literature however, on how targeted strengthening exercise interventions impact strength, functional performance, and quality of life in individuals with liver disease pre and post-liver transplantation. There has been minimal research performed to assess how an aerobic exercise intervention improves strength, function and quality of life.\(^{103,123}\) Only one intervention study has been performed, by Krasnoff et al., a randomized trial of an aerobic home exercise program and dietary counseling, that has included subjects post-liver transplantation that did not include strengthening exercises.\(^{103}\) The study used the modality of cardiovascular exercise and observed improvements in exercise capacity but did not observe significant differences in
improvement in muscle strength from the group receiving the “usual” post-transplantation care. Cardiovascular exercise requires individuals to use leg musculature to advance the lower extremities to walk or run progressively longer distances and at faster rates. However, there is no targeted musculature strengthening component that increases muscle mass, alters muscle fiber type, and / or increases motor unit size resulting in a significant increase in muscular strength when performing cardiovascular exercise.

As mentioned previously, studies by Rooks et al. and Sarsan et al. have demonstrated minimal improvement in muscle strength through aerobic cardiovascular activities.\textsuperscript{100,101} To date, only one study reports of an exercise intervention that includes muscle strengthening in individuals post-liver transplantation. Beyer et al. performed an intervention study with patients who had undergone orthotopic liver transplantation from September 1993 to April 1995.\textsuperscript{25} The intervention involved warm up exercises, aerobics, and training for muscle strength, balance, and flexibility in patients three weeks post-liver transplantation. After discharge from the hospital, the patients were offered a one hour outpatient exercise program, twice a week, for six months and then issued a home exercise program they performed two to three times a week. They reported knee flexion and extension strength measured isokinetically increased 65\% and 125\%; functional performance of the Six Minute Walk increased 27\%; and the amount of time to perform a supine to stand transfer and three unsupported squats decreased 25\%.\textsuperscript{25} Beyer et al. report the main activities of these patients post-operative were cycling, swimming, aerobics, and jogging. These activities are all aerobic in nature. The initial three week inpatient exercise program and six month outpatient exercise program were performed by
the physical therapy department, and one must assume that some targeted muscle
strengthening activities were included, but the research report provides no evidence to
what specific exercises were performed to increase strength and function. No
information or descriptions were provided on the types of exercise used for strengthening
and what muscles were targeted. No information was provided on how the researchers
prescribed or advanced the patient’s exercise load and intensity.

In summary, individuals with liver disease are subject to impairments in muscle
strength as a result of catabolic protein malnutrition. Liver transplantation promotes
survival but does not return individuals to pre-liver disease states of health. Current
“usual care” post-liver transplantation manages individuals medically without attention
to functional recovery. Decreased muscle strength is a major limiting factor to functional
activity. If muscle strength can be improved then functional activity may be performed
more easily and more frequently, resulting in improved quality of life.

The purpose of the primary study was to determine whether implementation of a home
exercise program of resistance exercise targeted to the lower extremities would improve
lower extremity muscle strength and increase the ability to perform functional activities
required by the lower extremities more than the “usual care” of progressive gradual
walking in individuals post-liver transplantation.

The dissertation includes a preliminary study designed to evaluate measures of
lower extremity muscle strength, activity limitation, and quality of life for their validity
to use in the population with chronic liver disease pre and post-liver transplantation. (See
Chapter 2)
Chapter three pertains to the primary study involving a randomized clinical trial of resistance exercise for muscle strengthening and evaluated by the measures validated in chapter two. The hypotheses to follow pertain only to the primary intervention study.

**Specific Aims and Hypotheses**

*Specific Aim 1:* Compare the effectiveness of Resistance Strengthening to Usual care ambulation in rehabilitation post liver transplantation.

*Hypothesis 1:* Subjects who receive a resistance strengthening home program, targeted at the lower extremity musculature, guided by a physical therapist, will increase strength and improve functional performance more than subjects who receive the normal post-liver transplant recovery program of progressive walking and increased activity.

*Hypothesis 2:* Subjects in the exercise group who performed the exercise program on average at least 50% of the time would demonstrate greater improvement than subjects who were less compliant.

*Hypothesis 3:* Strength will be positively correlated with increased function for subjects in the exercise group and for subjects in the control group.

*Specific Aim 2:* To examine the characteristics of subjects who demonstrated improvements in strength and function.
Specific Aim 3: To investigate what are the baseline characteristics of subjects who are compliant with the exercise program.

Methods

Study Design

The primary study was a prospective, randomized, non-blinded, repeated measures clinical trial. Institutional Review Board approval was received in October 2007. The first subjects enrolled in December 2007. The study was completed October 2009, two years later.

Subjects who agreed to participate were randomized into either the targeted strengthening intervention or the usual care progressive walking intervention for twelve weeks. A medical chart review was performed to find the following information: age, height, weight, past medical history, current medications, and their prognostic indicator for survival the model for endstage liver disease (MELD) score prior to transplant. Blood was drawn by the nurses and medical technicians at the clinic while the subjects were waiting to see the physician. The laboratory data was collected at baseline and at each liver clinic visit included: liver function, renal function; and blood levels of the anti-rejection medication Medrol.

Prior to the first strength or functional testing procedure and throughout the entire testing process, the subjects documented their current level of fatigue using the Stanford Visual Numeric Scale. The scale is a visual bar scale ranging from zero to ten, with the higher score indicating more fatigue. This information was used to ensure that the subjects were at their baseline level of fatigue prior to each strength and performance test.
Each performance test may result in increased fatigue. Since these tests are sensitive to fatigue it was necessary to have the subjects at their baseline level to prevent erroneous testing results. For safety, the individuals vital signs (heart rate and blood pressure) were monitored before and periodically throughout the testing process through radial pulse palpation and brachial artery arterial pressure using a sphygmomanometer.

Strength impairment and activity limitation measurements were recorded at baseline when the subjects entered the study and every four weeks thereafter over the twelve week period. Subjects were contacted by telephone follow up every couple of weeks and/or when they returned to the liver transplant outpatient clinic to see their surgeon.

Sampling Method and Recruitment

A convenience sample was recruited from patients attending the Miami Transplant Institute Post-Liver Transplant Clinic in the Highland Park Building on the Medical Campus of the University of Miami Miller School of Medicine and Jackson Memorial Health System.

A list of daily attendees to the post liver transplant clinic, including their diagnosis and transplant dates were provided to the physical therapist researcher. After selecting the appropriate candidates, the researcher approached the clinic nurse coordinator and inquired about their medical clearance to participate in the study. Once medically cleared, the physical therapist researcher would then present the project to each patient. If the patient was interested, the researcher further assessed the potential participant for eligibility according to the inclusion criteria. If these criteria were met, the
patient was invited to participate. Upon voluntary written consent, the patient was included in the study.

Subjects retention was facilitated through weekly telephone calls to the patient’s home phone or cellphone to assess adherence and encourage continued participation. When subjects individuals returned to the liver transplant clinic for regularly scheduled follow-up visits they were further encouraged to adhere to the study. Retraining and direction of the patient’s exercise program was performed during the clinic visit to maintain motivation and ensure proper performance of each exercise.

**Inclusion and Exclusion Criteria**

To participate in the study, subjects must have undergone liver transplant a minimum of 6 weeks prior to a maximum of 12 weeks prior to enrolling. The subjects liver disease that resulted in the liver transplant could be of any origin other than cancer. Hepatocellular Carcinoma (HCC) is the primary cancer of the liver and a major cause of cancer related death. In 2002 the United Network for Organ Sharing (UNOS) initiated the Model for End Stage Liver Disease (MELD) score to assist prioritization of individuals on the Liver Transplant List. Individuals with higher scores based on serum bilirubin, creatinine, and the international normalized ratio (INR) for prothrombin are given higher priority for transplantation. Recently revised in March 2005, individuals with stage II HCC are made priority over other patients on the liver transplant list through assignment of a higher exception MELD score of 22 points. The shorter time period the individuals remain on the transplantation list the less muscle wasting they develop and do not represent the typical patient population with liver cirrhosis awaiting
transplantation. Subjects had to be ambulatory without physical assistance but were permitted to use a cane or walker. Individuals are excluded if they used a wheelchair as their primary mode of mobility. Individuals with liver disease due to alcoholism must have abstained from alcohol greater than six months prior to their transplant and remain abstinent.

Because chemotherapy and radiation affect muscle fibers along with endurance, individuals were excluded from the study if they had cancer or were currently being treated for cancer of any origin. Individuals with significant cardiomyopathy, or other cardiopulmonary disease unrelated to those impairments of endurance and oxygen consumption resulting from liver disease were excluded. Individuals with significant osteoarthritis or other orthopedic injury that actively affected the lower extremities ability to ambulate or perform exercise were excluded. Individuals with neurological/neuromuscular disorders including Cerebral Vascular Accident, Parkinson’s disease, Alzheimer’s disease, Dementia unrelated to hepatic encephalopathy, Dystonia, Multiple Sclerosis, and Polio were excluded. Individuals who were blind and individuals who were not able to comprehend the English or Spanish language were excluded.

*Stratified Blocked Randomization*

Randomized assignment to condition was used to make the groups comparable at baseline. After participant inclusion, a stratified blocked randomization was used. Two strata were included: Well individuals (Mild) post-transplant and Less Well (Severe) individuals. Laboratory values from liver function studies, post-transplantation complications, and input from the transplant team (nurse coordinators and surgeons)
helped direct to which stratum each subject was placed. Patients with elevated values for liver enzyme studies and recent post transplant admissions to the hospital for infection, rejection, or other medical related cause resulted in subject placement in the Less Well (Severe) stratum. An investigator who was not involved in testing or consenting subjects was responsible for randomization. Randomization for each stratum was performed in blocks of six with three subjects assigned to the strengthening group and three to the walking group. Once consented, subjects were classified as “Mild” or “Severe” and assigned a stratum specific id number. The randomization assignment envelope corresponding to the id number was opened and subjects were assigned to either the Exercise or Walking Group.

**Blinding**

Blinding was not possible in this study. Subjects were aware of the intervention they were receiving. To control for the affect of attention, subjects assigned to the usual care comparison group received a pedometer and a daily walking log to track ambulation step counts and frequency, and received weekly phone calls identical to the intervention group. These three procedures provided an image to the control group that they were equally involved in the study and were receiving an intervention. The rater was not blinded and this was another limitation of the study design that will be discussed further in a later chapter. The investigator instructing the subjects on their home exercise program was also the sole rater collecting data during the measurement of strength impairment and activity limitation.
**Targeted Resistive Strengthening Exercise Intervention**

The intervention performed by the experimental group was a program of resistance strengthening exercises targeting the lower extremity musculature. Four specific muscle groups were targeted as those groups are responsible for performing functional activities such as rising from a chair, ambulating, and ascending stairs. The muscle groups included: Ankle Plantar flexors (Gastrocnemius and Soleus), Knee Extensors (Quadriceps), Hip Adductors (Gluteus Medius, Minimus, and Tensor Fascia Lata), and Hip Extensors (Gluteus Maximus, Lumbar Erector Spinae, and the Biceps Femoris). Resistance was supplied in the form of simple anti-gravity positioning and the use of Theraband® elastic resistance bands. Resistance was progressed from simple gravity eliminated positioning to antigravity positioning to the lightest level of Theraband® elastic resistance band (Yellow) gradually to more resistive Theraband® elastic bands as tolerated (Red, Green, and Blue). The Theraband® elastic band provides more resistance as the bands elongate. For example: the lightest resistive Theraband® (Yellow) provides 2.9 pounds of resistance when elongated to 100% of its length and 5.8 pounds when elongated 250%. The medium resistance Theraband® (Blue) provides 7.1 pounds of resistance when elongated to 100% of its length and 13.3 pounds when elongated 250%.

Subjects were instructed to progress to the next greater level of resistance when they were able to easily perform 10 repetitions of the exercise movement on the last of three sets without significant fatigue or loss of proper form. Emphasis was placed on the eccentric lowering portion of the muscle contraction during each repetition. To prevent injury to the abdominal surgical site emphasis was placed on
proper form with good trunk stabilization during the exercise. The subject’s trunk was stabilized during each exercise by the bed, couch, chair backrest, or the wall. Trunk stabilization directed resistance to the lower extremity musculature, decreasing any stress placed on the abdomen.

Subjects progressed through twenty exercises targeted at specific lower extremity musculature. Table 1 lists each muscle group, the exercises for that grouping, and the specific muscles targeted. See Appendix I for the exercise booklet providing pictures and verbal description of how to perform each exercise. See Appendix III for the algorithm on progression of exercises in each muscle group. Both the exercise booklet and algorithm were provided to each participant in the experimental intervention group. Subjects logged what exercises they performed each day, how many sets and repetitions of each exercise performed, and the date exercise was performed. (See Appendix V)

In addition to strengthening exercises, the intervention group performed their “Usual Care” of progressive ambulation and activity. Subjects were provided a pedometer which measured the total number of steps taken during their walking activities to monitor how much walking they performed. Subjects were instructed to wear the pedometer on their right hip aligned with the middle of their patella at the height of their umbilicus. Pedometers were worn for all designated walking exercise. The subjects documented the steps taken for each walk in a weekly walking log. (See Appendix VII)

Usual Care (Control) Group

These subjects did not receive any strengthening exercises. These individuals only received the “Usual Care” of progressive ambulation and activity instructions post-
transplant. Subjects were also provided a pedometer which measured the total number of steps taken during their walking activities to monitor how much walking they performed. Subjects were instructed to wear the pedometer on their right hip aligned with the middle of their patella at the height of their umbilicus. The subjects documented the steps taken for each walk in a weekly walking log. Subjects in the control group received the same frequency of weekly telephone and or liver clinic visit contact as the experimental strengthening group.

**Rationale for Intervention**

The main goal of rehabilitation of individuals with muscle wasting is to normalize lean body mass with the assumption that once the body structure is regained body function will return. Resistance training is the main method for normalizing lean body mass and strength training in individuals with muscle wasting. When designing a resistance program for individuals with muscle wasting, much can be learned from the literature on exercise and resistance training in older adults. Resistance training in older adults has demonstrated to markedly increase muscle mass, strength, power, and body composition. Energy expenditure is more efficient, activities of daily living are performed with increased ease, and individuals participate more easily in spontaneous physical activity. Improvements demonstrated in older adults with resistance training are precisely the same goals of resistance training necessary for individuals with chronic wasting diseases.

Research supports the benefits of resistance exercise in the closely related wasting disease of end stage renal disease. Twelve weeks of resistance training increased peak
quadriceps torque, six-minute walking distance, maximal walking speed, and performance on the sit to stand test.65

Our study used Theraband® elastic resistance bands to provide resistance for strengthening simulating the resistance of exercise gym equipment. A major advantage of the elastic band resistance for individuals with muscle wasting disease is the bands can be easily used for exercises within their own home. There are no moving parts or heavy weights to lift and risk injury. These individuals with liver disease have risks of bleeding and dropping weights or pinching fingers can lead to significant complications. The subjects were instructed to concentrically shorten and eccentrically lengthen musculature against the resistance of the Theraband® in postures that stabilized the trunk against the bed or couch, the back of a chair, or a wall to prevent stressful forces near the surgical abdominal incisions. The positions of exercise focused the strengthening on specific (targeted) muscles of the lower extremities only. Resistance training using Theraband® elastic resistance bands has been demonstrated to increase gait velocity in healthy older adults, a population of individuals with similar muscle wasting and frailty that limits their safety during strengthening exercise with traditional weightlifting equipment.68

Muscle strengthening involves a muscle shortening or “concentric” component and a muscle lengthening or “eccentric” component as the limb is moved through the exercise. Our study emphasized the eccentric lengthening component. The subjects were instructed to maintain the force of contraction and slowly release the resistance band to its starting length rather than relaxing immediately after the shortening concentric contraction. Eccentric strengthening is advantageous for protein synthesis and increasing lean body mass. Eccentric contractions produce microscopic tears in contractile protein
muscle cells stimulating increased muscle protein turnover and prolonging the rate of protein degradation.\textsuperscript{97} Repetitive eccentric contractions induce local accumulation of peptide growth factors, including insulin like growth factor, fibroblast growth factor, and platelet derived growth factor. These factors have been reported to increase satellite cell proliferation in vitro and increase whole body protein synthesis in vivo.\textsuperscript{97} These growth factors are released by macrophages and there is belief that the resultant muscle hypertrophy is related to the inflammatory response to exercise induced muscle injury.\textsuperscript{97} Additionally, eccentric exercise decreases the body’s requirement of insulin for nearly two days. The increased amount of insulin in the blood results in increased muscle protein synthesis. In addition, insulin’s anabolic effect on skeletal muscle decreases the rate of muscle protein degradation, resulting in less muscle wasting.\textsuperscript{97} Emphasis was placed on the eccentric portion of the contraction during resistance training specifically for these reasons.

The ICF model relates body impairments to activity limitations.\textsuperscript{76} Impairment in muscular strength is related to limitations in activities such as transfers and ambulation.\textsuperscript{79,80,83,85} The muscle groups targeted in the intervention are specific to the activities of sit to stand transfers, and ambulation. Bassey observed leg extensor strength was related to stair climbing, chair rising, and walking speed.\textsuperscript{79} Bohannon observed knee extension strength to be moderately correlated with sit to stand activity.\textsuperscript{81} Therefore resistance strengthening exercise targeted at these muscle groups should improve the activities of standing and walking.
Intensity and Duration of Strengthening Program

Individuals performed at minimum one exercise from each of the four targeted muscle groupings at a frequency of every other day. This provided the subject three to four days a week to exercise. For example: Monday, Wednesday, Friday, and Saturday. One day of rest is required between days of muscle strengthening exercise. The day of rest permits rebuilding of microscopic muscle tears promoting increased muscle size and strength through protein synthesis.

Each individual exercise was performed for up to ten repetitions and repeated for up to three sets each session. The American College of Sports Medicine’s current guidelines are to use an exercise load that results in fatigue after 6 to 12 repetitions for 2-3 sets with a rest period of two minutes was taken between each set. The entire strengthening exercise routine required only 25-30 minutes to perform, including rest periods. This recommended frequency is supported by research stating that the majority of patients with chronic liver disease are able to exercise at 60-70 percent of their heart rate maximum, 20-30 minutes, three times per week.

Each grouping of exercises was designed to progress from minimal muscle effort required to moderate to maximal effort. Subjects were directed to progress from one exercise to the next based on the algorithm and frequent guidance from the physical therapist researcher. Subjects were not to progress to the next more advanced exercise in each muscle group until the subject was able to easily and comfortably perform 3 sets of 10 repetitions of that exercise.

In addition to the strengthening program, subjects in the experimental group performed progressive walking activity daily using the same instructions they would
received as part of their usual post-transplant care. The frequency, cadence, and distance of ambulation were solely determined by the participant. The researcher had no input into the usual care walking other than to provide a pedometer to monitor walking steps. The information within the subject’s daily logs from both the control and experimental groups permitted monitoring of adherence to walking interventions and monitoring of strengthening exercise program progression.

Outcome Measures

Demographic and Clinical Characteristics

Demographic data was collected on the first assessment. These included: age, gender, height, weight, smoking history, employment, number of weeks post transplant, and whether the participants currently exercised.

Laboratory

Individuals received their normal standard of care during each clinic visit with the nurses and physicians. One of the standard evaluations performed by the clinic is laboratory blood analysis to monitor general health and liver status. Some of these laboratory values were included in our data collection in order to compare the results from subjects in the experimental and control groups. Results of the Comprehensive Metabolic Panel (CMP), which is a combination of fourteen different items from electrolytes to liver enzymes, were documented. The items of the CMP includes in our data were: Albumin, Total Protein, Creatinine, Alkaline phosphatase (ALP), Alalnine Amino Transferase (ALT), Aspartine Amino Transferase (AST), and Bilirubin.
Additionally the blood levels of immunosuppressant medications Prograf and Medrol were documented. Research demonstrates that immunosuppressants can affect muscle which can impact the ability to strengthen and increase functional ability in this population.24,89

The information obtained from the laboratory blood analysis was used to examine whether resistance strengthening exercise increased liver function levels (a sign of liver stress and damage) and to observe if subjects on higher levels of steroid (Medrol) had decreased gains in strength than those subjects that were off steroids or on lesser prescribed levels.

*Liver Disease Severity Measures (Child-Pugh / MELD)*

Albumin is the most abundant circulating protein and produced only by the liver. A decrease in albumin has a major impact on metabolism, tissue fluid distribution, nutrition, and transport of substrates.126 Deteriorating hepatic function results in decreased serum albumin, increased serum bilirubin and INR / prothrombin times.5 The lab values albumin, bilirubin and INR / prothrombin times, along with assessment of encephalopathy and ascites make up the clinical and biochemical markers used by Child and Pugh to classify liver disease severity. Child first developed the liver classification system in 1964, and Pugh modified the system in 1973 adding prolongation of prothrombin time and omitting assessment of body nutrition.127 The Child-Pugh score originally was developed to predict mortality during surgery and is now used to assess prognosis of chronic liver disease.127 Scoring makes use of weighting; one, two, or three points are scored for increasing abnormality of each of the five parameters. Patients with good hepatic function have scores of 5 or less. Individuals with poor hepatic
function score up to 15 points. Scores totaling 5-6 points are classified "A", scores of 7-9 points are classified “B” (moderate severity), and scores greater than or equal to 10 are assigned a classification "C" (most severe). Individuals with Child class A cirrhosis may survive as long as 15 to 20 years, whereas those with Child class C cirrhosis may survive only one to three years. The Child–Pugh disease severity measure was used in the preliminary measurement validation study discussed in Chapter 2.

A more recently developed prognostic model, the Model for End-Stage Liver Disease (MELD) is currently used as a short term predictor (3 month mortality) in individuals awaiting liver transplant. Currently, organ allocation for liver transplantation is entirely based on the MELD score. Both the Child-Pugh and the MELD models are reliable for measuring the risk of mortality in patients with end-stage liver disease and are suitable for use as disease severity index; however, the Child-Pugh system has more discrete cut offs to move from one classification to the next. These discrete cutoffs allow more efficient comparisons of functional limitations and performance between liver disease severity classes. The MELD was shown to be less correlated with quality of life than the Child-Pugh Classification system in Liver Transplant candidates when measured by general and disease specific questionnaires. The MELD excludes ascites and encephalopathy and Saab et al. found encephalopathy and ascitics to be important factors when measuring quality of life.

Because the Miami Institute liver transplant clinic currently does not calculate a Child-Pugh score prior to transplant, only the MELD was available for data analysis in the primary study. The Child-Pugh score cannot be calculated in retrospect as it is impossible to score the levels of ascites and encephalopathy retrospectively. Future
research in this area would benefit from pre-transplant Child-Pugh calculation as the discrete levels of disease severity are beneficial to research and understanding in this population.

**Impairment (Strength) Measures**

The ICF defines impairments as loss in body structure and function.\textsuperscript{75,76} Liver disease results in significant loss of muscle mass, muscle fiber, and changes in muscle physiology; all forms of body structure.\textsuperscript{26,28,29,31,33,40,41} This loss in body structure results in a loss of body function (muscle strength). The muscles of the lower extremity, specifically the hip extensors and knee extensors, are very important to transfers and ambulation.\textsuperscript{79-81,83} The strength impairment measures used in this research are functional in nature. For example, individuals perform a heel rise to elevate their body to reach higher or bridge to perform scooting in bed or don clothes. These same muscles are used for standing from a chair and for ambulating. Because body function is related to body structure then body function measures can be used to assess body structure.

Measures of strength such as Manual Muscle Testing and Hand Held Dynamometry have been demonstrated to be reliable in various populations.\textsuperscript{130-132} However, these measures were found to be unreliable with discrepancies between raters and especially on grades below fair.\textsuperscript{133,134} Manual muscle testing may not be able to discern between small incremental differences in strength.\textsuperscript{130} Techniques to assess manual muscle strength differ between raters based on how they were trained, reducing reproducibility.\textsuperscript{133} Hand Held dynamometers are most reliable when strength is greater than fair.\textsuperscript{130} Some individuals with chronic liver disease become very weak and the hand
held dynamometer would not be able to accurately measure their strength. Also, hand held dynamometry is limited if the rater cannot stabilize the instrument or resist the subject. Because of these limitations in reliability and reproducibility we chose to use more functional based measures that were minimally impacted by the rater.

Heel-Rise Test

Lunsford and Perry recommend the standing heel-rise test be the clinical method of choice for evaluating ankle plantar-flexor function. The heel rise test was shown to be highly reliable with an ICC>0.90. Leiato et al. tested plantar flexor strength with the Perry (Heel Rise) test in pre-liver transplant individuals and data from our unpublished pilot study (See Chapter 2) on individuals with liver disease confirmed the Heel-Rise Test is a valid measure to use in individuals across all levels of Child Pugh liver disease severity including individuals post-liver transplant.

To perform the Heel-Rise test, subjects stood on their dominant leg only and raise their non-dominant leg in the air. Subjects rose up on the toes of the dominant leg and then back down until the foot was flat on the floor to the rate of a metronome. The maximum height the heel rose from the floor was observed. The total number of repetitions that the subject performed until he/she could not raise the heel at least 50% of the height of the initial heel-rise was recorded.
Bridging

The Bridge test is a measure of body function similar to the Heel Rise Test. The hip extensors perform a functional movement that requires muscle strength. By performing a functional movement we can measure body structure which the ICF relates to body function.

The Bridging Test is performed in supine on a plinth. The subjects bent their knees bilaterally so their feet were flat on the plinth with arms by their side. The subject’s were asked to lift their buttocks off the mat as high as they could. The height the buttocks cleared the plinth was recorded. The subjects bridged as many times as possible to the rate of a metronome. The number of bridges were recorded until the subjects could no longer rise greater than 50% of the height of their initial bridge.

This follows the same format of the Heel-Rise test for measuring ankle planter flexion strength. This information functionally reflects proximal lower extremity strength, primarily the hip extensor musculature. To date no published research has used bridging as a measurement tool, however data from our unpublished preliminary research...
on individuals with liver disease (see Chapter 2) demonstrated the Bridge Test is valid to use in individuals across all levels of liver disease severity and in individuals post-liver transplant.

![Bridging Test](image)

Fig. 1.2 Bridging Test

**Activity Limitation Measures**

**Six-Minute Walk Test**

The ICF describes activity limitations as difficulty in successfully performing usual activities. Walking, standing from a chair, transferring in and out of a car, and ascending and descending stairs are some examples of activities. Body structure and Body function are highly correlated with activity limitations. Individuals with impairments in body structure and function demonstrate limitations in activity.\(^{75,136}\)

Therefore by measuring the activity limitations of an individual we are able to make judgments about the individual’s body structure and body function. Some measures of body structure and function such as dual x-ray absorptiometry (DEXA), Magnetic Resonance Imaging (MRI), and isokinetic dynamometry can be very invasive and expensive. Using clinic based activity limitation measures is inexpensive and can
provide quick feedback on the patient’s body structure and function to the healthcare team.

The Six Minute Walk Test (6MWT) is an easy to use clinic based activity limitation measure. Originally the 6MWT was developed to be a prognostic indicator in individuals with cardiopulmonary disease with the assumption there was no impact of muscle strength impairment. Individuals with chronic liver disease, as previously described, have significant muscle strength impairment along with muscle endurance impairment.

Walking performance has many influences. Several of these include: muscle strength, health status, cognition, balance, sensory and perception, motor control, motivation, activity level, and the environment. Lord et al. found lower limb strength to be a major predictor of 6MWT performance in older adults. Bassey et al. also significantly correlated leg extension power with walking time in elderly individuals. Based on the theoretical construct that chronic liver disease results in significant muscle structure and muscle function impairment, and that activity of walking is related to muscle structure and function, we are implementing the activity limitation measure 6MWT as an assessment of muscle structure and function in this study population. The 6MWT has previously been used in several studies with individuals with liver disease post-liver transplant. Six Minute Walking distances were measured as mildly to severely limited in 82 percent of the subjects.

The American Thoracic Society reports the 6MWT test is a beneficial measure of functional capacity before and after surgical intervention for assessing response to interventions in individuals with pulmonary and cardiac disease. It has been shown to
be reliable and valid in individuals with pulmonary disease, lung transplantation, renal disease, and the elderly; all having similar disease processes and impairments as individuals with liver disease.\textsuperscript{144,145} The 6MWT was also found to have excellent test-retest reliability in older adults.\textsuperscript{146} Data from our unpublished preliminary study on individuals with liver disease demonstrated the 6MWT was a valid test to use in individuals across all levels of liver disease severity and in individuals post-liver transplant. (See Chapter 2)

To perform the 6MWT individuals walk back and forth along a 100 foot (30.5 meter) distance. The distance the subject walked over a timed period of six minutes was recorded. In a long straight hallway the subjects walked back and forth between two cones marking a 100ft.(30.5m) distance, as many times as they could in a timed period of six minutes. The subjects had the option to rest at any time during the six minutes. The clock was continuously running whether the subjects were walking or resting. The subjects were provided standardized cues to prevent unequal encouragement. The distance walked over six minutes was recorded. Once the test was completed, the subjects were permitted to rest and cool down.

\textit{30-Second Chair-Stand Test}

Individuals perform the activity of transferring from sit to stand multiple times from multiple surfaces (chairs, beds, sofas) throughout the day. This activity requires lower limb muscle strength. Similar to walking activity, evidence demonstrates that transferring sit to stand requires multiple sensorimotor parameters such as visual contrast sensitivity, lower limb proprioception, tactile sensitivity, foot reaction time, postural
sway, and body weight.\textsuperscript{147,148} Individuals with chronic liver disease demonstrate significant muscle wasting. Bean et al. observed muscle strength to be a predictor of chair-stand time.\textsuperscript{80} Based on the theoretical construct that chronic liver disease results in significant muscle structure and muscle function impairment, and that activity of transferring sit to stand is related to muscle structure and function, we implemented the 30 Second Chair Stand as an assessment of activity limitation related to muscle structure and function in this study population.

Sit to stand tests can be measured as the amount of time it takes to perform a given number of repetitions or the amount of repetitions performed over a given amount of time (10 or 30 seconds).\textsuperscript{149} McCarthy et al. observed a strong correlation between the 5-repetition chair stand test (the amount of time to perform 5 repetitions) and the 30-Second Chair-Stand test (the number of repetitions performed in 30 seconds).\textsuperscript{148} Bohannon reported measurements of time were more precise than counts of repetitions. Weak individuals may not be able to complete the required number of repetitions and therefore the total number of repetitions over a period of time would be more appropriate.\textsuperscript{149} Our study involved individuals with significant weakness; therefore, the measurement method of repetitions over time (30-Second Chair Stand) was used. To perform the 30-Sec Chair Stand the subjects come to a complete stand position from a straight-backed chair and then returns to a complete sitting position as rapidly as possible. The number of times the subject performed the complete stand and return to sitting in a timed period of thirty seconds was recorded.

To date there is no published data on the reliability and validity of the 30-Second Chair Stand in this population post-liver transplantation. Data from our unpublished
preliminary study (see Chapter 2) demonstrated the 30-Second Chair Stand test is valid for individuals across all levels of liver disease severity and in individuals post-liver transplant. Good test-retest reliability of the sit to stand test (ICC=0.84) has also been reported in renal transplant candidates. 81,149

Ideally the test should be performed with a consistent chair height. The chair back should be placed against a wall for stability. The upper extremities should not be used to assist standing. Individuals may be instructed to fold their arms across their chest to prevent use of their arms.149

Fig. 1.3 30 Second Chair Stand Test

_Pedometer Step Count_

Walking distances each subject performed at home for their usual care progressive ambulation was measured through tabulation of total step count for each walk. The Accusplit Eagle AE120XL pedometer, the American distributed version of the Japanese made spring-levered pedometer the Yamax Digiwalker SW200, was used to
measure the total number of steps. The Yamax pedometer has been found to be very
reliable and accurate and used repeatedly in research studies.150-153 Pedometers are an
easy to use, inexpensive, and objective measure of physical activity.152 Worn at the
subject’s waistline, pedometers respond to vertical accelerations of the hip during gait
cycles.152 Horvath et al. determined the most accurate pedometer position is the left mid
axillary position for right leg dominant individuals. This position was recommended for
individuals with slower walking speeds, such as those recovering from liver
transplantation and for intervention studies.125 Furthermore, Horvath reports that the left
mid axillary position reduces step count error levels for the Yamax spring-levered
pedometer as low as expensive piezoelectric pedometers, challenging Crouter’s findings
that piezoelectric pedometers are more accurate in obese and overweight individuals than
the Yamax.125,150 Additionally, pedometer determined physical activity has been shown
to be strongly related to the functional performance measure Six Minute Walk Test
(r=0.69)154 Subjects were asked to zero the pedometer before each walk and record the
number of steps taken at the end of each walk. The total numbers of steps were used
compare the amount of walking the exercise group performed to that of the usual care
walking group.

Quality of Life Measures

Quality of life is a combination of physical functioning and psychosocial factors.
Improvements in any of these factors may result in improved quality of life.155
Individuals with chronic liver disease have significant physical impairments related to
muscle wasting which may impact quality of life. The ICF theoretical model states body
structure and body function impairments are related to activity limitations and participation restrictions. Quality of life is impacted by activity limitations and participation restrictions. Through measurement of these activity limitations and participative restrictions by quality of life measures we can make judgements on body structure and function.

Short Form 36

The Short Form 36 (SF-36), one of the most widely used quality of life measures today, is a generic measure of health status designed for use in clinical practice and research, evaluation of health policy, and general population surveys. This 36-item self report survey measures eight concepts (subscales): 1) Physical functioning, 2) Role limitations due to Physical health problems, 3) Bodily pain, 4) General health, 5) Vitality (energy/fatigue), 6) Social functioning, 7) Role limitations due to Emotional problems, and 8) mental health (psychological distress and psychological well-being). The scales of the SF-36 are summarized into two components: Physical Health and Mental Health. Each component has some overlapping of subscales. The subscale scores, component scores, and total score are calculated using a mathematical formula. The subscale scores and component scores are typically used for analysis rather than the total score. For all three scores (subscale, component, and total scores) the lower scores indicate greater impairment. Higher scores indicate lesser impairment. Five scales (Physical Function, Role Physical, Bodily Pain, Social Functioning, and Role Emotional) are graded with higher scores when reports of absence of limitations only. Whereas, three scales (General Health, Vitality, and Mental Health), measure a broad range of positive
and negative responses of health status. Reports of no limitations only provide scores at the middle of the scoring range; however, positive responses of health status, greater than reports of no limitations, results in higher scores for these three scales of the SF-36.

The Physical Function subscale pertains to the performance of all types of physical activities from light to heavy and contains the following items: Vigorous activities such as running, lifting heavy objects, participating in strenuous sports; Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf; Lifting or carrying groceries; Climbing several flights of stairs; Climbing one flight of stairs; Bending, kneeling, or stooping; Walking more than a mile; Walking several blocks; Walking one block; and Bathing or dressing yourself. All the items in the Physical Function subscale pertain to activity limitations. The Role Physical subscale pertains to the “performance of work or other daily activities due to physical health” and contains the following items: Cutting down the amount of time you spend on other activities; Accomplishing less than you would like; Limited in the kind of work or other activities; and Having difficulty performing work or other activities (for example, taking extra effort). The Role Physical subscale items more represent participation restrictions. Through assessment of the Physical Function and Role Physical subscales we can measure activity limitations and participation restrictions and therefore be able to make conclusions on body structure and function, specifically of muscle. An advantage to using the SF-36 is the large volume of normative data in the United States and other countries that has been collected and published and can be used for comparison of well and diseased individuals.
The Vitality subscale items represent energy level and fatigue: “Did you feel full of pep?”, “Did you have lots of energy?”, “Did you feel worn out?”, “Did you feel worn out?”.

The General Health subscale evaluates personal health from the range of excellent to poor and likely to get worse: “I seem to get sick easier than other people”, “I am as healthy as anybody I know”, “I expect my health to get worse”, “My health is excellent”.

The Mental Health subscale items evaluate psychological health ranging from feelings of nervousness and depression to feelings of peace, happiness, and calmness: “Have you been a nervous person?”, “Have you felt calm and peaceful?”, “Have you felt down and blue?”, “Have you been a happy person?”.

The SF-36 has previously been used in research with individuals with liver disease. Wiesinger et al. observed the SF-36 Role physical subscale was significantly correlated with Child-Pugh liver disease severity levels. In a study comparing quality of life measures in individuals with chronic liver disease, the SF-36 was shown to be reliable and performed better than other measures such as the Sickness Impact Profile, the EuroQol instrument, the Liver Disease Symptom Index, and the Multidimensional Fatigue Inventory. Ware states the SF-36 has good test-retest reliability. Additionally, Johansen et al. observed the SF-36 to have good test-retest reliability and to be valid for use in individuals with end-stage renal disease; supporting the reliability in a similar chronic organ disease that also cause hypermetabolism and catabolic muscle wasting. Furthermore, the SF-36 has demonstrated to be a predictor of morbidity and mortality in patients with renal disease. The SF-36 complements other clinical outcomes, such as the Child-Pugh liver severity class, liver enzyme indicators,
histological stage, and mortality rates, helping to integrate biomedical and psychosocial models of health. As with any outcome measure, the SF-36 has limitations. Parker et al. report the SF-36 should not be used with older patients acutely ill in the acute hospital setting due to poor completion rates.

This dissertation study involved an exercise intervention and the SF-36 has demonstrated the ability to detect significant differences in health status between individuals with renal disease that underwent an exercise intervention and those that did not. Despite the development of several liver disease specific questionnaires, the SF-36 continues to be used in recent research studies involving: assessment of HRQOL, strength, function, and lean body mass in individuals 2 months to 24 months post-liver transplant, and in subjects status post Transjugular Intrahepatic Portal-Systemic Shunting.

In patients with renal disease awaiting kidney transplant, the SF-36 demonstrated good internal consistency (alpha =0.91, 95% CI). Even with reported high ceiling effects for the Role Emotional score, Gomez-Besterio concluded the SF-36 is a reliable and valid instrument to use in individuals with renal disease awaiting kidney transplant and is a good measure for use in research and clinical practice. Our intervention study used the new Version 2.0 of the SF-36 questionnaire due to its “substantially reduced” ceiling and floor effects and the improved internal consistency reliability from the original Version 1.0. (See Appendix IX)
Chronic Liver Disease Questionnaire

The Chronic Liver Disease Questionnaire (CLDQ) was the first published disease specific HRQL instrument designed for patients with chronic liver disease.\textsuperscript{156,167} (See Appendix XI) The CLDQ is the only measure that has been evaluated for use with all types of liver disease including both pre and post liver transplantation.\textsuperscript{167,168} Developed by Younossi et al., the CLDQ consists of 29 items divided into six domains: 1) Abdominal Symptoms 2) Activity: eating habits and movement of heavy objects 3) Emotional Function: measures mood and insomnia 4) Fatigue: perception of decreased energy and sleepiness 5) Systemic Symptoms, and 6) Worry: concerns regarding disease progression and family. The summary score for each domain ranges from 1 (most impairment) to 7 (least impairment).\textsuperscript{162} All items refer to the previous 2 weeks. Similar to the generic SF-36, lower CLDQ scores indicate more impairment. Higher scores indicate less impairment. The Fatigue and systemic subscales relate to body function and structure. The Activity subscale best represents activity limitations. Through assessment of the Activity, Fatigue, and Systemic subscales we can make conclusions of body structure and function.

Younossi et al. reported the CLDQ to have good test-retest reliability and cross sectional validity; and documented that the CLDQ is sensitive to all levels of liver disease severity and all types of liver disease making it a good measure for clinical based research.\textsuperscript{169} The CLDQ and SF-36 can complement clinical outcomes, such as the Child-Pugh liver severity class, liver enzyme indicators, histological stage, and mortality rates. Child-Pugh Class liver disease severity was determined to be a predictor of the
Ferrer et al. found that the Spanish version of the CLDQ is a theoretically equivalent measure to the English version. The Spanish version is valid and reliable and demonstrated high specificity with minimal ceiling and floor effects. The primary language of several subjects was Spanish; therefore we used the Spanish version for these individuals. Some individuals were bilingual, having the ability to speak, read, and comprehend both Spanish and English. For individuals who only spoke Spanish, they were instructed for testing and for the interventions by an individual from the clinic that was fluent in Spanish.

**Data Analysis**

*Hypothesis 1:* Repeated Measures Analysis of Variance was used to determine if there were differences between the control (walking) group and the experimental (strengthening) group for strength and performance. Group effects, time effects and group-time interaction was assessed using the strength impairment variables: Heel-Rise and Bridging; the activity limitation variables: 30-Second Chair-Stand and Six-Minute Walk; and the Quality of Life Measures: SF-36 and Chronic Liver Disease Questionnaire.

*Hypothesis 2:* Repeated Measures Analysis of Variance to determine if subjects in the exercise group who performed the strengthening program on average at least 50% of the time demonstrated greater improvement than subjects who were less compliant.
Hypothesis 3: To answer the question if increases in strength shown by subjects in experimental (strengthening) group were related to their increases functional performance, Spearman Correlation Analysis was performed using the Strength variables: Heel-Rise and Bridging; the Functional Performance variables: 30-Second Chair-Stand and Six-Minute Walk; and the Quality of Life Measures: SF-36 and Chronic Liver Disease Questionnaire.

Baseline Characteristic Relationships

To determine the baseline characteristics of the subjects who demonstrated improvements in strength and function; and to determine what were the baseline characteristics of subjects who were compliant with the exercise program, descriptive statistics of frequencies and means and Spearman Correlations were be performed using the following variables: Time in weeks post-transplantation, age, gender, pre-transplant MELD score, length of time with liver disease prior to transplant, ascites, albumin level, liver enzymes: bilirubin, AST, ALT, and GGTP, history of hepatits B or C, history of Diabetes Mellitus, smoking history, alcohol history, anti-rejection medication (Medrol), and performance of regular exercise prior to beginning this intervention study.

Compliance Definition

Individuals in the experimental group who performed the strengthening exercise program 50% of the time or more were considered compliant. Individuals who performed the exercise program less than 50% of the time were considered non-compliant. Subjects were instructed to exercise every other day in the intervention group,
resulting in exercising three to four days a week for twelve weeks. If individuals exercised one day or less a week and/or only exercised half of the total amount of weeks they were in the study they were considered non-compliant. Compliance was determined through each individual's exercise log or verbal report of their activity. Individuals in the control group who performed their progressive daily walking 50% of the time or more were considered compliant. Individuals who performed their progressive daily walking less than 50% of the time were considered non-compliant. This cutoff at 50% has been used in a recent randomized trial study by Krasnoff et al. in involving aerobic exercise in individuals post liver transplantation. Individuals in the intervention group and control group were to progressively walk every day, as part of their “usual care”. Individuals that walked less than three days a week or less than half of the weeks they were involved in the study they were considered noncompliant. Compliance was determined through each individual's walking log or verbal report of their activity.

**Sample Size**

Sample size was estimated for a Student's t-test comparing the exercise and walking groups on the pre-post change scores. The calculation was based on study a large effect size \(d = 0.70\). Based on an Alpha level equal to 0.05, 26 subjects were required in each group to obtain a power level of 0.80.
Severe muscle wasting or protein-energy malnutrition is a major problem in individuals with liver disease, affecting as many as eighty percent of individuals with liver cirrhosis. Muscle wasting is not obvious in many individuals with liver disease because fluid weight gain masks the loss of lean tissue. Loss of muscle mass is associated with poorer prognosis in individuals with liver disease who do not receive a transplant. In individuals who do receive a transplant, an additional ten percent of the body’s protein stores continue to be degraded for energy up to nine months after transplantation and this loss results in further impairments in strength, activity performance, fatigue, and quality of life for many months to years. One examination of quality of life post-liver transplant reported ninety-three percent of participants believed their tolerance to activity was limited before transplantation. Both before and after liver transplantation, impaired activity tolerance results in limitations in homemaking, working, going to school, walking several blocks, climbing stairs, and cooking, resulting in participation restrictions on social life, seeing friends, sex life, hobbies, sports, and going on vacations.

Patients treated for liver disease are traditionally assessed for pathology and physiology through laboratory tests, radiology, palpation, and auscultation. Few patients are assessed for the strength impairments and activity limitations that result from muscle loss associated with liver disease. Understanding the relationships among strength impairment and activity limitation and measuring changes in these relationships requires
reliable and valid measures. Reliability and validity must be established for a specific population and a specific purpose.

The International Classification of Functioning, Disability, and Health (ICF) model of disablement can be used to understand the negative impact of liver disease on body structure, body function, activity, and participation. The ICF describes impairments as “problems in body structure and function such as a significant deviation or loss”. Activity limitations are defined as “difficulties an individual may have in executing activities”. Participation restrictions are “problems an individual may experience in involvement in life situations”. The ICF model of disablement is easily applied to an individual with end stage liver disease. Liver organ damage due to virus, cirrhosis, inflammation, or other process can result in impaired liver functions such as altered metabolism of proteins, toxins and steroid hormones and these impairments may lead to impaired muscle strength and endurance. Impaired strength and endurance can produce limitations performing activities such as grasping or lifting objects, standing up from a low surface, or ambulating even household distances, dressing or bathing, opening jars or cleaning the house. Ultimately body function impairment and activity limitations result in participation restrictions such as decreased socialization and loss of employment. The ability to accurately measure the strength impairments and activity limitations common in individuals with liver disease will help health care providers identify these problems and assess the effectiveness of interventions directed at correcting the impairments and restoring activity performance.

Several studies have measured impairments and activity limitations in individuals with liver disease; however, few studies have validated the measures.
across the levels of liver disease severity.\textsuperscript{3,9} The purpose of this study was to examine the construct validity of a set of impairment and activity limitation measures that can be implemented in the clinic environment and are easily performed by individuals with varying levels of liver disease. Construct validity reflects the ability of an instrument to measure an abstract concept or construct that is not directly measurable.\textsuperscript{178} Constructs are defined using theories based on assumptions of how a phenomenon will behave under given conditions.\textsuperscript{178} Under the assumption that the impairments and activity limitations associated with liver disease will worsen as the liver disease progresses, we proposed to test the validity of the impairment and activity limitation measures by testing whether they differed across the levels of liver disease severity.

Liver disease produces muscle wasting and weakness. The severity of the muscle wasting and weakness is related to the severity of liver disease. Therefore, if strength (impairment) measures are valid for measuring changes in strength in individuals with liver disease, then they should be able to identify differences in strength among the groups of subjects assigned to different Child-Pugh categories. Similarly, activity limitations experienced by individuals with liver disease are related to muscle wasting and weakness that is subsequently related to the severity of their liver disease. Therefore, if activity limitation measures are valid for measuring changes in activity limitations in individuals with liver disease, then they should be able to differentiate differences in activity limitations among the groups of subjects assigned to different Child-Pugh disease severity categories.

Based on the ICF Disablement Model, there are theoretical relationships among, disease severity, impairments, and activity limitations. Therefore, if the impairment and
activity limitation measures are valid, they should be able to demonstrate these relationships. We proposed to examine the validity of these instruments by testing the theoretical relationships among disease severity, impairments and activity limitations.

**Patients and Methods**

Subjects were recruited from the University of Miami Transplant Institute outpatient liver clinic. Subjects were eligible for the study if they were male or female, between the ages of 18 and 65, had liver disease of any origin other than cancer, and were able to ambulate without physical assistance. Exclusion criteria included severe cardiomyopathy; severe osteoarthritis; blindness; wheelchair bound individuals; and individuals with neurological / neuromuscular disorders including but not limited to cerebral vascular accident, Parkinsonism, Alzheimer’s disease, dystonia, multiple sclerosis, and polio.

All subjects meeting the inclusion criteria signed a written informed consent of the University of Miami Institutional Review Board prior to entrance into the research study. Demographic data and medical history were obtained through direct interview and medical chart review.

**Measures**

A battery of six measures of strength and activity performance was performed on each subject during one testing session. Prior to beginning testing and throughout the entire process, the individuals current level of fatigue was measured using the Stanford Fatigue Visual Numeric Scale. 179 (See Appendix XIII) Because the outcome measures
being validated were potentially affected by fatigue, the Fatigue Scale was used to ensure the individuals were at or near their baseline fatigue level prior to performing each test.

*Disease Severity*

The Child-Pugh classification was used as the measure of disease severity in this study. In individuals with liver disease, serum albumin falls, serum bilirubin rises, and the International Normalized Ratio (INR) / Prothrombin Time increases as liver disease worsens and hepatic function deteriorates. These lab values in conjunction with evaluation of encephalopathy and ascites make up the clinical and biochemical markers used by the Child-Pugh classification system of liver disease severity. (Table 2.1) Child first developed the liver classification system in 1964, and Pugh modified the system in 1973. The Child-Pugh score originally was developed to predict mortality during surgery and is now used to assess prognosis of chronic liver disease. This classification uses a system of weighting: one, two, or three points are scored for increasing abnormality of each of the five parameters. Patients with good hepatic function have scores of 5 or less. Patients with poor hepatic function may score up to 15 points. Scores totaling 5-6 points are classified “A” (mild severity), scores of 7-9 points are classified “B” (moderate severity), and scores greater than or equal to 10 are assigned a classification "C" (most severe). The Child-Pugh liver disease severity measure is a valid predictor of mortality in patients with end-stage liver disease and is a preferred measure in clinical trials research for its discrete levels of disease severity classification. Hepatologists at the liver clinic calculated the Child-Pugh classification for each pre-liver transplant
subject included in the study. For data analysis post transplant status was combined with Child-Pugh classification to create a Childs-Pugh ordinal variable representing liver disease severity where “C-P A”=1, “Post Transplant”=2, “CP-B”=3 and “CP-C”=4. We placed individuals Post liver transplantation between “CP-A” and “CP-B’ on this ordinal scale because individuals return to more normal levels of metabolism, energy expenditure, and protein synthesis post transplant thus increasing the potential for muscle mass and strength improvements.

In addition, encephalopathy resolves resulting in improved eating habits and nutrition. Despite these physiological improvements strength and activity performance remain impaired. The length of time post-transplantation of patients in our study ranged from 6 months to 9.9 years. Only a few patients in the 6-12 month range post transplant still presented with minimal hyper-metabolic effects.

**Strength Impairment Measures**

**Bridging**

Bridging was used as a functional measure of proximal lower extremity strength, primarily the hip extensor musculature. Activities such as standing from chairs and ambulating have been demonstrated to be related to hip extension strength. To perform the test, subjects were positioned in supine, arms by their sides, both knees bent, and feet flat on the plinth. The subjects extended their hips towards the ceiling as high as possible. The maximum height the buttocks cleared the plinth was marked on a ruler. (Fig 2.1) The total number of bridges performed were recorded until the subjects could
no longer rise greater than 50% of the height of the maximal bridge. The greater the number of bridge repetitions indicates greater hip extensor muscle strength.

**Heel-Rise**

Heel-rise was used as a measure of distal lower extremity strength. Individuals perform a heel rise (ankle plantar flexion) to elevate their body to reach higher into cabinets and for propulsion during ambulation. The heel rise test has been shown to be highly reliable with an ICC>0.90. Leiato et al. tested plantar flexor strength with the Perry (Heel Rise) test in pre-liver transplant individuals. For this test, while standing only on their dominant leg, the subjects rose up on their toes and then back down until the foot was flat on the floor. The maximum height the heel rose from the floor was marked on a ruler. (Fig 2.2) The subject performed heel-rises until they were not able to perform at least 50% of the height of the initial heel-rise. Rather than assign grades of normal, fair, or poor, we recorded the total number of heel rises performed. The greater the number of heel rise repetitions indicates greater plantar flexor muscle strength.

**Grip Strength**

Grip strength was used as a measure of distal upper extremity strength. Grip strength is important for functional independence because it is required for almost all activities of daily living. In addition, grip strength has been shown to be a predictor of disability in the elderly. A Jamar adjustable handle dynamometer was used as it is considered the gold standard for measurement of grip strength. The American Society of Hand Therapists suggests using the second handle position to increase
reliability of measurement.\textsuperscript{45,180} High inter-rater reliability and test-retest reliability using the Jamar dynamometer has been shown.\textsuperscript{182,183} The highest intra-class correlations were obtained when the mean score of three trials was used.\textsuperscript{182,183} In this study, the subjects were positioned in the American Society of Hand Therapists recommended measurement position: seated with their shoulders adducted and neutrally rotated, elbow flexed at ninety degrees, and forearm and wrist in neutral. Subjects squeezed a Jamar adjustable handle dynamometer as hard as they could for a count of three seconds. Three trials were performed with one minute rest between each trial. The average of the three trial was used in data analysis.

\textit{Activity Limitation Measures}

\textit{Transfers: 30-Second Chair-Stand}

The 30-second Chair Stand was used as a measure of performance of sit to stand transfers.\textsuperscript{85} The ability to rise from a seated position and then return to the seated position is a critical component of many daily activities including getting out of bed, getting on and off the toilet, getting in and out of a car and getting up and down from a chair. To perform the test, subjects began seated in a straight back chair, came to a complete stand without the assistance of their arms and then returned to a complete sitting position as rapidly as possible. The number of times the subjects stood up from a straight-back chair in 30 seconds was recorded. A Ryobi stop watch was used to monitor the duration of the test. The greater the number of chair-stand repetitions indicates the lesser the activity limitation.
Mobility: Six-Minute Walk

The Six-Minute walk test (6MWT) was used as a measure of mobility limitation. This test measures the distance walked in six minutes which is related to functional mobility inside the home and in the community. The 6MWT has been shown to be reliable and valid in individuals with pulmonary disease, lung transplantation, renal disease, and the elderly, all pathologies with similar muscle wasting and impairments as individuals with liver disease. Excellent test-retest reliability is reported in studies on older adults. Studies found the 6MWT was better tolerated by patients with respiratory disease than the 12-Minute Walk test and more accurately reflected the endurance required to perform activities of daily living than did the Two-Minute Walk test. In this study, the 6MWT test was administered by having subjects walk 100 ft. (30.5m) distance in a straight hallway back and forth, as many times as possible in six minutes. The subject had the option to rest at any time during the six minutes. The clock was kept running whether the subject was walking or resting. Standardized cues were provided to prevent unequal encouragement. The total distance walked over six minutes was recorded. This protocol was based on the American Thoracic Society guidelines.

Physical Activities: Short Form 36 (SF-36)

The Physical Function subscale on the SF-36 was used to measure activity limitations. The SF-36 is a generic health related quality of life instrument measuring eight concepts (subscales): Physical Functioning; Role Limitations due to physical health problems; Bodily pain; General Health; Vitality; Social Functioning; Role Limitations due to emotional problems; and Mental Health. In this study we only used the Physical
Function subscale. The Physical Function subscale addressed limitations in the ability to perform a variety of physical activities from light to heavy and contains the following items: Vigorous activities such as running, lifting heavy objects, participating in strenuous sports; Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf; Lifting or carrying groceries; Climbing several flights of stairs; Climbing one flight of stairs; Bending, kneeling, or stooping; Walking more than a mile; Walking several blocks; Walking one block; and Bathing or dressing yourself. Lower scores on the SF-36 sub-scales indicate greater limitations.

Data Analysis

All statistics were calculated using PC SAS Version 9.1.3. One-way analysis of variance followed by Tukey post-hoc tests were calculated to test whether significant differences in impairments (grip strength, heel rise, and bridging) and activity limitations (6MWT, 30-Second Chair-Stand, and SF-36 physical function subscale) existed among known Child-Pugh classes (groups) of liver disease severity. Spearman correlations were used to examine the relationships among liver disease severity (Child-Pugh variable), impairment measures (grip strength, heel rise, and bridging) and the activity limitation measures (6MWT, 30-Second Chair-Stand, and SF-36 physical function subscale).

Results

Thirty-two patients were included in the study. Twenty had chronic liver disease and twelve were post-liver transplant. A total of 62% of patients were female, and patient’s mean age was 58.3 years [standard deviation (SD) = 7.5]. Of the total sample,
6% had Child-Pugh Class A cirrhosis, 25% had Child-Pugh Class B cirrhosis, 31% had Child-Pugh Class C cirrhosis, and 38% were Post-Liver Transplant. Table 2.2 presents these characteristics by severity of liver disease.

*Differences among Disease Severity Groups*

Overall, there were statistically significant differences among the disease severity classification groups for all of the strength impairment measures of Grip Strength, Heel-Rise, and Bridging. However, post-hoc testing revealed that not all of the severity groups differed from each other. In general, the most severe CP-C group differed from some or all of the other groups. (Table 2.3)

There were also overall differences among the Child-Pugh severity groups for all of the activity limitation measures except the SF-36 Physical Function subscale. There were a substantial differences in mean 6MWT and 30-second chair-stand scores among the severity groups with the greatest differences occurring between the CP-C and both the CP-A and Post-Transplant groups. In contrast, mean scores on the Physical Function subscale were very similar for the post transplant, CP-B and CP-C groups. The score for the CP-A group was substantially higher than that for the other groups, but this difference did not achieve statistical significance.

*Relationships among Disease Severity, Impairment and Activity Limitation Measures*

Liver disease severity as measured by the Child-Pugh variable was moderately correlated with the strength impairment measures Bridging and Heel Rising but was not
correlated with Grip strength. Liver disease severity was moderately correlated with the activity limitation measures 6MWT and 30-Second Chair-Stand but was not significantly correlated to the SF-36 physical function scale. Strength impairment measures were strongly correlated with the activity limitation measures. Both Heel Rising and Bridging strongly correlated with 30-Second Chair-Standing and 6MWT distance. Grip strength moderately correlated with 30-Second Chair-Standing. These results support our second assumption that valid measures should follow the theoretical relationships of the ICF disablement model in that individuals with more severe liver disease should have greater strength impairments and activity limitations. Table 2.4 presents the correlations among Child-Pugh variable liver disease severity, strength impairment measures, and activity limitation measures.

**Discussion**

**Validity of Strength Measures**

Our study demonstrated that scores on the tests (Heel Rise, Bridging, Grip strength) meant to reflect the severity of the muscle wasting and weakness observed in patients with liver disease were related to the severity of their liver disease. The assumption that strength impairments worsen as liver disease progresses was demonstrated in that the measures were able to differentiate differences in strength impairments and activity limitations among the levels of disease severity described using the Child-Pugh variable. Additionally our assumption that valid measures should demonstrate the theoretical relationships between disease severity, strength, and activity limitation was supported by the significant correlations among liver disease severity,
strength impairment, and activity limitation measures. Results suggested that proximal lower extremity strength as measured by bridging was more strongly related to disease severity than was upper extremity strength. Although grip strength differed significantly different between Child Pugh liver disease severity groups Child-Pugh A and Child-Pugh C, it was weakly or not at all correlated with liver disease severity and the majority of the impairment and activity limitation measures. Our findings correspond with reports by Franssen et al. and of studies on other chronic organ diseases such as chronic obstructive pulmonary disease, congestive heart failure, and chronic renal failure demonstrating more profound proximal muscle weakness in the lower extremities compared to the upper extremities.\textsuperscript{18,45} The modest difference we found in grip strength among known groups may be due to the continual use of the hands and forearms for almost all our daily activities. Individuals with end stage liver disease still use their hands even if limited to sitting and wheelchair mobility. However, our results are similar to the findings of Abbott et al., who reported that grip strength is lower in patients with Child-Pugh class C liver disease severity.\textsuperscript{42} Our findings contrast those of Wiesinger et al. who found a significant correlation between hand grip strength and Child-Pugh liver classifications \((r = -.45, p =0.019)\) among patients on a liver transplant waiting list.\textsuperscript{9} Abbot et al. found grip strength to be lower in Child-Pugh classes B and C.\textsuperscript{42} Our observations of muscle wasting in the shoulder girdle and upper arm would imply muscle strength is impaired proximally in the upper extremity. Further studies are recommended to examine the validity of measures of proximal upper extremity strength.
Our findings suggest that the strength impairment measures (Grip Strength, Heel-Rise, and Bridging) are valid for use in the specific population of individuals with chronic liver disease pre and post-liver transplant.

**Validity of Activity Limitation Measures**

Our study demonstrated that scores on the tests (6MWT and 30-Second Chair-Stand) are valid measures of the severity of activity limitations observed in patients with liver disease in that our findings supported the assumption that activity limitations worsen as liver disease progresses. The measures were able to differentiate severity of activity limitations among the levels of the Child-Pugh liver disease severity variable. Additionally we were able to demonstrate the theoretical relationships between disease severity, muscle strength, and activity limitation. The relationship between lower extremity muscle strength and activity limitation has been demonstrated in many populations. It was reported as the main factor limiting ability to rise from a chair in weak elderly individuals and Bohannon demonstrated a relationship between knee extension strength and ability to stand up from a chair. Our study was able to demonstrate similar relationships in individuals with liver disease in that the 30-Second Chair-Stand test was with the strength of the plantar flexors (Heel Rise) and hip extensors (Bridging).

Stockton recommended the 6MWT test as a safe measure for determining an exercise prescription in individuals with chronic liver disease. The ability to examine the relationship between muscle weakness and activity limitation can help clinicians prescribe exercise. Alameri et al. demonstrated the 6MWT correlated with the Child-
Pugh Liver disease classification when assessing functional capacity of individuals with chronic Hepatitis B, C and those with liver cirrhosis.\textsuperscript{187} Our study supports the findings of Alameri et al. as we observed correlations between the 6MWT and liver disease severity measured by Child-Pugh classification.

The SF-36 Physical function scores were not different across the levels of liver disease severity in our study. These results are similar to the findings of Younossi et al. that some of the subscales, specifically the vitality and mental health scales, of the SF-36 did not show changes with deterioration due to disease severity.\textsuperscript{3} However our findings are different from Wiesinger et al. who demonstrated physical function subscale scores declined as Child-Pugh liver disease severity increased.\textsuperscript{9}

There are many outcome measures available to measure strength, activity performance, and health related quality of life; however, many are not appropriate for use in individuals with liver disease in the in-patient or out-patient clinical setting. Although dynamometer computer systems (Cybex 6000 and Biodex II) have been used to measure muscle strength and peak torque in individuals across the levels of liver disease severity and in individuals post-transplant.\textsuperscript{9,102} such systems are both large and expensive. In addition these studies only measured quadriceps strength. Chandler was able to demonstrate that quadriceps strength gains in older adults were significantly associated with improved chair rise ability, gait, stooping, and stair climbing using isokinetic dynamometers.\textsuperscript{83} However, these functional activities also require hip extension and ankle strength neither of which was measured.\textsuperscript{79,80} Individuals with endstage liver disease frequently have large ascetic abdomens and edematous lower extremities making it difficult or impossible to use isokinetic machines to measure hip extension. The
measures examined in this study, Heel Rising, Bridging, Grip Strength, 30 Second Chair Stand, and 6MWT required minimal equipment and can be easily performed bedside or in an outpatient clinic.

Leitao et al. ran a similar battery of clinical based easy to use impairment level and activity limitation measures in a study on individuals with liver disease. The impairment measures included: MMT for assessing quadriceps muscle and the Perry test for assessing plantar flexor muscle strength. The activity limitation measures included: gait velocity over ten meters, the Six-Minute Walk test; the Timed Up and Go Test (TUG), and the Karnofsky Index. This study found quadriceps strength of less than fair in 32% of the subjects; reduced ambulation speed in 66% of the population; mildly to severely compromised Six-Minute Walk distances in 82% of the subjects; and 44% of the patients needed considerable assistance based on the Karnofsky index. Although this study demonstrated changes in strength and activity level in patients with liver disease; it did not examine the relationships among disease severity, strength and activity limitations.

There were only two patients in the liver disease severity level Child-Pugh A in our sample. Most individuals classified as Child-Pugh A present with minimal disease related symptoms and may be followed by a Hepatologist but not typically followed by a liver transplantation service as there liver disease has not reached the severity requiring treatment by transplantation. Therefore, the available pool of individuals with Child-Pugh A level of liver disease severity from which to recruit was very small. However; despite only two subjects in the Child-Pugh A severity level, we were still able to achieve statistically significant results.
Limitations

During the data collection sessions, there were multiple tests performed in a short period of time. Fatigue can impact muscle strength and performance. The Fatigue Visual Numeric was used to determine which individuals needed more time to recover between tests, however this was based on the patient’s subjective reports not their actual physical fatigue measurement.\textsuperscript{179} The testing was performed after individuals had already been examined by their physicians. Some individuals may have reported less fatigue to complete their testing in a shorter period of time to be able to leave the transplant clinic sooner.

This study used several impairment and activity limitation measurements to indirectly assess strength impairment for hip extensor, knee extensor, and ankle plantar flexor musculature. Such indirect measures are useful because many individuals with chronic liver disease cannot perform the traditional one repetition maximal strength test. Although these indirect measures do not provide strength estimates for individual muscle groups, previous studies have demonstrated a strong relationship between the indirect strength measures and lower extremity strength measured by more traditional means.\textsuperscript{79,80,84,85,135} Therefore, we feel comfortable that these indirect measures valid indicators of lower extremity strength.

The SF-36 surveys used were English language versions only. There were several patients with native languages other than English. These patients may have responded inaccurately due to differences in translation, and it is possible that this contributed to weak or non-existent relationship between SF-36 Physical Function sub-scale and other strength and activity limitation measures.
We did not control for length of time post-transplantation patients were tested. Of the twelve patients post-transplant, only one was less than one year post-transplant and could still be in the hypermetabolic state. The mean post-transplant time for the other eleven patients was 5.5 years suggesting the patients were back to a more normal metabolic state. These patients post-transplant should have recovered some muscle mass and improved in functional performance over the years, but most had not received any structured rehabilitation and were still in a deconditioned state.

Patients with severe ascites and large distended abdomens are at a biomechanical disadvantage when standing from a chair, but these patients also tended to have the more severe Child-Pugh liver disease severity level. The 30-Second Chair Stand results should not be affected, since ascites is a factor considered in the Child Pugh liver disease severity classifications. The greater the liver disease severity, the greater the ascites, the fewer the number of chair stands performed.

The present study was designed to validate the ability of six impairment and activity limitation measures to assess strength and function in individuals with liver disease. Results of Spearman correlations, Students T-Tests, and ANOVA statistics support our assumptions validating the strength impairment and activity limitation measures tested in this study. These validated measures can be used to assess the effects of targeted muscle strengthening interventions in this population with liver disease.
### Table 2.1 Child-Pugh Classification of Liver Disease Severity

<table>
<thead>
<tr>
<th>Clinical and Biochemical Measurements</th>
<th>Child Class (Points Scored for Increasing Abnormality)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
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<tr>
<td>Encephalopathy (grade)</td>
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<td>Ascities</td>
<td>Absent</td>
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<td>Albumin (g/L)</td>
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<td>Prothrombin time (sec &gt;normal) (INR)</td>
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<td></td>
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<tr>
<th>Mean (sd)</th>
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<th>Post-Transplant</th>
<th>CP- B</th>
<th>CP- C</th>
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<td>N</td>
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<td>12</td>
<td>8</td>
<td>10</td>
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<td>% Female</td>
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<td>87.5</td>
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<tr>
<td>Mean Height [cm]</td>
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<td>175 (7)</td>
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<td>166 (8)</td>
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<td>Mean Weight [kg]</td>
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<td>92 (20)</td>
<td>80 (19)</td>
<td>72 (21)</td>
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<tr>
<td>Mean Age</td>
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<td>60.5 (8.1)</td>
<td>55 (6.1)</td>
<td>59.8 (7.2)</td>
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Table 2.3  Comparison of Means for Child-Pugh Groups on Strength Impairment & Activity Limitation Measures

<table>
<thead>
<tr>
<th></th>
<th>Mean (sd)</th>
<th>CP- A n=2</th>
<th>Post-Transplant n=12</th>
<th>CP- B n=8</th>
<th>CP- C n=10</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength Impairment Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heel-Rise</td>
<td>19.5 (3.5) (^1)</td>
<td>11.5 (5.2) (^1)</td>
<td>15.1 (7.2) (^1)</td>
<td>5.4 (3.0) (^2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Bridging</td>
<td>32.5 (2.1) (^{1,2})</td>
<td>29.4 (18.7) (^1)</td>
<td>26.1 (8.6) (^{1,2})</td>
<td>11.2 (8.1) (^2)</td>
<td>.019</td>
<td></td>
</tr>
<tr>
<td>Grip Strength [kg]</td>
<td>36.9 (15.2) (^1)</td>
<td>24.6 (8.0) (^1)</td>
<td>23.5 (4.7) (^1)</td>
<td>21.7 (3.4) (^2)</td>
<td>.044</td>
<td></td>
</tr>
<tr>
<td><strong>Activity Limitation Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Min Walk [m]</td>
<td>562.9 (67.7) (^1)</td>
<td>388.8 (76.3) (^2)</td>
<td>371.1 (40.8) (^2)</td>
<td>247 (111) (^3)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>30-Sec Chair-Rise</td>
<td>18.5 (3.54) (^1)</td>
<td>10.3 (4.5) (^2)</td>
<td>10 (3) (^{2,3})</td>
<td>5.7 (3.6) (^3)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>SF-36 Physical Function</td>
<td>23.5 (9.2)</td>
<td>19.7 (4.3)</td>
<td>17.2 (2.4)</td>
<td>17 (3.8)</td>
<td>.172</td>
<td></td>
</tr>
</tbody>
</table>

Groups with different numbers differ statistically at the .05 level.
Table 2.4  Relationship Among Measures of Disease Severity, Impairment, and Activity Limitations

<table>
<thead>
<tr>
<th></th>
<th>Bridge</th>
<th>Heel Rise</th>
<th>Grip Strength</th>
<th>6 Min Walk</th>
<th>30 Sec Chair Stand</th>
<th>SF 36 Physical Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Pugh</td>
<td>r = -0.554</td>
<td>r = -0.557</td>
<td>r = -0.224</td>
<td>r = -0.629</td>
<td>r = -0.514</td>
<td>r = 0.318</td>
</tr>
<tr>
<td></td>
<td>p = 0.001</td>
<td>p = 0.001</td>
<td>p = 0.218</td>
<td>p &lt; 0.001</td>
<td>p = 0.023</td>
<td>p = 0.114</td>
</tr>
<tr>
<td>Bridge</td>
<td>r = 0.6412</td>
<td>r = 0.3507</td>
<td>r = 0.779</td>
<td>r = 0.598</td>
<td>r = 0.258</td>
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</tr>
<tr>
<td></td>
<td>p = 0.001</td>
<td>p = 0.0534</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.228</td>
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</tr>
<tr>
<td>Heel Rise</td>
<td>r = 0.3438</td>
<td>r = 0.741</td>
<td>r = 0.568</td>
<td>r = 0.387</td>
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</tr>
<tr>
<td></td>
<td>p = 0.0582</td>
<td>p = &lt; 0.001</td>
<td>p = &lt; 0.001</td>
<td>p = 0.055</td>
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<td></td>
</tr>
<tr>
<td>Grip Strength</td>
<td>r = 0.346</td>
<td>r = 0.404</td>
<td>r = 0.022</td>
<td>r = 0.22</td>
<td></td>
<td>p = 0.915</td>
</tr>
<tr>
<td></td>
<td>p = 0.066</td>
<td>p = 0.022</td>
<td>p = 0.066</td>
<td>p = 0.011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Min Walk</td>
<td>r = 0.5466</td>
<td>r = 0.5144</td>
<td>r = 0.5422</td>
<td>r = 0.2748</td>
<td></td>
<td>p = 0.1742</td>
</tr>
<tr>
<td></td>
<td>p = 0.0022</td>
<td>p = 0.0101</td>
<td>p = 0.066</td>
<td>p = 0.1742</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig 2.1 Heel Rise Test
Fig 2.2 Bridging Test
CHAPTER 3: RANDOMIZED CLINICAL TRIAL OF TARGETED LOWER EXTREMITY RESISTANCE STRENGTHENING VS. PROGRESSIVE AMBULATION

Chronic liver disease affects more than five million Americans, and frequently results in protein-energy malnutrition that results in significant muscle wasting, activity limitations and participation restrictions.\(^3\) The pattern and degree of muscle wasting in persons with chronic liver disease is similar to those of other chronic diseases such as End-Stage Renal Disease (ESRD) and Human Immunodeficiency Virus (HIV).\(^{60,62,65}\) The International Classification of Functioning, Disability, and Health (ICF) model of disablement is easily applied to an individual with end stage liver disease.\(^{76}\) Liver organ damage due to virus, cirrhosis, inflammation, or other process can result in impaired liver functions such as altered metabolism of proteins, toxins and steroid hormones and these impairments may then lead to impaired muscle strength and endurance. Impaired strength and endurance can produce limitations performing activities such as grasping or lifting objects, standing up from a low surface, or ambulating even household distances, dressing or bathing, opening jars or cleaning the house. Ultimately body function impairment and activity limitations result in participation restrictions such as decreased socialization and loss of employment.

Liver transplantation is the only cure for end-stage liver disease with cirrhosis. However, the pre-transplant hyper-metabolic state may continue for up to nine months post-transplant. Further muscle wasting continues decreasing strength and quality of life and in many individuals limits return to pre-liver disease employment.\(^{18,25}\)
One common treatment to address weakness and muscle wasting after liver transplantation may involve a program of progressive intensity exercise using walking as the mode. Walking activity is beneficial to increasing lower extremity muscle strength; however, walking at a self-selected pace results in strengthening of the lower limbs to a lesser extent than resistance exercise. Thus, individuals with liver disease who limit their exercise to aerobic walking improve their cardiovascular conditioning, but not strength and activity performance. This may result in persistent muscle strength impairments and activity limitations after transplantation.\textsuperscript{11,25,102,103}

Cardiovascular endurance is impaired in individuals with liver disease, however, muscle strength may be more important initially post transplantation. Although both strength and endurance are required to perform basic mobility activities such as transferring in and out of bed and walking to the bathroom or living room. A threshold level of strength is needed to perform the type of activities such as walking and climbing that are used for cardiovascular endurance training.

To date, an optimal program of rehabilitation after liver transplantation has yet to be identified. Beyer et al. conducted the only documented strengthening intervention study with patient’s post- liver transplantation involving both aerobic exercise and training for muscle strength.\textsuperscript{25} The intervention was performed both as outpatient and home exercise programs; however, no specific information or descriptions were provided on the types of exercise performed for strengthening, the muscles targeted, or the pathway used to progress the program. This intervention produced improved muscle strength and activity performance; however, a treatment plan cannot be formulated from this study. Aerobic exercise in the form of a progressive walking program is the “usual
care” recommendation to improve strength and activity performance post-liver transplantation. The purpose of this study was to compare the benefits of a home exercise program of lower extremity resistance exercise to that of progressive walking in individuals who have undergone liver transplantation.

**Methods**

**Design Overview**

The study used a two group randomized, pretest-posttest design. The protocol was approved by the Institutional Review Board at University of Miami Miller School of Medicine.

**Settings and Participants**

A convenience sample was obtained from patients attending the Miami Transplant Institute Post-Liver Transplant Clinic at the Miller School of Medicine. Subjects who agreed to participate provided written consent.

**Inclusion Criteria**

To be included subjects had to be 18 years of age or older and had undergone liver transplantation a minimum of 6 weeks and a maximum of 12 weeks prior to enrollment. Subjects were ambulatory without physical assistance, but were permitted to use a cane or walker.
Exclusion Criteria

Individuals with liver disease due to alcoholism had to have abstained from alcohol consumption for at least six months prior to their transplant and to the time of study testing. A diagnosis of Hepatocellular Carcinoma (HCC) was an exclusion criterion. Subjects were also excluded if they had significant cardiopulmonary disease, osteoarthritis or other orthopedic injury that severely limited ability to ambulate, transfer, or perform exercises. Individuals with neurological/ neuromuscular disorders including cerebral vascular accident, Parkinson’s disease, Alzheimer’s disease, dementia unrelated to hepatic encephalopathy, dystonia, multiple sclerosis, and polio were also excluded. Individuals who were blind or were not able to comprehend the English or Spanish language were excluded.

Randomization

A stratified blocked randomization was used to assign subjects to treatment condition. The randomization was devised by an investigator outside the data collection process. Transplanted subjects were classified as having “Mild” or “Severe” disease based on liver function lab values, and history of post-transplantation complications. Randomization for each stratum was performed in blocks of six with three subjects assigned to the strengthening group and three to the walking group. Once consented, subjects were classified as “Mild” or “Severe” and assigned a stratum specific id number. The randomization assignment envelope corresponding to the id number was opened and subjects were assigned to either the Exercise or Walking Group.
**Intervention**

*(Exercise Group)*

Participants randomized to the exercise group underwent a program of resistance strengthening exercises targeting the lower extremity musculature. Four specific muscle groups were targeted for training to enhance functional activities such as rising from a chair, ambulating, and ascending stairs. The muscle groups included: Ankle Plantar flexors (Gastrocnemius and Soleus), Knee Extensors (Quadriceps), Hip Abductors (Gluteus Medius, Gluteus Minimus, and Tensor Fascia Lata), and Hip Extensors (Gluteus Maximus, Lumbar Erector Spinae, and the Biceps Femoris). Resistance was applied in the form of anti-gravity positioning and Theraband® elastic resistance bands.

Progression of the resistance exercise program along with the intensity and duration were directed by guidelines from the American College of Sports Medicine. The program was initiated with the least resistance of moving the lower limb in a gravity-eliminated position. Once the subject could perform 3 sets of 10 repetitions easily, the lower limb was repositioned to move against the resistance of gravity. Next the subject progressed to moving the limb against a light Theraband® elastic resistance band (Yellow) and eventually progressed to more resistive Theraband® elastic bands as tolerated (Red, Green, and Blue). The level of resistance increases as the Theraband® elastic band elongates. For example: the light resistive Theraband® (Yellow) provides 2.9 pounds of resistance when elongated to 100% of its length and 5.8 pounds when elongated 250%. The medium resistance Theraband® (Blue) provides 7.1 pounds of resistance when elongated to 100% of its length and 13.3 pounds when elongated 250%. During performance of the resistance exercises, emphasis was placed on the eccentric
lowering portion of the muscle contraction during each repetition. To prevent injury to the abdominal surgical site emphasis was placed on proper form with good trunk stabilization during the exercise. The subject’s trunk was stabilized by the bed, couch, chair backrest, or the wall. Trunk stabilization directed resistance to the lower extremity musculature, decreasing any stress placed on the abdomen and surgical incision.

Individuals performed at minimum of one exercise from each of the four targeted muscle groupings on alternating days. This provided the subjects an exercise frequency of 3-4 times weekly and allowed one day of rest between exercise days. The prescribed intensity was for completion of 3 sets of 10 repetitions for each exercise. A rest period of two minutes was taken between each set. The entire strengthening exercise routine required 25-30 minutes to perform, including rest periods.

Exercises progressed from minimal muscle effort to maximal effort. Subjects were instructed to progress to the next greater level of resistance when they were able to easily perform 10 repetitions of the movement on the last of three sets without significant fatigue or breakdown in proper form.

An exercise booklet with pictures and written descriptions of how to perform each exercise (Appendix I) along with an algorithm (Appendix III) on how to progress each of the exercises provided to each participant in the exercise group.

Subjects were provided a daily exercise log that documented level of Theraband® resistance, sets of exercise, and repetitions of each exercise performed. In addition to strengthening exercises, the exercise group performed their usual care progressive ambulation and activity.
(Walking Group)

The walking group performed progressive ambulation as part of the usual care of post- transplantation recovery. The walking group subjects did not receive strengthening exercise. As part of the usual post liver transplantation treatment program they were instructed to walk further each day and to monitor the distance walked.

To measure the total number of steps taken during designated walking exercise, subjects in both the exercise and walking groups were provided an Accusplit Eagle AE120XL pedometer, which has been found to be very reliable and accurate for measurement of total number of steps taken during ambulation in multiple subject populations. Subjects were instructed to wear the pedometer on their hip aligned with the middle of their patella at the height of their umbilicus. The pedometer was to be reset to zero before each designated walk and then subjects were to record the number after immediately finishing their walk. Both groups were provided a walking log to document pedometer readings. An investigator contacted subjects in both groups bi-weekly by telephone and/ or during liver clinic visits to monitor safety, assist in proper performance and progression of the exercise program, and encourage participation.

Adherence

Performance of the resistance strengthening and/or the walking intervention 50% of the time or more was defined as adherent. Previous clinical trials with individuals post liver transplantation have used this definition of adherence.
Safety Monitoring

Laboratory blood tests of Albumin, Total Protein, Creatinine, Alkaline phosphatase (ALP), Alalnine Amino Transferase (ALT), Aspartine Amino Transferase (AST), and Bilirubin were drawn every two weeks by the liver transplant clinic nurses. The laboratory values were monitored by the transplant nursing coordinators for liver and kidney function. Liver enzyme levels above norms post transplantation reflect liver organ injury. The investigator consulted with the transplant nursing coordinators to determine if liver function was being affected by the exercise intervention and if the subject required withdrawal from the study.

Performance on outcome measures of strength and function are impacted by fatigue. The Fatigue Visual Numeric Scale was used to monitor fatigue prior to outcome measurement. The scale is a visual bar scale ranging from zero to ten, with the higher score indicating greater fatigue. Subjects were delayed from beginning each successive outcome measure until their energy level returned to baseline.

Outcome Measures

Demographic and clinical information including age, gender, height, weight, smoking history, Model for End Stage Liver Disease (MELD) severity score, employment, number of weeks post-transplant, and exercise behaviors immediately prior to enrollment were collected for all subjects.
Impairment (Strength) Measures

Plantar flexor strength was measured using the Heel-Rise test. Subjects stood on their dominant leg and raised their non-dominant leg in the air. Subjects rose up on the toes of the dominant leg and then lowered until the foot was flat on the floor. The activity was performed to the rate of a metronome (60Hz). The maximum height of the heel rise was marked on a ruler. The total number of repetitions performed until the subject failed to achieve 50% of the initial heel-rise height was recorded. The heel rise test has good reliability ICC>0.90 and has previously been used to assess plantar flexor strength in individuals with liver disease awaiting transplantation.

Hip extensor strength was measured using the Bridge test. While supine on an examination plinth subjects bent their knees so their feet were flat on the plinth and arms placed by their side for trunk stability. Subjects extended their hips toward the ceiling. The maximum height between the buttocks and plinth was marked on a ruler. The subjects performed the bridge as many times as possible to the rate of a metronome (60Hz). The total number of repetitions performed until the subject failed to achieve 50% of the initial bridge height was recorded.

Activity Limitation Measures

The Six-Minute Walk Test (6MWT) was used as a measure of functional mobility. Subjects walked back and forth along a 30.5 meter course for six minutes. The total distance ambulated was recorded. The 6MWT has excellent test-retest reliability in older adults. It has been shown to be reliable and valid in individuals with pulmonary disease, lung transplantation, renal disease, and the elderly; all having similar muscle
wasting and impairments as individuals with liver disease.\textsuperscript{145,184,185} The 6MWT has been used to determine functional capacity in individuals with chronic liver disease and post liver transplant\textsuperscript{25,122,144,187} 6MWT distances are moderately limited in the majority of individuals post liver transplant.\textsuperscript{122} This activity limitation measure has been shown to be related to lower limb muscle strength.\textsuperscript{79,143}

The 30-second chair-stand was used to measure ability to perform sit-to-stand-to-sit transfers. Using an straight-back chair the subjects come to a complete stand position and then return to a complete sitting position without upper extremity assistance. The number of times the subjects performed the complete maneuver in a 30 second period was recorded. Good test-retest reliability of the sit to stand test (ICC=0.84) has been reported in renal transplant candidates.\textsuperscript{81,149} This activity limitation measure has been shown to be related to muscle strength.\textsuperscript{80}

The Short Form 36 (SF-36) is a generic measure of health status comprised of eight subscales.\textsuperscript{156} Our research focused on the physical function subscale. The physical function subscale pertains to the performance of all types of physical activities from light to extreme and contains the following items: Vigorous activities such as running, lifting heavy objects, participating in strenuous sports; Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf; Lifting or carrying groceries; Climbing several flights of stairs; Climbing one flight of stairs; Bending, kneeling, or stooping; Walking more than a mile; Walking several blocks; Walking one block; and Bathing or dressing yourself.\textsuperscript{158} The scale is scored from 0-100; higher scores reflect fewer limitations. The SF-36 was demonstrated to have good test-retest reliability and be valid and sensitive to change in an exercise intervention study involving individuals with
end-stage renal disease.\textsuperscript{158,160,164} Wiesinger et al. demonstrated the physical function subscale score is related to liver disease severity.\textsuperscript{9}

**Quality of Life Measure**

The Chronic Liver Disease Questionnaire (CLDQ) consists of 29 items divided into six domains: 1) Abdominal Symptoms 2) Activity: eating habits and movement of heavy objects 3) Emotional Function: measures mood and insomnia 4) Fatigue: perception of decreased energy and sleepiness 5) Systemic Symptoms, and 6) Worry: concerns regarding disease progression and family. The Summary score for each domain ranges from 1 (most impairment) to 7 (least impairment).\textsuperscript{162} All items refer to the previous 2 weeks. Similar to the generic SF-36, lower CLDQ scores indicate more impairment. Higher scores indicate less impairment. The Fatigue and systemic subscales relate to body function and structure. The Activity subscale best represents the construct of activity limitations. As previously discussed using the ICF disablement model, chronic liver disease impairs body structure (muscle fibers) and body function (muscle strength) resulting in activity limitations. Through assessment of the Activity, Fatigue, and Systemic subscales representing activity limitations we can make conclusions of body structure and body function. The CLDQ has good test-retest reliability and cross sectional validity; and documented to be sensitive to all levels of liver disease severity and all types of liver disease.\textsuperscript{167, 169}
Data Collection

Baseline measurements on all outcome measures were recorded upon enrollment. Subjects were retested at four weeks, eight weeks, and twelve weeks when they returned to the liver transplant clinic for follow-up with the surgeons. Many subjects lived out of the Miami area and only returned to the clinic when scheduled with the surgeon. As a result several subjects missed retest dates at four, eight and twelve weeks because they did not return to see the surgeon at those time intervals. Therefore, only the final 12 week post-test data was analyzed against the baseline. When 12 week data was missing for subjects we used their 8 week data.

Data Analysis

Descriptive statistics were used to summarize baseline characteristics. T-tests were performed to compare baseline characteristics of subjects who did and did not complete the study and to compare the baseline characteristics of subjects in the Exercise and Walking groups. Repeated Measures Analysis of Variance was used to determine if there were differences between the control (walking) group and the experimental (strengthening) group in pretest-posttest change in strength, activity limitation and quality of life.

Repeated Measures Analysis of Variance was used to determine if subjects who were adherent to the strengthening and walking interventions demonstrated greater improvements in strength and activity performance that subjects who were non-adherent.

Spearman correlation coefficients were calculated to examine the relationships among changes in strength, changes in activity limitations and changes in quality of life.
Results

A total of 74 subjects were screened for eligibility. Fifty subjects satisfied the eligibility requirements and were enrolled in the study and randomly assigned to the intervention (n=25) and control (n=25) groups. Subjects were excluded for cardiopulmonary impairments unrelated to liver disease, chronic orthopedic impairments resulting in pain and limitations in mobility, peripheral neuropathy for advanced diabetes, and for planning to leave the Miami area to return home out of the state or country. Twenty-five subjects completed the study and were included in the analysis [Intervention (n=14) Control (n=11)]. Of subjects unable to complete the study (n=26), two subjects died from complications due to immune suppression; 14 subjects were withdrawn from the study as they were unable to participate in the intervention or usual care walking for medical reasons. These included: prolonged hospitalization for infection, recurrence of hepatitis virus attacking the new liver, renal failure requiring dialysis, and painful leg abscesses that developed at surgical drain sites. One subject moved out of the area and terminated participation. Eight subjects lacked time or interest in continuing participation (Fig 3.1).

There was no significant difference in attrition from the exercise or walking groups. There were no statistically significant differences between the baseline characteristics of subjects who completed the study and those withdrawn. However, it appears the withdrawn subjects were a little weaker and had slightly higher liver enzyme levels at baseline. (Table 3.1) Plantar flexor strength measured by the heel rise test, hip extensor strength measured by the bridge test, and activity performance measured by the 30-second chair-stand and (6MWT) all were slightly lower at baseline for the withdrawn
subjects. Baseline group characteristics for subjects completing the trial did not significantly differ from one another (Table 3.2).

Adherence for the Exercise group was good as 9 subjects out of 11 performed the Exercise intervention at least 50% of the time. For the usual care walking group 12 of 14 individuals walked at least 50% of the time.

**Strength Measures**

Both the Exercise and Walking groups had increased heel rise and bridging repetitions at post-test (Table 3.3). The number of bridge repetitions for the exercise group increased 121% compared to 24% for the walking group (p=.004). The number of heel rise repetitions for the exercise group increased 100% compared to 45% for the walking group. The difference approached statistical significance (p=.065)

**Activity Limitation Measures**

Both the exercise and walking groups improved in 30-second chair-stand repetitions, 6MWT distance, and SF-36 Physical Function scale scores (Table 3.3) There was a 33 percent increase in number of 30-second chair-stand repetitions for the exercise group compared to a 9 percent increase for the control group (p=.02). Although the 6MWT distance of exercise group improved somewhat more than those of the walking group, the difference was not statistically significant (p=.17). There was a 22 percent increase in walking distance for the exercise group compared to an 18 percent increase
for the walking group. There was no statistical significance between groups in the change in SF-36 Physical Function Subscale (p=.79)

**Health Related Quality of Life**

Both groups improved in health related quality of life scores on the CLDQ. (Table 3.3) However there was no statistically significant differences between the groups for change in CLDQ scores (p=.54)

**Relationships between Changes in Outcome Measures**

Changes in plantar flexion strength were moderately correlated with changes in hip extension strength (r=.46, p=.02). Changes in hip extension strength were moderately correlated with changes in 6MWT (r=.36, p=.08) and more strongly correlated with changes in 30-second chair-stand repetitions (r=.60, p=.002). Changes in plantar flexor strength were not related to changes in 6MWT distance(r=.1-, p=.637) or 30-second chair-stand repetitions(r=.32, p=.124).

Change in the SF-36 Physical Function subscale was not related to change in strength impairment, activity limitation, or health related quality of life. Change in health related quality of life measured by the CLDQ was related to change in hip extensor strength (Bridging) and activity performance measured by the 30-Sec Chair Stand and the 6MWT. (Table 3.4)
Discussion and Conclusion

The results of the present study demonstrated that subjects from both the intervention and usual care walking groups improve in lower extremity strength and in their ability to perform functional activity. Both groups performed a form of progressive activity, either usual care progressive walking or lower extremity resistance strengthening in addition to progressive walking. However, the Exercise group demonstrated greater increases in strength and activity performance than the walking group. The finding that the subjects in the walking group improved from baseline but did not improve as much as the subjects in the exercise group is consistent with the findings that subjects do not reach prior levels of strength and function 1 year post-liver transplantation and do not equal the strength and function of age related healthy sedentary individuals. Also, this is consistent with the findings of Rooks et al. in community dwelling older adults, knee extension strength increased with resistance training while there was still a loss of knee extension strength in those who only walked. Furthermore, these results support the recommendations by Painter et al. to include resistance training exercise, in addition to aerobic exercise, to return muscle strength to previous levels in the population post-renal transplantation who are also recovering from severe muscle wasting. The walking group in this study likely walked more than the typical patient post liver transplantation because the investigator provided them with pedometers and walking logs and biweekly phone calls to monitor activity. Because these individuals probably walked more than would be typical for patients post transplant, the differences between the usual care and an exercise program may be even more clinically significant than the findings of this study.
Our study did not find a significant difference between groups for the 6MWT most likely for the reason that the control group was performing progressive walking as their usual care. However, we still observed a slightly greater percent increase in walking distance for the strengthening group.

Health related quality of life was related to increases in hip muscle strength and increases in activity performance of chair standing and walking. Therefore, increasing strength and activity performance through a targeted resistance strengthening program appears to promote the feeling of improved health related quality of life in these individuals post-liver transplantation.

Subjects who were adherent to the exercise program improved more than those who were not for all the strength and functional outcome measures. However, these differences were not statistically significant because of the small sample size. Figures 3.2 and 3.3 present the marked differences for the Bridging and Chair Standing measures.

The monitored lab values of liver function remained within normal post-liver transplant ranges for subjects in both the strengthening and the walking groups. There were no verbal reports of severe muscle pain or joint pain or other adverse events from subjects in either group. Therefore, we conclude there were no negative effects of the resistance strengthening exercise and or walking on the newly transplanted liver. Fear of damaging the new liver is a major concern with both patients and family. This study demonstrated progressive resistance strengthening initially instructed by a physical therapist is safe to perform from a liver function standpoint.
One substantial limitation of this study is the small sample size. There were a large number of subjects who could not complete the study for medical reasons. Most subjects post-transplant were greatly affected by the immunosuppressant medications resulting in hospitalizations that prevented individuals from performing the home exercise and walking interventions. This study enrolled subjects 6 to 12 weeks post transplantation. During this time period patients are still receiving higher doses of immune suppressant medications to prevent organ rejection and are at greater risk for infection. Withdrawal of subjects may be reduced in future studies if the intervention was initiated after immune suppression medications are reduced to much lower levels. Other reasons for subject withdrawal were surgically related such as abscesses from drain sites in the groin resulting in pain and limiting ability to perform the intervention. Delaying the time to begin the intervention may permit these surgical/medical post operative impairments to lessen and permit the ability of subjects to remain out of the hospital able to perform the interventions.

Despite the small number of subjects, differences between the groups for pre-post intervention changes in Heel Rise test, Bridging test and 30-Second Chair Stand test achieved statistical significance. Although the pre-post intervention change in 6MWT score was greater for the exercise group than the walking group this difference failed to reach statistical significance. Power Analysis calculations indicated that the current sample size provides power to detect this difference of only .55 and we would require an additional 25 subjects in each group to increase the power to .80.

The lack of blinding is a limitation to the study. Neither the rater nor the subjects were blinded. The investigator who instructed both the walking and exercise groups on
their respective programs and provided all phone follow-up was also the rater for all the outcome measurement. To decrease the risk of bias due to lack of blinding strict procedures were followed for all outcome testing. The heel rise test and bridge test both used a measurement device to objectively determine when the subject had dropped below 50% of the height of the initial movement. A standard set of instructions were used to for the timed chair stand test. Finally, the 6MWT testing followed strict guidelines for instructing and encouraging the subject. Identical procedures were used for testing both groups. In addition, the subjects were not blinded. The walking group was aware they were not receiving strengthening exercise. To prevent subject bias, we provided the same amount of contact with the walking group by clinic visit and telephone as the exercise group. The walking group was also provided a pedometer and a walking log.

Our sample is representative of the South Florida population in that two-thirds of the sample completing the study was Hispanic. Therefore our findings may not be easily generalized to other populations.

Our study did not address the role of nutrition in the recovery of strength post liver transplant. Future studies should examine the possible role of increased protein intake under the guidance of a nutritionist in facilitating muscle rebuilding. Our study only targeted the lower extremities; future studies could also address proximal upper extremity strengthening.

Liver disease results in muscle strength impairments and activity limitations that continue post liver transplantation. Data from our study suggest that progressive walking decreases strength impairments and activity limitations, however a resistance strengthening program in addition to progressive walking provides greater improvement.
in strength and function. Post-liver transplant care should include goals and strategies to optimize strength and function. Resistance strengthening exercise is a necessary modality to add to post transplant protocols.
**The Consort Flowchart**

**Assessed for eligibility**

N = 74

**Enrollment**

50 Randomly Allocated

Excluded (n=24)
- Not meeting inclusion criteria (n=16)
- Declined to participate (n=8)

**Allocation**

- Allocated to Resistance Strengthening Intervention (n=25)
  - Discontinued intervention (n=14)
    - 1 death
    - 1 returned to work and no time
    - 1 no interest once started
    - 7 hospitalized immune compromised
    - 1 too much knee pain
    - 2 groin abscess formation
    - 1 renal failure placed on dialysis
  - Analyzed (n=11)

- Allocated to Usual Care Walking Control (n=25)
  - Discontinued intervention (n=11)
    - 1 death
    - 3 no interest once started
    - 1 unrelated fall with hil leg injuries
    - 1 moved out of state
    - 5 hospitalized immune compromised
  - Analyzed (n=14)
Table 3.1  Baseline Comparison of Subjects who did and did not Complete the Study

<table>
<thead>
<tr>
<th></th>
<th>Completed N =25</th>
<th>Did not Complete N =25</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.5 (9.9)</td>
<td>54.6 (12.0)</td>
<td>.36</td>
<td>.722</td>
</tr>
<tr>
<td>Height(cm)</td>
<td>170.6 (9.0)</td>
<td>170.4 (11.1)</td>
<td>-.06</td>
<td>.953</td>
</tr>
<tr>
<td>Weight(kg)</td>
<td>69.1 (15.0)</td>
<td>76.6 (28.7)</td>
<td>1.15</td>
<td>.26</td>
</tr>
<tr>
<td>Weeks Post Transplant</td>
<td>8.4 (2.6)</td>
<td>8.2 (2.1)</td>
<td>-.26</td>
<td>.794</td>
</tr>
<tr>
<td>MELD</td>
<td>22.1 (5.3)</td>
<td>23.6 (8.7)</td>
<td>.74</td>
<td>.463</td>
</tr>
<tr>
<td>Heel Rise Test (reps)</td>
<td>11.2 (6.4)</td>
<td>7.8 (5.8)</td>
<td>-1.94</td>
<td>.058</td>
</tr>
<tr>
<td>Bridge Test (reps)</td>
<td>25.6 (11.2)</td>
<td>22.5 (9.9)</td>
<td>-1.04</td>
<td>.305</td>
</tr>
<tr>
<td>30 Sec Chair Stand (reps)</td>
<td>9.9 (4.3)</td>
<td>8.3 (4.2)</td>
<td>-1.36</td>
<td>.181</td>
</tr>
<tr>
<td>6 Min Walk Test (m)</td>
<td>379.4 (123.9)</td>
<td>352.3 (160.8)</td>
<td>-.65</td>
<td>.517</td>
</tr>
<tr>
<td>Physical Function</td>
<td>45.2 (21.2)</td>
<td>48.9 (25.7)</td>
<td>.55</td>
<td>.584</td>
</tr>
<tr>
<td>CLDQ total score</td>
<td>5.2 (0.9)</td>
<td>4.9 (0.8)</td>
<td>-.65</td>
<td>.519</td>
</tr>
<tr>
<td>Bilirubin Total</td>
<td>0.78 (0.46)</td>
<td>0.87 (0.4)</td>
<td>.80</td>
<td>.429</td>
</tr>
<tr>
<td>Bilirubin Direct</td>
<td>0.27 (0.32)</td>
<td>0.23 (0.2)</td>
<td>-.54</td>
<td>.591</td>
</tr>
<tr>
<td>SGPT</td>
<td>72.4 (72.3)</td>
<td>113.3 (175.9)</td>
<td>1.06</td>
<td>.299</td>
</tr>
<tr>
<td>SGOT</td>
<td>53.9 (64.4)</td>
<td>57.7 (66.8)</td>
<td>.20</td>
<td>.839</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.9 (0.5)</td>
<td>3.8 (0.4)</td>
<td>-.57</td>
<td>.574</td>
</tr>
</tbody>
</table>
Table 3.2 Baseline Equivalency of Subjects who Completed the Study

<table>
<thead>
<tr>
<th></th>
<th>Strength Group</th>
<th>Control Group</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 11</td>
<td>N = 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>54.2 (12.1)</td>
<td>52.9 (8.4)</td>
<td>.31</td>
<td>.763</td>
</tr>
<tr>
<td>Height(cm)</td>
<td>172.1 (7.7)</td>
<td>169.4 (10.1)</td>
<td>.72</td>
<td>.477</td>
</tr>
<tr>
<td>Weight(kg)</td>
<td>67.2 (9.7)</td>
<td>70.5 (18.4)</td>
<td>-.53</td>
<td>.601</td>
</tr>
<tr>
<td>Weeks Post Transplant</td>
<td>8.5 (2.4)</td>
<td>8.2 (2.2)</td>
<td>.36</td>
<td>.727</td>
</tr>
<tr>
<td>MELD</td>
<td>21.8 (5.2)</td>
<td>22.4 (5.6)</td>
<td>-.25</td>
<td>.806</td>
</tr>
<tr>
<td>Heel Rise Test (reps)</td>
<td>11.3 (6.7)</td>
<td>11.1 (6.4)</td>
<td>.05</td>
<td>.961</td>
</tr>
<tr>
<td>Bridge Test (reps)</td>
<td>25.5 (10.8)</td>
<td>25.6 (11.9)</td>
<td>-.02</td>
<td>.983</td>
</tr>
<tr>
<td>30 Sec Chair Stand (reps)</td>
<td>9.7 (3.9)</td>
<td>10.1 (4.8)</td>
<td>-.19</td>
<td>.849</td>
</tr>
<tr>
<td>6 Min Walk Test (m)</td>
<td>416.3 (141.7)</td>
<td>350.9 (104.4)</td>
<td>1.33</td>
<td>.197</td>
</tr>
<tr>
<td>Physical Function</td>
<td>47.3 (22.5)</td>
<td>43.5 (20.8)</td>
<td>.43</td>
<td>.671</td>
</tr>
<tr>
<td>CLDQ total score</td>
<td>4.9 (1.1)</td>
<td>5.4 (1.1)</td>
<td>-1.0</td>
<td>.317</td>
</tr>
<tr>
<td>Bilirubin Total</td>
<td>0.9 (0.6)</td>
<td>0.7 (0.3)</td>
<td>1.15</td>
<td>.260</td>
</tr>
<tr>
<td>Bilirubin Direct</td>
<td>0.3 (0.4)</td>
<td>0.3 (0.2)</td>
<td>.38</td>
<td>.705</td>
</tr>
<tr>
<td>SGPT</td>
<td>60.5 (52.1)</td>
<td>81.8 (85.6)</td>
<td>-.72</td>
<td>.477</td>
</tr>
<tr>
<td>SGOT</td>
<td>49.1 (50.7)</td>
<td>57.7 (75.2)</td>
<td>-.33</td>
<td>.747</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.9 (0.5)</td>
<td>3.9 (0.5)</td>
<td>.11</td>
<td>.914</td>
</tr>
<tr>
<td>Outcome</td>
<td>Intervention N=11</td>
<td>Control N=14</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------</td>
<td>--------------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre Post</td>
<td>Pre Post</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heel Rise (reps)</td>
<td>11.3 (6.7)</td>
<td>22.6 (11.1)</td>
<td>11.1 (6.4)</td>
<td>16.1 (7.1)</td>
</tr>
<tr>
<td>Bridging (reps)</td>
<td>25.5 (10.8)</td>
<td>56.4 (26.3)</td>
<td>25.6 (11.9)</td>
<td>31.8 (17.6)</td>
</tr>
<tr>
<td>30 Second Chair Stand (reps)</td>
<td>9.7 (3.9)</td>
<td>14.4 (6.6)</td>
<td>10.1 (4.8)</td>
<td>11.1 (3.9)</td>
</tr>
<tr>
<td>6 Min Walk (m)</td>
<td>416.3 (141.7)</td>
<td>509.1 (146.9)</td>
<td>350.8 (104.4)</td>
<td>412.6 (81.3)</td>
</tr>
<tr>
<td>Physical Function</td>
<td>47.3 (22.5)</td>
<td>69.5 (26.8)</td>
<td>44.5 (21.3)</td>
<td>68.8 (20.3)</td>
</tr>
<tr>
<td>CLDQ Total Score</td>
<td>4.7 (1.1)</td>
<td>5.4 (1.1)</td>
<td>5.3 (1.1)</td>
<td>5.6 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Heel Rise Change</td>
<td>Bridge Change</td>
<td>6 Min Walk Change</td>
<td>30 Sec Chair Stand Change</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Heel Rise Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bridge Change</td>
<td></td>
<td>r = 0.356, p = 0.080</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Min Walk change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 Sec Chair Stand Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Function SF-36 Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLDQ Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 3.2: Exercise Group Pretest-Posttest Change in Chair Standing by Adherence Group

![Graph showing the change in chair standing by adherence group.](image-url)
Figure 3.3: Exercise Group Pretest-Posttest Change in Bridging by Adherence Group

![Graph showing pretest-posttest change in bridging by adherence group. The graph compares adherent and not adherent groups with pretest and posttest scores.]
CHAPTER 4: SUMMARY AND CONCLUSION

The primary question addressed in this dissertation was whether a targeted home exercise program would improve strength and the ability to perform activities more than the usual post operative treatment of progressive ambulation in individuals post-liver transplantation. Although energy metabolism normalizes and muscle protein catabolism resolves post-liver transplantation, muscle strength and activity performance fail to return to the levels of normal healthy adults. 8,25 Currently progressive ambulation is recommended post-liver transplantation to restore strength and ability to perform daily activities. However, some evidence suggests that it is not as effective for increasing muscle strength as targeted resistance strengthening exercises.100,101 A program of progressive ambulation gradually increases the distance individuals are able to walk as the liver disease related cardiovascular impairments resolve post-liver transplant. Unfortunately, these same individuals do not regain strength or achieve the levels of activity performance that are normal for healthy adults.9,11,25,102,103

To answer the broad question of whether the targeted home exercise program was effective as an intervention to restore strength and function in individuals post liver transplantation, several specific questions were asked.

Research Question 1: Did the performance of progressive resistance strengthening exercises by the exercise group lead to more improvements as compared to that of the walking group?

Both the exercise group and the walking group increased in strength and activity performance; however, the exercise group demonstrated greater increases in both strength
and activity performance. These results are consistent with previous investigations of cardiovascular exercise and muscle strengthening post liver transplantation.\textsuperscript{25,103} Home based cardiovascular exercise during the first year post liver transplantation has been shown to increase quadriceps muscle strength and exercise capacity; however, a muscle strengthening intervention performed in an inpatient rehabilitation center combined with a home muscle strengthening program demonstrated even greater increases in strength and activity performance.\textsuperscript{25,103}

Both the exercise and walking groups in the clinical trial demonstrated increases in 6MWT distances after the intervention; however, the exercise group walked further. Post intervention, the exercise group improved to a mean of 509 meters and while the mean for the walking group was only 413 meters. Enright et al. reported norms on the 6MWT for healthy men (576m) and women (494m) for subjects with a mean age of 60.\textsuperscript{189} The subjects in this clinical trial, with a mean age of 53.5 years, walked distances far less than the norm reported by Enright et al. The exercise group almost reached the mean ambulation distances of healthy adults, whereas the walking group did not. These findings support the need to add resistance exercise to the current treatment of progressive ambulation for improvement in strength and activity performance.

The individuals in the walking group received more direct and more frequent encouragement to walk than is usual post-liver transplant. Typically, individuals are told to generally increase their activity and begin walking as part of the usual care instructions post-liver transplantation. This trial provided the subjects with a pedometer, walking log, and regular phone call follow up to monitor their walking. The addition of the pedometer and walking log alone may have encouraged these individuals to walk more and receive
more aerobic exercise than is typical during the usual recovery post-transplant. Therefore, the differences between the resistance training group and a true usual care control group might have been greater than those we found in this clinical trial.

There are other reasons for decreased activity performance besides myopathy and strength impairments in individuals post liver-transplantation. Incisional pain often limits mobility and decreases the intensity of activity. The multiple medications required to prevent organ rejection also may affect activity tolerance. As pain resolves and medications dosages are reduced, activity performance and quality of life tend to improve. Rehabilitation of individuals is after liver transplantation is multi-factorial. As pain subsides and medications dosages are reduced, the resistance strengthening exercise program in this study should work synergistically to increase strength and activity performance.

**Research Question 2: Did strength and activity performance of subjects who adhered to the prescribed intensity of the exercise intervention improve more than those who were less adherent?**

Adherence to both the resistance exercise and the progressive ambulation programs was good as 9 of 11 subjects in the exercise group and 12 of 14 in the walking group were considered adherent. Individuals must have performed strengthening exercise at least 50% of the time (2 days a week) and individuals must have walked at least 50% of the time (2 days a week) to be considered adherent. Adherence was critical because the subjects who were most adherent to the exercise and walking treatments increased strength and function more than those who were not adherent. This finding provides
additional evidence that the exercise program was effective, and that strategies to improve adherence should be an integral part of the exercise plan.

The finding that the vast majority of subjects were adherent to a home program is encouraging and clinically relevant. For individuals recovering from liver transplantations who are often fatigued by the high energy requirements of daily routine activities, traveling to outpatient clinics for multiple sessions of physical therapy each week could potentially increase fatigue and decreases ability to perform the recommended exercises. Therefore, the exercise intervention in this study was designed as a home program to minimize fatigue and promote adherence. Subjects performed the exercises at their own pace and planned the exercises around their fatigue level and medication schedules. Additionally, easy to follow handouts describing each exercise and biweekly contact with the subjects appeared to assist promotion of adherence.

Home exercise programs have many advantages for improving patient outcomes.. Acute care hospital lengths of stay are becoming shorter. Individuals are returning home with more strength impairments and activity limitations that in the past. Many insurance providers limit individuals to a few, brief, intense home physical therapy sessions. A home exercise program that individuals can perform and progress on their own is ideal post liver transplantation. Post liver transplantation individuals often returns home while still weak and dependent on others to assist with activity performance. A physical therapist can design a strengthening and walking program specific for the individual. Initial instruction of the home program could be performed at the liver clinic over 2 to 3 visits to ensure proper techniques for safety and to maximize results. Contact between the physical therapist and the patient could then be decreased to approximately once a month
over 4 to 5 months to extend the amount of time the individual would be under the supervision a physical therapist. This type of protocol would utilize approximately the same number of treatment sessions as the typical intense but short term physical therapy protocols.

The results of this study support the effectiveness and feasibility of this model as a tool for rehabilitation of individuals post liver transplant with chronic muscle wasting. Also, this model for rehabilitation could be applied to many other populations with chronic disease. The ability perform the exercise in the home should decrease fatigue and increase adherence while still being monitored regularly by a professional for safety and effectiveness. The goal of the rehabilitation model is not just for improving strength, activity performance, and quality of life but also to promote a new lifestyle of fitness in these populations with chronic disease.

Fear is a major limiting factor to activity post-transplantation often resulting in a more sedentary lifestyle. Patients and family members express concerns that physical activity will harm the new liver. Therefore, patients, family members and caregivers all must be educated on the benefits of exercise for the recovery of strength, activity performance and quality of life. Fear was not measured in the clinical trial; however, it appeared that the patients who were very compliant with their exercise and walking programs had very encouraging family members and in some cases the spouses performed the exercises along with the subjects.
Research Question 3: Was increased strength related to increased function, activity performance, and health related quality of life?

The International Classification of Functioning, Disability, and Health (ICF), describes a theoretical relationship between muscle tissue (body structure) and muscle strength (body function) with activity performance. Strength is related to activities such as walking, standing from a chair, and climbing stairs. Therefore, muscle wasting (body structure) impairments due to chronic liver disease that continue post-transplantation are theoretically related to many activity limitations and participation restrictions.

In the clinical trial, improvements in lower extremity strength from baseline assessment to the end of the intervention were correlated with improvements in activity performance. Specifically, increased hip extensor muscle strength was related to improved performance standing up from a chair (r=.60, p=.002) and walking (r=.36, p=.08). The physical function subscales of the SF-36 activity performance measure were not related to improvements in muscle strength. However change in the SF-36 physical function sub-scale item “ascending a flight of stairs” was moderately correlated with increased hip extensor muscle strength (r=.40, p=0.08). This is consistent with findings by Chandler et al. that lower extremity strength is correlated with climbing stairs.

If muscle strength is required for activity performance, then results from the clinical trial support the need for resistance muscle strengthening after liver transplantation to improve activity performance. Subjects who only walked improved their activity performance; however, subjects who performed resistance exercise in
addition to walking improved activity performance much greater and approached levels
of normal healthy adults.

The results of this clinical trial demonstrate that increases in strength and activity
performance positively impact health related quality of life. The change in hip extensor
muscle strength measured by the Bridge test (r=.48, p=.02) and activity performance on
the 30 Second Chair Stand test (r=.54, p=.01) and the 6MWT (r=.58, p=.004) were
moderately correlated with change in disease specific health related quality of life
measured by the CLDQ. The improvement in activity performance as a result of
strengthening may lead to a decrease in factors that affect quality of life such as anxiety,
depression, fatigue, irritability, worry of never feeling better, and the impact of their
disease on family members. Both groups improved in the change in health related quality
of life; and, the exercise group improved 12% compared to only 6% for the walking
group however this difference failed to reach statistical significance.

Limitations

Outcome Measures

Before conducting the clinical trial intervention study, we conducted a pilot study
(Chapter 2) to determine the validity of outcome measures of strength impairment (Heel-
Rise and Bridging) and activity limitation (6MWT, 30-Second Chair-Stand and SF-36
Physical Function subscale) in individuals with liver disease related muscle wasting.
These measures of strength impairment and activity limitation were determined to be
valid to assess the effectiveness of the exercise intervention as they distinguished among
levels of liver disease severity and post-liver transplantation and because disease severity, impairment and activity limitation measures were correlated.

The Heel-Rise, Bridging test, 6MWT and 30-Second-Chair stand met both criteria for validity. However, the SF-36 physical function activity limitation measure was not valid for the purposes of this study involving the population with chronic liver disease pre and post transplantation. The measure was not able to distinguish among the known group of liver disease severity, and was weakly correlated with liver disease severity and with the strength impairment and activity limitation measures (Heel-Rise, Bridging test, 6MWT and 30-Second-Chair). The pilot study only measured the physical function subscale and therefore the results cannot be compared to other studies using all the subscales of the SF-36 as a whole. However, the pilot study results contrasted with those of Wiesinger et al. who found that the physical function subscale score was related to liver disease severity. Despite our inability to validate the SF-36 physical function subscale in the pilot study, we used the SF-36 as an outcome measure in the clinical trial as we needed a measure of activity limitation and health related quality of life.

Individuals with chronic liver disease are very ill and present with many symptoms and activity limitations prior to liver transplantation. After transplant many of the symptoms related to endstage liver disease such as encephalopathy, ascites, abdominal bloating, fatigue, and poor appetite clinically resolve. The symptoms of fatigue, large volume ascites, and encephalopathy impact activity performance. Activity performance improves as these symptoms clinically improve through the medical treatment of liver transplantation. Post transplantation the increments of improvement will be smaller and require a more sensitive measure. The SF-36 physical function
subscale has only three levels for scoring. (Limited a lot, Limited a little, Not limited at all). The subjects likely improved at least one level from the medical treatment of transplantation alone, resulting in only one level of the scale remaining to detect differences between groups. Results from the clinical trial demonstrated that both the exercise and walking groups increased in reported activity performance from baseline, but the change was very similar. Additionally, the pre-post intervention change on the SF-36 physical function scale was not correlated with the change in strength impairment, activity limitation, and health related quality of life measures. However, the pre-post intervention change in health related quality of life measure CLDQ was correlated with the strength impairment and activity limitation measures. Because the health related quality of life measure is more correlated with change in strength and activity performance than the SF 36 physical function measure of activity performance it appears that other factors are responsible for the changes in the SF-36 sub-scale. For the purposes of this study and in this population of individuals post liver transplantation, the SF-36 physical function subscale appears to be a poor measure to detect change between groups after an exercise intervention such as that tested in this clinical trial.

**Blinding**

In the clinical trial neither the subjects nor the rater were blinded to group assignment. Lack of blinding increased the potential for bias by the rater when evaluating the effectiveness of the intervention versus the control. If the rater knows the group assignment of the subject he/she may unknowingly encourage subjects to perform better on the outcome measures. Methods for measuring the performance based outcomes were
strictly standardized to minimize bias from lack of blinding. During administration of the 6MWT, the rater provided identical instructions and cues to subjects in both groups based on guidelines developed by the American Thoracic Society. The 30 Second Chair Stand is a timed test. The rater verbalized a standardized set of instructions but did not provide any encouragement during the 30 seconds of testing. The Heel Rise and Bridge tests were performed at a pace set by the rate of a metronome. A measurement device was used to mark the height of the initial rise and to indicate the 50% level used to determine a specific and consistent stopping point of tallying the repetitions for each subject.

The subjects were not blinded. However, both the exercise and the walking groups were aware they were both receiving a potentially beneficial intervention. Several procedures were implemented to reduce the bias from lack of subject blinding. Both groups received equal amount of contact with the investigator through telephone or direct contact in the liver clinic, kept daily logs to document activity, and were provided pedometers to monitor the number of steps walked each day.

**Attrition**

A large proportion of the subjects in the clinical trial withdrew for medical reasons unrelated to the exercise intervention. Half of the subjects enrolled in the trial were not able to complete the study. There was no significant difference in attrition from the exercise or walking groups. Seventy-six percent of withdrawn subjects were from the mild post operative recovery classification. Thus medical status post transplant was not an indicator of who could tolerate the strengthening intervention. Fifteen subjects were
withdrawn because of medical complications from immune suppression or the surgical procedure. Because these subjects were hospitalized for several weeks at a time, they were unable to continue the exercise or walking program. There were no statistically significant differences between the baseline characteristics of subjects who completed the study and those withdrawn. However, it appears the withdrawn subjects were a little weaker and had slightly higher liver enzyme levels at baseline. (Table 3.1) Plantar flexor strength measured by the heel rise test, hip extensor strength measured by the bridge test, and activity performance measured by the 30-second chair stand and 6MWT all were slightly lower at baseline for the withdrawn subjects. These individuals may have some clinical significance for determining if they would not be appropriate candidates for a strengthening intervention such as the elevation in liver enzymes, however there were no statistically significant characteristics for determining appropriateness for intervention from this study.

Subjects were enrolled as early as six weeks post transplantation. However, immune suppression medication is at the highest levels early post-transplantation to prevent organ rejection. High levels of immune suppression may lead to increased risk for systemic infection and frequent hospitalization. Future studies should consider enrolling subjects after the dosage of immune suppression medications is significantly reduced. Such individuals would be more medically stable; therefore, more likely to successfully complete the intervention.
Sample Size

The large attrition of subjects resulted in a small sample size. However, even with the low number of subjects, differences between the groups for pre-post intervention changes in heel rise test, bridging test and 30-second chair stand test achieved statistical significance. Although the pre-post intervention change in 6MWT score was greater for the exercise group than the walking group this difference failed to reach statistical significance. Power Analysis calculations indicated that the current sample size provided power to detect this difference of only .55 and we would require an additional 25 subjects in each group to increase the power to .8.

There are a number of strategies that could be used in future research to recruit a larger number of subjects post liver transplantation. One strategy would be to include more sites for data collection. Only a small number of liver transplants are performed at each transplantation center each year due to the limited availability of viable organs per region of the country. Additionally, a large portion of liver transplants are performed on individuals with Hepatocellular Carcinoma (HCC). This past year nearly one-third of the liver transplants performed at the Miami Transplant Institute involved subjects with HCC. These individuals were excluded from the study because they are weighted higher on the transplant list and received a transplanted liver in a significantly shorter time period resulting in a lesser amount of muscle wasting. Additionally these individuals must undergo chemotherapy, which has multiple negative effects such as fatigue, nausea, myopathy and neuropathy excluding their participation. Therefore including more sites for data collection would maximize the subject pool. Research must continue at the
Miami Transplant Institute; however, multiple transplant centers must be included in future research to obtain a larger sample size for increased power to find statistically significant results.

Generalization of the results of a study is important. If the results of a study can only be applied to a very distinct population usefulness of the findings will be limited. Adding multiple sites for data collection in different geographic areas of the country will increase the ability to generalize the findings. Two thirds of the subjects in our study were Hispanic. Although the numbers of individuals of Hispanic culture are increasing around the United States; our sample of convenience is primarily representative of South Florida, South America, and Cuba. Therefore the ability to generalize our results is limited.

**Directions for Future Research**

**Upper Extremity**

This clinical trial did not address strength impairments or activity limitations related to the upper extremity. We targeted the lower extremity as it is responsible for basic mobility of standing and ambulating. Additionally, surgeons place lifting restrictions on patients post-operatively to prevent abdominal incision dehiscence. Transplantation teams remove lifting restrictions six weeks post-operatively, but many transplant surgeons recommend not lifting heavy objects for significantly longer periods. Enrolling subjects after lifting restrictions are waived would permit subjects to perform upper extremity strengthening. Grip strength was found to be related to liver disease severity in the pilot study. As liver disease severity increased, grip strength decreased.
Future research should examine the effectiveness of a home program targeted at upper extremity resistance strengthening with Theraband® elastic bands. Grip strength measurement can be performed to assess distal upper extremity strength. Proximal upper extremity strength also needs to be addressed as the shoulder complex contains many small muscles that weaken easily and often sustain significant muscle wasting in this population. The Jamar Hand Held dynamometer was used in the pilot as an easy to use, portable measurement tool to assess grip strength in the clinical setting. A similar strain gauge type hand held dynamometer can be used in the clinic as the outcome measure for proximal upper extremity strength.

**Metabolism and Diet**

Muscle wasting may continue as long as nine months post-transplant. Pre-transplant serum albumin level is inversely correlated with post-transplant loss of lean body mass. Hussaini et al. reports the low serum albumin levels reflect persistent hypercatabolism, and accounts for further decreased lean mass post-transplant. Increased dietary protein intake increases muscle protein synthesis in older individuals. Short term and long term strength training in adults also increases the rate of muscle protein synthesis. As hypercatabolism decreases one would anticipate the potential for muscle to rebuild and strength and activity performance to improve. Is there a relationship between normalized energy metabolism, and increased muscle strength and improved activity performance? Do the subjects who demonstrate the greatest strength gains also have more normal energy metabolism than those who do not increase in strength? Future research should include measures of metabolism and energy
expenditure such as a portable gas analyzer. Energy expenditure could be measured during activity limitation measures such as the 6MWT.

This clinical trial did not measure or control nutritional intake. Proper nutrition post transplantation is necessary to provide adequate amounts of protein and caloric intake to prevent further muscle protein breakdown for energy and to promote muscle growth.\textsuperscript{26} The addition of a registered dietitian/nutritionist is required in future clinical trials to provide individualized recommendations on total caloric intake and the most appropriate diet to restore protein stores and increase potential for muscle strengthening. Perhaps with proper protein intake, resistance exercise could produce even greater strength gains and greater improvement in activity performance.

Current research initiatives are now beginning to focus on activity limitations, participation restrictions and the role of exercise in chronic conditions. Pilot data from this randomized trial could be used to support funding to continue research in the area of exercise and chronic disease. Funding would provide more personnel to ensure proper blinding of the rater, access to multiple transplant centers to increase sample size, and help obtain clinic friendly equipment such as hand held dynamometers and a portable gas analyzer.

**Conclusions**

Individuals with liver disease have significant muscle wasting. Liver transplant diminishes or eliminates the rapid energy metabolism that catabolically degrades muscle protein. Current treatment after liver transplantation is insufficient in restoring muscle strength and functional performance to levels of normal healthy adults. The research
reported in this dissertation demonstrated that a home program of lower extremity resistance strengthening increased strength greater than progressive ambulation alone. A home exercise program of resistance strengthening exercise using Theraband ® elastic bands was safe to perform with no negative impact on liver health. Therefore, we recommend the treatment plan for individuals post-liver transplantation include a home exercise program of resistance training in addition to progressive ambulation.

The results of the randomized clinical trial have implications for populations with other similar muscle wasting diseases. Renal disease and pulmonary disease often require transplantation at end stage disease. Individual’s post-renal and pulmonary transplantation have the same potential for improvements in strength and function from resistance strengthening exercise. Previous research has demonstrated resistance strengthening is beneficial for improvement in strength and activity performance in individuals with end stage renal disease. Similar to liver transplantation, as the systemic effects of renal disease resolve post-transplantation, strength and activity performance should clinically improve when treated with a resistance strengthening intervention in addition to progressive ambulation. A home exercise program would also be ideal for the population post-renal transplantation for the same reasons of preventing fatigue for increasing exercise tolerance and promoting adherence as this clinical trial used with post-liver transplant individuals.

Currently, physical therapists are not members of transplantation teams. Physical therapists may treat patients in the acute setting if post operatively these patients are unable to perform basic bed mobility, transfer in and out of bed and ambulate. However, once discharged from the acute hospital setting, patients no longer are under the guidance
of a physical therapist. Providing individuals a new liver is not sufficient to return strength and function to pre-disease levels. Treatment using resistance strengthening of the lower extremities in addition to the current medical care is required to address impaired strength and activity performance. Physical therapists are experts in designing exercise treatment plans for individuals with complex chronic diseases, and are well qualified to develop exercise programs specific for each disease specific transplantation team. To promote the best quality of care for individuals post-transplantation and with chronic disease, physical therapists should be incorporated into the transplant team along with the surgeons, hepatologists, nurses, and nutritionists.
References


158. Ware JE. *SF-36 Health Survey and Interpretation Guide*. Boston, Massachusetts: The Health Institute New England Medical Center; 1997.


APPENDIX I

Post Liver-Transplant Research Exercise Program

Miami Transplant Institute
ANKLE PLANTAR FLEXOR STRENGTHENING EXERCISES

ANKLE PUMPS

NO THERABAND
- Lie on bed or floor with one leg bent.
- Keeping straight leg flat on bed, move the foot forward and backward.
- Perform 3 sets of 12 forward and backward movements.

TOE POINTING USING THERABAND
- Sit on bed or floor with leg in front.
- Hold theraband taught in hands.
- Secure other end of theraband to forefoot of shoe.
- Push toe of foot forward.
- Slowly return and repeat.

PROGRESSION

1) ANKLE PUMPS NO THERABAND
   When you can perform 10 repetitions on the third set easily then begin using theraband. Continue this rule as you progress through the colors of Theraband.

2) YELLOW THERABAND

3) RED THERABAND

4) GREEN THERABAND

5) DOUBLE LEG HEEL RAISES (see next page)

6) SINGLE LEG HEEL RAISES (see next page)
HEEL RAISES

**DOUBLE** Leg Heel Raises

- Stand with your feet shoulder width apart.
- Feet flat on floor.
- Lightly place hands on chair for balance.
- Rise up on toes, hold 3 seconds.
- Slowly return to feet flat on floor.

**SINGLE** Leg Heel Raises

- Stand with one foot flat on floor.
- Bend knee of opposite leg to raise foot off the floor.
- Lightly place hands on chair for balance.
- Rise up on toes of foot on floor.
- Hold 3 seconds.
- Slowly return until foot is flat on floor.
- After 3 sets on the same leg, switch to the opposite leg or alternate legs between sets.

PROGRESSION:

When you can perform 10 repetitions on the third set easily of the **Double** Leg Heel Raises then begin **Single** Leg Heel Raises.
GLUTEUS MEDIUS STRENGTHENING EXERCISES

HIP SIDE GLIDES

HIP SIDE GLIDES ON YOUR BACK
• Lie on your back on the bed or floor.
• Keep one leg still.
• Slide your other leg to the side, keeping your knee straight.
• Then return leg to original position.

SIDELEYING HIP LEG RAISES
• Lie on your side on the bed or floor.
• Bend the knee on the side you are laying for support.
• Raise the upper leg toward the ceiling.
• Slowly lower leg back down to the floor.

PROGRESSION
• Begin performing the HIP SIDE GLIDES ON YOUR BACK exercise.
• When you can perform 10 repetitions on the third set easily then begin the SIDELEYING HIP LEG RAISES exercise.
• When you can perform 10 repetitions on the third set easily then begin STANDING HIP LEG RAISES (see next page).
• When you can perform 10 repetitions on the third set easily then begin STANDING HIP LEG RAISES USING THERABAND (see next page).

1) YELLOW THERABAND
2) RED THERABAND
3) GREEN THERABAND
4) BLUE THERABAND
STANDING HIP SIDE RAISES

**NO THERABAND**
- Stand sideways with feet together near a chair.
- Hold onto chair for balance support only.
- Slowly raise leg opposite chair out to the side.
- Keep trunk and head straight upright.
- Do not lean trunk to raise leg.

**USING THERABAND**
- Stand sideways with feet together near a chair.
- Hold onto chair for balance support only.
- Place towel around leg opposite chair.
- Loop theraband around towel on leg opposite chair.
- Attach other end of theraband to chair leg.
- Slowly raise leg opposite chair out to the side.
- Keep trunk and head straight upright.
- Do not lean trunk to raise leg.
GLUTEUS MAXIMUS STRENGTHENING EXERCISES

BUTTOCK SQUEEZE

- Lie supine on bed or floor.
- Legs together and straight.
- Slowly tighten both buttocks together.
- Hold for 3 seconds and relax.
- Perform 3 sets of 10 repetitions.
- When you can perform 10 repetitions on the third set easily progress to Double Leg Bridging.
LEG PRESS

- Sit in chair.
- Loop theraband around bottom of one shoe.
- Hold theraband with hands.
- Push leg down straightening your knee.
- Slowly return to starting position.
- After the third set switch legs and perform 3 more sets.

PROGRESSION

1) LEG PRESS NO THERABAND
   When you can perform 10 repetitions on the third set easily then begin using theraband. Continue this rule as you progress through the colors of theraband.

2) YELLOW THERABAND

3) RED THERABAND

4) GREEN THERABAND

5) BLUE THERABAND
BRIDGING

DOUBLE LEG

- Lie on bed or floor with knees bent and feet flat.
- Slowly raise buttocks, keeping stomach tight.
- Hold 3 seconds.
- Slowly return to starting position.

SINGLE LEG

- Lie on bed or floor with only one knee bent, foot flat.
- Keep other leg straight.
- Slowly raise buttocks using only the bent leg.
- Hold 3 seconds.
- Slowly return to starting position.
- After completion of the third set, switch legs and perform 3 more sets.

PROGRESSION:
Begin with Double Leg Bridging. When you can perform 10 repetitions easily on the third set, begin Single Leg Bridging. Continue with Single leg bridging 3 sets of 10 until the end of the study.
THIGH SQUEEZE

- Lie on your back on a firm bed or floor.
- Bend one leg so foot is flat on bed or floor.
- Slowly tighten the muscles in the thigh of the straight leg.
- Hold for 3 seconds and relax.
- Perform 3 sets of 10 repetitions.
  - Then switch and perform with other leg.
KNEE EXTENSION

NO THERABAND
- Sit with knee bent to 90 degrees.
- Straighten leg at the knee.
- Hold for 3 seconds
- Slowly return to start position.

USING THERABAND
- Sit with knee bent to 90 degrees.
- Wrap hand towel/cloth around ankle loosely.
- Attach theraband to ankle of right leg around the towel.
- Wrap theraband around chair and anchor to left leg.
- Straighten leg at the knee
- Hold for 3 seconds.
- Slowly return to start position.

PROGRESSION

1) KNEE EXTENSION NO THERABAND
   When you can perform 10 repetitions on the third set easily then begin using theraband. Continue this rule as you progress through the colors of theraband.

2) YELLOW THERABAND

3) RED THERABAND

4) GREEN THERABAND

5) BLUE THERABAND
CHAIR STANDS

**NO THERABAND**
- Sit on edge of chair, feet flat on floor.
- Stand upright, extend knees fully.
- Slowly return to sitting position.

**USING THERABAND**
- Sit on edge of chair, feet flat on floor.
- Anchor theraband under feet.
- Stand upright, extend knees fully.
- Slowly return to start position.

PROGRESSION

1) **NO THERABAND**
   - When you can perform 10 repetitions on the third set easily then begin using theraband. Continue this rule as you progress through the colors of theraband.

2) **YELLOW THERABAND**

3) **RED THERABAND**

4) **GREEN THERABAND**

5) **BLUE THERABAND**
WALL SLIDES

NO THERABAND

- Lean on wall, feet shoulder width apart.
- Slowly bend knees to 45 degrees.
- Hold 3 secs.
- Return to standing, straightening knees fully.

USING THERABAND

- Lean on wall, feet shoulder width apart.
- Anchor theraband under feet.
- Slowly bend knees to 45 degrees
- Straighten knees fully.
- Slowly return to bent knee position.

PROGRESSION

1) WALL SLIDES NO THERABAND
   When you can perform 10 repetitions on the third set easily then begin using theraband. Continue this rule as you progress through the colors of theraband.

2) YELLOW THERABAND

3) RED THERABAND

4) GREEN THERABAND

5) BLUE THERABAND
STEP UPS

- Place one foot on a sturdy book that will not slide.
- Keep opposite foot flat on floor.
- If needed you may touch the wall or a chair back with your hands to help you maintain your balance.
- Straighten the knee of the leg you placed on the book elevating your opposite foot off the floor.
- Slowly bend your knee until the opposite foot returns to flat on floor.

PROGRESSION:

Once you can perform 10 repetitions easily on the third set, slowly increase the thickness of the book or use a step of 4 inches in height. Once you can easily perform 10 repetitions on the third set progress to a step of 6 inches in height and then progress to a step of 8 inches in height.
Programa de Ejercicios en Investigación Post-Transplante Hepático

Miami Transplant Institute
FLEXIONES DE TOBILLO

**SIN THERABAND**
- Acuéstese en la cama o en el piso con una pierna doblada.
- Mantenga recta la pierna estirada sobre la cama, mueva el pie hacia adelante y hacia atrás.
- Realice 3 series de 12 movimientos hacia adelante y hacia atrás.

**CON THERABAND APUNTAR DEDOS DEL PIE**
- Siéntese en la cama o en el piso con las piernas hacia adelante.
- Sostenga en sus manos la Theraband tensa.
- Fije el otro extremo de la Theraband al antepié del zapato.
- Empuje el dedo del pie hacia delante.
- Regrese lentamente y repita.

PROGRESO

1) FLEXIONES DE TOBILLO SIN THERABAND
   Cuando pueda realizar fácilmente 10 repeticiones en la tercera serie entonces comience a utilizar la Theraband. Continúe con esta regla en la medida que progresa con los colores de Theraband.

2) THERABAND AMARILLA
3) THERABAND ROJA
4) THERABAND VERDE
5) ELEVACIONES DE LAS DOS PIERNAS AL MISMO TIEMPO (Véase la página siguiente)
6) ELEVACIONES DE UNA PIerna (Véase la página siguiente)
ELEVACIONES DE TALÓN

ELEVACIONES DE LAS DOS PIERNAS

- Póngase de pie con los pies separados a la distancia de los hombros.
- Apoye las plantas de los pies en el piso.
- Coloque sus manos ligeramente sobre la silla para mantener el equilibrio.
- Elevese sobre sus dedos, manténgase así por 3 segundos.
- Regrese lentamente a la posición de pie apoyado en el piso.

ELEVACIONES DE UNA SOLA PIerna

- Póngase de pie con un pie apoyado en el piso.
- Flexione la rodilla de la pierna opuesta para elevar el pie.
- Coloque sus manos ligeramente sobre la silla para mantener el equilibrio.
- Elevese con los dedos del pie apoyado en el piso.
- Manténgase así por 3 segundos.
- Regrese lentamente hasta que el pie esté apoyado en el piso.
- Después de 3 series sobre la misma pierna, cambie de pierna o alterne las piernas entre cada serie.

PROGRESO:
Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie de la Elevación de Dos Piernas la Elevación de Una Pierna.
Deslizamiento Lateral de Caderas

DESLIZAMIENTO LATERAL DE CADERA SOBRE SU ESPALDA

· Acuéstese boca arriba en la cama o en el piso.
· Mantenga inmóvil una pierna.
· Deslice la otra pierna hacia un lado manteniendo derecha la rodilla.
· Regrese la pierna a su posición original.

ELEVACIÓN DE PIerna CON CADERA EN POSICIÓN LATERAL

· Acuéstese de lado en la cama o en el piso.
· Flexione la rodilla del lado acostado para apoyarse.
· Eleve la pierna superior hacia el techo.
· Regrese lentamente la pierna al piso.

PROGRESO

· Comience el ejercicio DESLIZAMIENTO LATERAL DE CADERAS SOBRE SU ESPALDA.
· Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie comience el ejercicio ELEVACIÓN DE PIerna CON CADERA EN POSICIÓN LATERAL.
· Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie comience los ejercicios ELEVACIÓN LATERAL DE CADERA DE PIE (Véase próxima página).
· Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie comience el ejercicio ELEVACIÓN LATERAL DE CADERA DE PIE UTILIZANDO THERABAND (Véase próxima página).

1) THERABAND AMARILLA
2) THERABAND ROJA
3) THERABAND VERDE
4) THERABAND AZUL
ELEVACIÓN LATERAL DE CADERA DE PIE

**SIN THERABAND**
- Párese de lado con sus pies juntos cerca de una silla.
- Sostenga la silla sólo para mantener el equilibrio.
- Eleve lentamente la pierna del lado opuesto de la silla hacia un lado.
- Mantenga el torso y cabeza erguidos.
- No doble el torso para elevar la pierna.

**CON THERABAND**
- Párese de lado con sus pies juntos cerca de una silla.
- Sostenga la silla sólo para mantener el equilibrio.
- Coloque una toalla alrededor de la pierna del lado opuesto de la silla.
- Enlace la Theraband en la toalla sobre la pierna del lado opuesto de la silla.
- Coloque el otro extremo de la Theraband a la pata de la silla.
- Eleve lentamente la pierna del lado opuesto de la silla hacia afuera de lado.
- Mantenga el torso y la cabeza erguidos.
- No doble el torso para elevar la pierna.
APRETAR GLÚTEOS

- Acuéstese boca arriba en la cama o en el piso.
- Coloque las piernas juntas y derechas.
- Apriete glúteos lentamente.
- Manténgase así por 3 segundos y suelte.
- Realice 3 series de 10 repeticiones.
- Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie avance a Puente con Dos Piernas.
PRENSA DE PIERNAS

1. Siéntese en una silla.
2. Enlace la Theraband en la planta de un zapato.
3. Sostenga la Theraband con las manos.
4. Empuje la pierna hacia abajo enderezando la rodilla.
5. Regrese lentamente a la posición inicial.
6. Después de la tercera serie cambie de pierna y realice 3 series adicionales.

PROGRESO

1) PRENSA DE PIERNAS SIN THERABAND
   Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie comience a utilizar la Theraband. Continúe esta regla mientras progresse en los colores de Theraband.

2) THERABAND AMARILLA

3) THERABAND ROJA

4) THERABAND VERDE

5) THERABAND AZUL
PUENTE

DOS PIERNAS

· Acuéstese en la cama o en el piso con las rodillas dobladas y pies apoyados.
· Eleve glúteos lentamente, manteniendo el estomago tenso.
· Mantenga esta posición 3 segundos.
· Regrese lentamente a la posición inicial.

UNA PIERNA

· Acuéstese en la cama o en el piso con sólo una rodilla flexionada, pie apoyado.
· Mantenga la otra pierna recta.
· Eleve glúteos lentamente utilizando sólo la pierna flexionada.
· Mantenga esta posición 3 segundos.
· Regrese lentamente a la posición inicial.
· Al culminar la tercera serie, cambie de pierna y realice 3 series adicionales.

PROGRESO:
Comience con **Puente de Dos Piernas.** Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie, inicie el **Puente de una Pierna.** Continúe con el **Puente de una Pierna 3 series de 10 hasta finalizar el estudio.**
APRETAR MUSLO

1. Acuéstese boca arriba en una cama firme o en el piso.
2. Flexione una pierna de manera que el pie quede apoyado en la cama o en el piso.
3. Presione lentamente los músculos del muslo de la pierna recta.
4. Manténgase así por 3 segundos y suelte.
5. Realice 3 series de 10 repeticiones.
6. Cambie y realice el ejercicio con la otra pierna.
EXTENSIÓN DE LA RODILLA

SIN THERABAND

- Siéntese con la rodilla flexionada a 90 grados.
- Enderece la rodilla.
- Manténgase por 3 segundos
- Regrese lentamente a la posición inicial.

CON THERABAND

- Siéntese con la rodilla flexionada a 90 grados.
- Envuelva holgadamente una toalla de mano o paño alrededor del tobillo.
- Coloque la Theraband en el tobillo de la pierna derecha alrededor de la toalla.
- Pase la Theraband alrededor de la silla y ánclela en su pierna izquierda.
- Enderece la rodilla
- Manténgase por 3 segundos.
- Regrese lentamente a la posición inicial.

PROGRESO

1) EXTENSIÓN DE RODILLA SIN THERABAND
   Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie comience a utilizar la Theraband. Continúe esta regla mientras progrese en los colores de Theraband.

2) THERABAND AMARILLA

3) THERABAND ROJA

4) THERABAND VERDE

5) THERABAND AZUL
SENTADOS EN SILLAS

SIN THERABAND
- Siéntese en el borde de la silla con los pies apoyados en el piso.
- Párese derecho, extienda rodillas completamente.
- Regrese lentamente a la posición sentada.

CON THERABAND
- Siéntese en el borde de la silla con los pies apoyados en el piso.
- Añada la Theraband debajo de los pies.
- Párese derecho, extienda rodillas completamente.
- Regrese lentamente a la posición inicial.

PROGRESO
1) SIN THERABAND
   Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie comience a utilizar la Theraband. Continúe esta regla mientras progrese en los colores de Theraband.

2) THERABAND AMARILLO
3) THERABAND ROJO
4) THERABAND VERDE
5) THERABAND AZUL
DESLIZAMIENTO CONTRA LA PARED

**SIN THERABAND**
- Recuééstese de la pared, pies separados a la anchura de los hombros.
- Flexione lentamente rodillas a 45 grados.
- Mantenga esta posición por 3 segundos.
- Únese, enderece completamente las rodillas.

**CON THERABAND**
- Recuééstese de la pared, pies separados a la anchura de los hombros.
- Anclar la Theraband debajo de los pies.
- Flexione lentamente rodillas a 45 grados.
- Enderece completamente las rodillas.
- Regrese lentamente a la posición de rodilla flexionada.

PROGRESO

1) DESLIZAMIENTO CONTRA PARED SIN THERABAND
   Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie comience a utilizar la Theraband. Continúe esta regla mientras progresa en los colores de Theraband.

2) THERABAND AMARILLO

3) THERABAND ROJO

4) THERABAND VERDE

5) THERABAND AZUL
· Coloque un pie sobre un libro firme que no se deslice.
· Mantenga el otro pie apoyado en el piso.
· Si es necesario, puede tocar la pared o el espalda de la silla con sus manos para ayudar a mantener el equilibrio.
· Enderece la rodilla de la pierna que colocó sobre el libro elevando su otro pie del piso.
· Flexione lentamente su rodilla hasta que el pie opuesto regrese a apoyarse en el piso.

PROGRESO:

Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie, incremente progresivamente el grosor del libro o utilice un escalón de 4 pulgadas de altura. Cuando pueda realizar 10 repeticiones fácilmente en la tercera serie incremente el escalón a 6 pulgadas de altura y luego incremente a 8 pulgadas de altura.
## APPENDIX IV

### ¿Cuándo cambio al próximo ejercicio?

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## APPENDIX V

### YOUR DAILY EXERCISE LOG

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<td>Set 3 Reps</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sidelying Hip Leg Raises</td>
<td>Set 1 Reps ___</td>
<td>Set 2 Reps ___</td>
<td>Set 3 Reps</td>
<td>☐</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing Hip Leg Raises</td>
<td>Set 1 Reps ___</td>
<td>Set 2 Reps ___</td>
<td>Set 3 Reps</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Buttock Squeeze</td>
<td>Set 1 Reps ___</td>
<td>Set 2 Reps ___</td>
<td>Set 3 Reps</td>
<td>☐</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bridging</td>
<td>Set 1 Reps ___</td>
<td>Set 2 Reps ___</td>
<td>Set 3 Reps</td>
<td>☐</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg Press</td>
<td>Set 1 Reps ___</td>
<td>Set 2 Reps ___</td>
<td>Set 3 Reps</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Thigh Squeeze</td>
<td>Set 1 Reps ___</td>
<td>Set 2 Reps ___</td>
<td>Set 3 Reps</td>
<td>☐</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee Extension</td>
<td>Set 1 Reps ___</td>
<td>Set 2 Reps ___</td>
<td>Set 3 Reps</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Chair Stands</td>
<td>Set 1 Reps ___</td>
<td>Set 2 Reps ___</td>
<td>Set 3 Reps</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Wall Slides</td>
<td>Set 1 Reps ___</td>
<td>Set 2 Reps ___</td>
<td>Set 3 Reps</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Step Ups</td>
<td>Set 1 Reps ___</td>
<td>Set 2 Reps ___</td>
<td>Set 3 Reps</td>
<td>Book</td>
<td>&quot;&quot; Step</td>
<td>&quot;&quot; Step</td>
<td>☐</td>
</tr>
</tbody>
</table>

### Color Code

<table>
<thead>
<tr>
<th>No Theraband</th>
<th>Yellow Theraband</th>
<th>Red Theraband</th>
<th>Green Theraband</th>
<th>Blue Theraband</th>
</tr>
</thead>
</table>

### Instructions:

1) Fill in the repetitions completed for each set of only the exercises you performed based on your progression sheet. (When Do I Switch to the Next Exercise?)

2) Check the box of the color of Theraband you used.

---

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## APPENDIX VI

### SU REGISTRO DIARIO DE EJERCICIOS

<table>
<thead>
<tr>
<th>Fecha: Lunes</th>
<th>Martes</th>
<th>Miércoles</th>
<th>Jueves</th>
<th>Viernes</th>
<th>Sábado</th>
<th>Domingo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flexiones de tobillo</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apuntar dedos del pie</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Elevación de talón</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Deslizamiento lateral de cadera</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Elevación de pierna con cadera en posición lateral</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Elevación de cadera estando de pie</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apretar glúteos</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Puente</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prensa de piernas</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apretar muslo</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extensión de la rodilla</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Levantarse de la silla</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Deslizamiento contra la pared</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Escalón</strong></td>
<td>Set 1 Reps</td>
<td>Set 2 Reps</td>
<td>Set 3 Reps</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Código de Colores

| Sin Theraband | Theraband Amarilla | Theraband Roja | Theraband Verde | Theraband Azul |

**Instrucciones:**

1. Llene las repeticiones completadas solamente para los sets de ejercicios que usted realizó buscándose en su hoja de progreso (¿Cuándo cambio el próximo ejercicio?)
2. Marque (✓) el recuadro del color de la Theraband que utilizó.
### WEEK # 1

#### WEEKLY WALKING LOG

<table>
<thead>
<tr>
<th>Sunday</th>
<th>Date:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk 1</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td>Walk 2</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td><strong>Total # of Steps for the Day</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monday</th>
<th>Date:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk 1</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td>Walk 2</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td><strong>Total # of Steps for the Day</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tuesday</th>
<th>Date:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk 1</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td>Walk 2</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td><strong>Total # of Steps for the Day</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wednesday</th>
<th>Date:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk 1</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td>Walk 2</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td><strong>Total # of Steps for the Day</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thursday</th>
<th>Date:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk 1</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td>Walk 2</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td><strong>Total # of Steps for the Day</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Friday</th>
<th>Date:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk 1</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td>Walk 2</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td><strong>Total # of Steps for the Day</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Saturday</th>
<th>Date:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk 1</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td>Walk 2</td>
<td># of Steps</td>
<td></td>
</tr>
<tr>
<td><strong>Total # of Steps for the Day</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX VIII

SEMANA # 1 REGISTRO SEMANAL DE CAMINATAS

<table>
<thead>
<tr>
<th>Día</th>
<th>Fecha</th>
<th>Caminata 1</th>
<th># de Pasos</th>
<th>Caminata 2</th>
<th># de Pasos</th>
<th>Total # de Pasos del Día</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domingo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lunes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miércoles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jueves</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viernes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sábado</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX IX

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ✗ in the one box that best describes your answer.

1. **In general, would you say your health is:**

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✗</td>
</tr>
</tbody>
</table>

2. **Compared to one year ago, how would you rate your health in general now?**

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>✗</td>
<td></td>
</tr>
</tbody>
</table>

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(SF-36v2 Standard, US Version 2.0)
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports: □ □ □
- **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf: □ □ □
- Lifting or carrying groceries: □ □ □
- Climbing several flights of stairs: □ □ □
- Climbing one flight of stairs: □ □ □
- Bending, kneeling, or stooping: □ □ □
- Walking more than a mile: □ □ □
- Walking several hundred yards: □ □ □
- Walking one hundred yards: □ □ □
- Bathing or dressing yourself: □ □ □
4. During the *past 4 weeks*, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Cut down on the *amount of time* you spent on work or other activities
- *Accomplished less* than you would like
- *Were limited in the kind of* work or other activities
- *Had difficulty* performing the work or other activities (for example, it took extra effort)

5. During the *past 4 weeks*, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Cut down on the *amount of time* you spent on work or other activities
- *Accomplished less* than you would like
- Did work or other activities *less carefully than usual*
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

7. How much bodily pain have you had during the past 4 weeks?

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

1. Did you feel full of life? ........................................... □ □ □ □ □
2. Have you been very nervous? ...................................... □ □ □ □ □ □
3. Have you felt so down in the dumps that nothing could cheer you up? ........................................ □ □ □ □ □
4. Have you felt calm and peaceful? ................................. □ □ □ □ □ □ □ □
5. Did you have a lot of energy? ....................................... □ □ □ □ □ □ □ □
6. Have you felt downhearted and depressed? ........................ □ □ □ □ □ □ □ □
7. Did you feel worn out? ............................................... □ □ □ □ □ □ □ □
8. Have you been happy? ................................................... □ □ □ □ □ □ □ □
9. Did you feel tired? .................................................... □ □ □ □ □ □ □ □

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

□ □ □ □
11. How TRUE or FALSE is each of the following statements for you?

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don't know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>


THANK YOU FOR COMPLETING THESE QUESTIONS!
APPENDIX X

Su Salud y Bienestar

Esta encuesta le pide sus opiniones acerca de su salud. Esta información permitirá saber cómo se siente y qué tan bien puede hacer usted sus actividades normales. ¡Gracias por contestar estas preguntas!

Para cada una de las siguientes preguntas, por favor marque con una X la casilla que mejor describa su respuesta.

1. En general, ¿diría que su salud es:

<table>
<thead>
<tr>
<th>Excelente</th>
<th>Muy buena</th>
<th>Buena</th>
<th>Pasable</th>
<th>Mala</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

2. Comparando su salud con la de hace un año, ¿cómo la calificaría en general ahora?

<table>
<thead>
<tr>
<th>Mucho mejor ahora que hace un año</th>
<th>Algo mejor ahora que hace un año</th>
<th>Más o menos igual ahora que hace un año</th>
<th>Algo peor ahora que hace un año</th>
<th>Mucho peor ahora que hace un año</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>
3. Las siguientes preguntas se refieren a actividades que usted podría hacer durante un día típico. ¿Su estado de salud actual lo/la limita para hacer estas actividades? Si es así, ¿cuánto?

<table>
<thead>
<tr>
<th>Actividad</th>
<th>Sí, me limita mucho</th>
<th>Sí, me limita un poco</th>
<th>No, no me limita en absoluto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actividades vigorosas, tales como correr, levantar objetos pesados, participar en deportes intensos</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Actividades moderadas, tales como mover una mesa, empujar una aspiradora, jugar al bowling o al golf o trabajar en el jardín</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Levantar o cargar las compras del mercado</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Subir varios pisos por la escalera</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Subir un piso por la escalera</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Doblarse, arrodillarse o agacharse</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Caminar más de una milla</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Caminar varias cuadras (varios cientos de metros)</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Caminar una cuadra (unos cien metros)</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Bañarse o vestirse</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

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4. **Durante las últimas 4 semanas, ¿cuánto tiempo ha tenido usted alguno de los siguientes problemas con el trabajo u otras actividades diarias regulares a causa de su salud física?**

<table>
<thead>
<tr>
<th>frecuencia</th>
<th>siempre</th>
<th>casi</th>
<th>algunas veces</th>
<th>casi nunca</th>
<th>nunca</th>
</tr>
</thead>
<tbody>
<tr>
<td>sí</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. Ha reducido el tiempo que dedicaba al trabajo u otras actividades
b. Ha logrado hacer menos de lo que le hubiera gustado
c. Ha tenido limitaciones en cuanto al tipo de trabajo u otras actividades
d. Ha tenido dificultades en realizar el trabajo u otras actividades (por ejemplo, le ha costado más esfuerzo)

5. **Durante las últimas 4 semanas, ¿cuánto tiempo ha tenido usted alguno de los siguientes problemas con el trabajo u otras actividades diarias regulares a causa de algún problema emocional (como sentirse deprimido/a o ansioso/a)?**

<table>
<thead>
<tr>
<th>frecuencia</th>
<th>siempre</th>
<th>casi</th>
<th>algunas veces</th>
<th>casi nunca</th>
<th>nunca</th>
</tr>
</thead>
<tbody>
<tr>
<td>sí</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. Ha reducido el tiempo que dedicaba al trabajo u otras actividades
b. Ha logrado hacer menos de lo que le hubiera gustado
c. Ha hecho el trabajo u otras actividades con menos cuidado de lo usual

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6. **Durante las últimas 4 semanas**, ¿en qué medida su salud física o sus problemas emocionales han dificultado sus actividades sociales normales con la familia, amigos, vecinos o grupos?

<table>
<thead>
<tr>
<th>Nada en absoluto</th>
<th>Ligeramente</th>
<th>Medianamente</th>
<th>Bastante</th>
<th>Extremadamente</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5  ☐ 6

7. **¿Cuánto dolor físico ha tenido usted durante las últimas 4 semanas?**

<table>
<thead>
<tr>
<th>Ningún dolor</th>
<th>Muy poco</th>
<th>Poco</th>
<th>Moderado</th>
<th>Severo</th>
<th>Muy severo</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5  ☐ 6

8. **Durante las últimas 4 semanas**, ¿cómo ha dificultado el dolor su trabajo normal (incluyendo tanto el trabajo fuera de casa como los quehaceres domésticos)?

<table>
<thead>
<tr>
<th>Nada en absoluto</th>
<th>Un poco</th>
<th>Medianamente</th>
<th>Bastante</th>
<th>Extremadamente</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5  ☐ 6

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9. Estas preguntas se refieren a cómo se siente usted y a cómo le han ido las cosas durante las últimas 4 semanas. Para cada pregunta, por favor dé la respuesta que más se acerca a la manera como se ha sentido usted. ¿Cuánto tiempo durante las últimas 4 semanas...

<table>
<thead>
<tr>
<th>Siempre</th>
<th>Casi siempre</th>
<th>Algunas veces</th>
<th>Casi nunca</th>
<th>Nunca</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- se ha sentido lleno/a de vida? □ 1 □ 2 □ 3 □ 4 □ 5
- se ha sentido muy nervioso/a? □ 1 □ 2 □ 3 □ 4 □ 5
- se ha sentido tan decepcionado/a de ánimo que nada podía alentarlo/la? □ 1 □ 2 □ 3 □ 4 □ 5
- se ha sentido tranquilo/a y sosogado/a? □ 1 □ 2 □ 3 □ 4 □ 5
- ha tenido mucha energía? □ 1 □ 2 □ 3 □ 4 □ 5
- se ha sentido desanimado/a y deprimido/a? □ 1 □ 2 □ 3 □ 4 □ 5
- se ha sentido agotado/a? □ 1 □ 2 □ 3 □ 4 □ 5
- se ha sentido feliz? □ 1 □ 2 □ 3 □ 4 □ 5
- se ha sentido cansado/a? □ 1 □ 2 □ 3 □ 4 □ 5

10. Durante las últimas 4 semanas, ¿cuánto tiempo su salud física o sus problemas emocionales han dificultado sus actividades sociales (como visitar amigos, parientes, etc.)?

<table>
<thead>
<tr>
<th>Siempre</th>
<th>Casi siempre</th>
<th>Algunas veces</th>
<th>Casi nunca</th>
<th>Nunca</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

□ 1 □ 2 □ 3 □ 4 □ 5

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11. ¿Qué tan CIERTA o FALSA es cada una de las siguientes frases para usted?

<table>
<thead>
<tr>
<th>Claramente</th>
<th>Mayormente</th>
<th>No sé</th>
<th>Mayormente</th>
<th>Claramente</th>
</tr>
</thead>
<tbody>
<tr>
<td>certa</td>
<td>certa</td>
<td></td>
<td>falsa</td>
<td>falsa</td>
</tr>
</tbody>
</table>

1. Parece que yo me enfermo un poco más fácilmente que otra gente.

2. Tengo tan buena salud como cualquiera que conozco.

3. Creo que mi salud va a empeorar.

4. Mi salud es excelente.

¡Gracias por contestar estas preguntas!
APPENDIX XI

The Chronic Liver Disease Questionnaire (CLDQ)

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.

1. How much of the time during the last two weeks have you been troubled by a feeling of abdominal bloating?
   1 All of the time
   2 Most of the time
   3 A good bit of the time
   4 Some of the time
   5 A little of the time
   6 Hardly any of the time
   7 None of the time

2. How much of the time have you been tired or fatigued during the last two weeks?
   1 All of the time
   2 Most of the time
   3 A good bit of the time
   4 Some of the time
   5 A little of the time
   6 Hardly any of the time
   7 None of the time

3. How much of the time during the last 2 weeks have you experienced bodily pain?
   1 All of the time
   2 Most of the time
   3 A good bit of the time
   4 Some of the time
   5 A little of the time
   6 Hardly any of the time
   7 None of the time

4. How often during the last two weeks have you felt sleepy during the day?
   1 All of the time
   2 Most of the time
   3 A good bit of the time
   4 Some of the time
   5 A little of the time
   6 Hardly any of the time
   7 None of the time

Younossi 1997
Revised December 28, 1998
5. How much of the time during the last two weeks have you experienced abdominal pain?
   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

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. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

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. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

8. How much of the time in the last two weeks have you been bothered by having decreased strength?
   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

9. How often during last 2 weeks have you had trouble lifting or carrying heavy objects?
   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

Younossi 1997
Revised December 28, 1998
10. How often during the last two weeks have you felt anxious?
   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

11. How often during the last 2 weeks have you felt a decreased level of energy?
   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

12. How much of the time during the last two weeks have you felt unhappy?
   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

13. How often during the last two weeks have you felt drowsy?
   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

14. How much of the time during the last two weeks have you been bothered by a limitation of your diet?
   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

Younossi 1997
Revised December 28, 1998
15. How often during the last two weeks have you been irritable?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

16. How much of the time during the last two weeks have you had difficulty sleeping at night?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

17. How much of the time during the last two weeks have you been troubled by a feeling of abdominal discomfort?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

18. How much of the time during the last two weeks have you been worried about the impact your liver disease has on your family?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

19. How much of the time during the last two weeks have you had mood swings?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Younossi 1997
Revised December 28, 1998
20. How much of the time during the last two weeks have you been unable to fall asleep at night?

1. All of the time  
2. Most of the time  
3. A good bit of the time  
4. Some of the time  
5. A little of the time  
6. Hardly any of the time  
7. None of the time  

21. How often during the last two weeks have you had muscle cramps?

1. All of the time  
2. Most of the time  
3. A good bit of the time  
4. Some of the time  
5. A little of the time  
6. Hardly any of the time  
7. None of the time  

22. How much of the time during the last two weeks have you been worried that your symptoms will develop into major problems?

1. All of the time  
2. Most of the time  
3. A good bit of the time  
4. Some of the time  
5. A little of the time  
6. Hardly any of the time  
7. None of the time  

23. How much of the time during the last two weeks have you had a dry mouth?

1. All of the time  
2. Most of the time  
3. A good bit of the time  
4. Some of the time  
5. A little of the time  
6. Hardly any of the time  
7. None of the time  

24. How much of the time during the last two weeks have you felt depressed?

1. All of the time  
2. Most of the time  
3. A good bit of the time  
4. Some of the time  
5. A little of the time  
6. Hardly any of the time  
7. None of the time  

Younossi 1997  
Revised December 28, 1998
25. How much of the time during the last two weeks have you been worried about your condition getting worse?

1  All of the time
2  Most of the time
3  A good bit of the time
4  Some of the time
5  A little of the time
6  Hardly any of the time
7  None of the time

26. How much of the time during the last two weeks have you had problems concentrating?

1  All of the time
2  Most of the time
3  A good bit of the time
4  Some of the time
5  A little of the time
6  Hardly any of the time
7  None of the time

27. How much of the time have you been troubled by itching during the last two weeks?

1  All of the time
2  Most of the time
3  A good bit of the time
4  Some of the time
5  A little of the time
6  Hardly any of the time
7  None of the time

28. How much of the time during the last two weeks have you been worried about never feeling any better?

1  All of the time
2  Most of the time
3  A good bit of the time
4  Some of the time
5  A little of the time
6  Hardly any of the time
7  None of the time

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  All of the time
2  Most of the time
3  A good bit of the time
4  Some of the time
5  A little of the time
6  Hardly any of the time
7  None of the time

Younossi 1997
Revised December 28, 1998
APPENDIX XII

Cuestionario de la Enfermedad Hepática Crónica

Este cuestionario ha sido diseñado para averiguar cómo se ha estado sintiendo durante las dos últimas semanas. Le preguntaremos acerca de sus síntomas relacionados con su enfermedad hepática, cómo se ha visto afectado en la realización de sus actividades, y cómo ha estado su ánimo. Por favor, responda todas las preguntas y seleccione solamente una respuesta para cada pregunta.

1) ¿Cuánto tiempo durante las dos últimas semanas ha sentido molestia por hinchazón abdominal?
   1) Todo el tiempo
   2) La mayor parte del tiempo
   3) Una buena parte del tiempo
   4) Parte del tiempo
   5) Poco tiempo
   6) Casi nunca
   7) Nunca

2) ¿Cuánto tiempo durante las dos últimas semanas se ha sentido cansado o fatigado?
   1) Todo el tiempo
   2) La mayor parte del tiempo
   3) Una buena parte del tiempo
   4) Parte del tiempo
   5) Poco tiempo
   6) Casi nunca
   7) Nunca

3) ¿Cuánto tiempo durante las dos últimas semanas sintió dolor corporal?
   1) Todo el tiempo
   2) La mayor parte del tiempo
   3) Una buena parte del tiempo
   4) Parte del tiempo
   5) Poco tiempo
   6) Casi nunca
   7) Nunca

4) ¿Con qué frecuencia durante las dos últimas semanas ha tenido sueño durante el día?
   1) Todo el tiempo
   2) La mayor parte del tiempo
   3) Una buena parte del tiempo
   4) Parte del tiempo
   5) Poco tiempo
   6) Casi nunca
   7) Nunca
5) ¿Cuánto tiempo durante las dos últimas semanas sintió dolor abdominal?
   1) Todo el tiempo
   2) La mayor parte del tiempo
   3) Una buena parte del tiempo
   4) Parte del tiempo
   5) Poco tiempo
   6) Casi nunca
   7) Nunca

6) ¿Cuánto tiempo durante las dos últimas semanas la dificultad para respirar ha sido un problema para usted en sus actividades diarias?
   1) Todo el tiempo
   2) La mayor parte del tiempo
   3) Una buena parte del tiempo
   4) Parte del tiempo
   5) Poco tiempo
   6) Casi nunca
   7) Nunca

7) ¿Cuántas veces durante las dos últimas semanas no ha podido comer tanto como quisiera?
   1) Todo el tiempo
   2) La mayor parte del tiempo
   3) Una buena parte del tiempo
   4) Parte del tiempo
   5) Poco tiempo
   6) Casi nunca
   7) Nunca

8) ¿Cuánto tiempo durante las dos últimas semanas le ha molestado sentir que tiene menos fuerzas?
   1) Todo el tiempo
   2) La mayor parte del tiempo
   3) Una buena parte del tiempo
   4) Parte del tiempo
   5) Poco tiempo
   6) Casi nunca
   7) Nunca

9) ¿Cuánto tiempo durante las dos últimas semanas ha tenido problemas levantando o cargando objetos pesados?
   1) Todo el tiempo
   2) La mayor parte del tiempo
   3) Una buena parte del tiempo
   4) Parte del tiempo
   5) Poco tiempo
   6) Casi nunca
   7) Nunca
10) ¿Con qué frecuencia durante las dos últimas semanas se ha sentido ansioso?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

11) ¿Con qué frecuencia durante las dos últimas semanas ha sentido que tiene menos energías?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

12) ¿Cuánto tiempo durante las dos últimas semanas se ha sentido triste?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

13) ¿Con qué frecuencia durante las dos últimas semanas se ha sentido somnoliento?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

14) ¿Cuánto tiempo durante las dos últimas semanas le ha molestado alguna limitación de su dieta?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca
15) ¿Con qué frecuencia durante las dos últimas semanas se ha sentido irritable?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

16) ¿Cuánto tiempo durante las dos últimas semanas ha tenido dificultad para dormir en la noche?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

17) ¿Cuánto tiempo durante las dos últimas semanas le ha incomodado una sensación de malestar abdominal?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

18) ¿Cuánto tiempo durante las dos últimas semanas se ha sentido preocupado por el impacto que su enfermedad hepática tiene sobre su familia?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

19) ¿Cuánto tiempo durante las dos últimas semanas ha tenido cambios de ánimo?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca
20) ¿Cuánto tiempo durante las dos últimas semanas no ha podido conciliar el sueño en la noche?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

21) ¿Con qué frecuencia durante las dos últimas semanas sintió calambres musculares?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

22) ¿Cuánto tiempo durante las dos últimas semanas le ha preocupado que sus síntomas se conviertan en problemas mayores?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

23) ¿Cuánto tiempo durante las dos últimas semanas ha sentido la boca seca?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

24) ¿Cuánto tiempo durante las dos últimas semanas se ha sentido deprimido?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca
25) ¿Cuánto tiempo durante las dos últimas semanas le ha preocupado que su condición empeore?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

26) ¿Cuánto tiempo durante las dos últimas semanas ha tenido problemas de concentración?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

27) ¿Cuánto tiempo durante las dos últimas semanas le ha molestando la picazón?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

28) ¿Cuánto tiempo durante las dos últimas semanas le ha preocupado que nunca se sienta mejor?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca

29) ¿Cuánto tiempo durante las dos últimas semanas le ha preocupado la disponibilidad de un hígado si necesita un trasplante de hígado?

1) Todo el tiempo
2) La mayor parte del tiempo
3) Una buena parte del tiempo
4) Parte del tiempo
5) Poco tiempo
6) Casi nunca
7) Nunca
Fatigue Visual Numeric

We are interested in learning whether or not you are affected by FATIGUE. Please circle the number below that describes your fatigue.

Fatigue

No

1 2 3 4 5 6 7 8 9 10

Severe

Fatigue

Stanford Research Center
Patient Education
Spanish Fatigue Visual Numeric
## APPENDIX XV

### Child-Pugh Classification of Liver Disease Severity

<table>
<thead>
<tr>
<th>Clinical and Biochemical Measurements</th>
<th>Child Class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Points Scored for Increasing Abnormality</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>(Stage I-II)</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>Prothrombin time (sec &gt;normal) (INR)</td>
<td>&lt;4</td>
</tr>
<tr>
<td></td>
<td>&lt;1.7</td>
</tr>
<tr>
<td>Child Grade:</td>
<td>A</td>
</tr>
<tr>
<td>Total Score:</td>
<td>5-6</td>
</tr>
</tbody>
</table>

APPENDIX XVI

University of Miami - Medical Informed Consent Form
EPROSS # 20070787
Version Date 11.5.07

Consent (Permission) to Participate in a Research Study

Title of Study: Comparison of Targeted Lower Extremity Strengthening and Usual Care Progressive Ambulation in Subjects Post-Liver Transplant: A Randomized Controlled Trial

Principal Investigator: KATHRYN ROACH, PhD, PT
Department: Physical Therapy
Phone Number: (305) 284-4535
Email Address: kerouch@miami.edu

Study Contact Name: DAVID MANDEL, MSPT
Study Contact Telephone Number: (954) 540-0048
Study Contact Email: d.mandel@umiami.edu

READ THE FOLLOWING CAREFULLY

This consent form contains important information, so that you can decide if you wish to take part in this study. If you have any questions that remain unanswered, please ask the study doctor or one of his/her research study personnel before signing this form.

You are being asked to give permission for you to volunteer to participate in a research study. Before you give your consent (permission) for you to be part of this study, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve.

PURPOSE

You are being asked to be in the study because you recently underwent a liver transplantation. Many individuals with liver disease develop muscle wasting and weakness. Their muscle wasting and weakness remain after liver transplantation and lead to difficulty with performing daily activities such as walking, getting up and down from chairs, and interacting in the community. After individuals have a transplant, there is no standard rehabilitation program for increasing muscle strength and improving mobility. The purpose of this research study is to compare a program of resistance strengthening exercise to a program of walking to improve strength and function in individuals after liver transplantation.

To participate in this study you must be at least 6 weeks, but no more than 12 weeks, out from undergoing liver transplantation for liver disease. You must be able to walk without the help of another person. You may use a cane or walker. If you currently are being treated for cancer, severe cardiac disease, chronic obstructive pulmonary disease (COPD), severe osteoarthritis, or a neurological disorder such as Parkinson’s disease or a prior stroke you cannot participate in the study.

NUMBER OF STUDY PARTICIPANTS

If you decide to be in this study, you will be one of approximately 70 people in this research study.

Revised 2/1/07
DURATION OF STUDY

The study will last 12 weeks starting from today. The study will include a baseline measurement session. You will then perform either the exercise or the walking intervention 4 days a week. You will then be re-measured at the 4th week, the 8th week, and the 12th week. After the 12th week measurement session, your participation in the study will end.

Measurement time at baseline, 4th week, 8th week, and 12th week will take approximately 30 minutes. Education and training of the exercise program at the first session will take an additional 30 minutes. Each time you come back to the liver clinic, review of the exercises and discussion of your progress will take approximately 15 minutes.

Your exercise and/or walking program at home will take approximately 30 minutes each day, at least 4 days a week.

PROCEDURES

After you have given informed consent your baseline measurements will be taken on two handwritten quality of life questionnaires, two lower leg strength tests, and two functional performance tests of standing and walking.

Quality of Life Questionnaires
The Short Form 36 (SF-36) will ask you to rate your answers on 36 items related to your general health status, your ability to perform activities, your ability to perform work, your pain level, your emotional health, and your social health. This questionnaire should take less than 5 minutes to complete.

The Chronic Liver Disease Questionnaire (CLDQ) will ask you 29 questions on how you have been feeling the last two weeks. You will be asked about your symptoms related to liver disease, how you have been affected in doing activities, and how your mood has been. This survey should take less than 5 minutes to complete.

You may choose to skip questions on the surveys if you feel uncomfortable answering them.

Strength Measurements
The Heel Rise test will be performed to measure your lower leg strength. You will stand on the foot of your dominant leg only. You will balance yourself by placing your fingertips on the tabletop next to you. You will then rise up on your toes as high as you can, for as many times as you can, until you cannot rise any more. The speed at which you rise up and down will be paced with a metronome. A research investigator will be standing next to you to ensure your balance and safety.

The Bridging Test measures your hip strength. While lying on your back on an assessment table with your legs bent and your feet on the table, you will raise your buttocks off the table as high as you can, for as many times as you can, until you cannot rise any more. The speed at which you rise up and down will be paced with a metronome.
**Functional Performance Measurements**

The 30-Second Chair-Rise test measures your leg strength and how well you can get out of a chair. From the chair, with your arms folded across your chest, you will stand up fully and sit back down completely as many times as you can over 30 seconds. The study investigator will be standing next to you to ensure your balance and safety.

The Six Minute Walk Test measures your endurance and your leg strength. You will walk back and forth along a 100-meter hallway as many times as you can for 6 minutes. You are allowed to stop and rest at any time during the walking test. You may sit to rest or remain standing. Chairs will be available in the hallway if needed. You will be notified of how much time is remaining at 2 minutes, 4 minutes and 5 minutes. You will stop walking at six minutes. The study investigator will be standing nearby as you walk to you to ensure your balance and safety.

**Walking and Exercise Programs**

You will be randomly assigned to one of two exercise groups. If you are selected to be in the walking group, you will walk daily at your own pace. Each day, you will try to gradually increase your distance and length of time walked up to 15 minutes each walk. You will be issued a pedometer that you will wear only during these specific walks. You also will be provided with a packet of easy to complete daily logs to document the distance of your walking. When you first begin you may only be able to walk one session for 5 or 10 minutes. Then you will progress your walking to eventually perform two walks a day for 15 minutes each walk for a total time requirement of 30 minutes each day.

If you are selected to the home strengthening exercise group, you will perform resistance exercise 3 to 4 days a week. The exercise program targets the leg muscles; those muscles needed for standing from a chair, walking, and going up and down stairs. Strengthening will progress from moving your legs in positions of no resistance, to positions of moving your legs against gravity, and then progressing to moving your legs against resistance of an elastic band. The elastic bands provide a low level of resistance, without the risk of loose weights rolling around or dropping. The exercises are easy to perform in your own home. You can perform all the exercises at one time or spread them out over a few sessions of the day. The time to complete all the exercises in one session is approximately 15-20 minutes. You will be instructed how to perform each exercise properly and safely. All the exercise positions stabilize your trunk to prevent any stress on your abdomen or liver.

Additionally, in the strengthening group you will also perform one session of daily walking. When you first begin you may only be able to walk for 5 or 10 minutes. Then you will progress your walking to eventually reach 15 minutes. You will also be issued a pedometer that you will wear only during the specific daily walk activity. You will be provided with a packet of easy to complete daily logs to document the amount of repetitions of each exercise and the resistance level, and to document the distance of your walks. Between the time to complete the exercises (15-20 minutes) and the time of walking (15) minutes, the time requirement of this group is 30-40 minutes daily.

Prior to beginning the first procedure, you will rate your level of fatigue using the Stanford Visual Analog Scale. You will rest between tests and the investigator will begin the next test after you return to your prior level of fatigue. You will be allowed to rest as long as you need too. You may stop at any time during the tests if you feel pain or discomfort of any kind.

The entire measurement process will take approximately 30 minutes to complete.
You will be assigned by chance, like flipping a coin, to one of two study groups. The two groups will receive different activity programs to determine their benefit on muscle strengthening after liver transplantation.

After the baseline measurements are completed the investigator will instruct you in your specific activity program. The first time the instruction is provided in the clinic it may take approximately 30 minutes. Every week the investigator will call you on the telephone or meet with you at a post-transplant clinic visit to monitor and provide direction with your activity program and answer any questions you may have. These telephone sessions should take only 5-10 minutes.

The entire research study will be 12 weeks long. You will be re-tested on the same measurements described above at the 4th week, the 8th week, and finally on the 12th week. Each testing session will take approximately 30 minutes. The testing sessions will be performed at the post-transplant clinic.

If at any time you feel your health is at risk you should contact Dr. Jang Moon MD, transplant surgeon at: (305) 355-5006.

If you have any questions or need direction with your activity program please contact David Mandel PT, investigator at: (954) 540-0048.

RISKS AND DISCOMFORTS

Even though the tests in this study are very similar to your normal everyday activities, you should be aware there are risks associated with your participation in the study:

• You may experience fatigue or shortness of breath when performing the functional or strength tests and the activity program. You will be allowed to rest as needed during testing and you are encouraged to take rest breaks at home if you become fatigued during your activity program.
• You may fall during the walking, chair-rise, and heel-rise tests. During these activities, the investigator will stand beside you to minimize your chances of falling.
• You may develop muscle soreness after the activity programs. This is normal and you will be instructed to rest between days you perform the activity.

You will be asked to complete questionnaires that ask questions about your feelings and behaviors. Some questions may discuss issues that might make you feel uncomfortable or cause you stress.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to Dr. Jang Moon, David Mandel, and/or your transplant nurse.

You have the right to ask any questions about the potential and/or known hazards of this study at any time. You will be asked to tell the study investigator about any possible side effects you might have at any time during the study.
BENEFITS

Research is designed to benefit society by gaining new knowledge. The exercise and walking programs post-transplantation are theorized to increase your strength and improve your ability to perform activities of daily living; however, no direct benefits can be promised to you for your participation in this study.

ALTERNATIVES

You have the alternative not to participate in this study. You can decide to stop participating in this study at any time. Not participating in this study will not affect your medical care.

COSTS

There are no costs to you for participating in this study.

INCENTIVES/PAYMENTS TO PARTICIPANTS

You will not be paid for taking part in this study.

COMPENSATION FOR STUDY-RELATED INJURY

Although risks are unlikely, if injury should occur, treatment will in most cases be available. If you have insurance, your insurance company may or may not pay for these costs. If you do not have insurance, or if your insurance company refuses to pay, you will be expected to pay. Funds to compensate for pain, expenses, lost wages and other damages caused by injury are not available.

VOLUNTARY PARTICIPATION / WITHDRAWAL FROM STUDY

Your participation in this study is voluntary. You may refuse to participate, or withdraw from the study at any time, without penalty or loss of benefits to which you are otherwise entitled. This will not affect the medical care you receive from the study doctor or UM/Jackson Memorial Hospital. You must tell the study investigator(s) if you wish to stop taking part in the study. Your participation in this study may be discontinued, without your consent, at any time by the study investigator, if he/she believes that participation in the study is no longer in your best interest. The Institutional Review Board (IRB) or regulatory authorities may also discontinue your participation in the study.

If you cancel your permission after you have started in the study, the study staff and the study investigator(s) will stop collecting your health information. Although they will stop collecting new information about you, they may need to use the information they have already collected to evaluate the study results. If you start the study and then you cancel your permission, you will not be able to continue to participate in the study. This is because the study staff and/or the Study investigator would not be able to collect the information needed.
CONFIDENTIALITY

By signing this consent, you authorize the Investigators and staff to access your medical records and associated information as may be necessary for purposes of this study. Your records and results will not be identified as pertaining to you in any publication without your expressed permission. The Investigators and staff will consider your records confidential to the extent permitted by law. The Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) may review these research records. Your records may also be reviewed for audit purposes by authorized University of Miami employees or other agents who will be bound by the same provisions of confidentiality.

Your information will be kept in a secured file in an office at the Miami Transplant Institute. Only study investigators will have access to your information. Your name will be assigned a number code and all your information will only be identifiable through the number code.

The investigators will use your information to call you at home to monitor your study related activity and remind you of any study related testing appointments.

WHOM TO CONTACT

If at any time you have any questions about the study, you may contact David Mandel PT at (954) 540-0048.

In case of study-related injury, please contact Dr. Jang Moon MD at (305) 355-5006 and David Mandel PT at (954) 540-0048.

If you have any questions relating to your rights as a research subject, please contact the University of Miami's HUMAN SUBJECTS RESEARCH OFFICE (HSRO), at 305-243-3195.

You will receive a copy of this signed informed consent form.
I have read this consent, which is printed in English (a language which you read and understand). This study has been explained to my satisfaction and all of my questions relating to the study procedures, risks and discomforts, and side effects have been answered. If I have any further questions regarding this study, or in the event of a study-related injury, I should contact the appropriate person named above. Based on this information, I voluntarily agree to give permission (consent) for me to take part in this study.

Signature of Participant ___________________________ Date __________

Printed Name of Participant ___________________________

Signature of Person Obtaining Consent ___________________________ Date __________

Printed Name of Person Obtaining Consent ___________________________
APPENDIX XVII

Consentimiento (Permiso) para Participar en un Estudio de Investigación

Título del Estudio: Comparación entre el fortalecimiento de extremidad inferior específica y la ambulación progresiva con la atención usual en sujetos post-transplante hepático: Ensayo controlado aleatorizado.

Investigadora Principal: KATHRYN ROACH, PhD, PT
Departamento: Fisioterapia
Teléfono: (305) 284-4535
Correo electrónico: keroach@miami.edu

Nombre del Contacto del Estudio: DAVID MANDEL, MSPT
Teléfono del Contacto del Estudio: (954) 540-0048
Correo electrónico del Contacto del Estudio: d.mandel@umiami.edu

LEA CUIDADOSAMENTE LO SIGUIENTE

El presente documento de consentimiento contiene información importante, con el fin de que usted decida si desea tomar parte en el estudio. Si aún tiene preguntas sin responder, por favor solicite al doctor del estudio o al personal del estudio de investigación que se las aclaren antes de firmar el formulario.

Se le está pidiendo permiso para que participe en calidad de voluntario en un estudio de investigación. Antes de dar su consentimiento (permiso) con el fin de participar en el estudio, por favor lea lo siguiente y formule todas las preguntas que considere necesarias para que no tenga dudas sobre lo que implica su participación.

OBJETO

Se le ha solicitado que participe en el estudio porque recientemente se sometió a un trasplante de hígado. Un gran número de individuos con el hígado enfermo desarrollan desgaste y debilidad muscular. Este desgaste y debilidad muscular permanecen después del trasplante de hígado y conduce a dificultades en la realización de actividades diarias tales como caminar, incorporarse o sentarse en sillas, e interactuar en la comunidad. Después de someterse a un trasplante, no existe un programa estándar de rehabilitación para fortalecer los músculos y mejorar la movilidad. El objeto del presente estudio de investigación es comparar un programa de ejercicio para aumentar la resistencia con un programa de caminatas para incrementar la fortaleza y la función en individuos después de un trasplante de hígado.

Con el fin de participar en el estudio, usted debe poder por lo menos 6 semanas, pero no más de 12 semanas, de haberse sometido a un trasplante de hígado debido a enfermedad del hígado. Debe ser capaz de caminar sin ayuda de otra persona. Puede utilizar un bastón o una caminadora. Si actualmente está sometido a un tratamiento de cáncer, enfermedad cardíaca grave, enfermedad
pulmonar obstructiva crónica (EPOC), osteoartritis severa, o enfermedad neurológica tal como el mal de Parkinson o haya sufrido un derrame cerebral no podrá participar en el presente estudio.

**NÚMERO DE PARTICIPANTES EN EL ESTUDIO**

Si decide participar en el estudio, será uno entre aproximadamente 70 personas que participarán en el estudio de investigación.

**DURACIÓN DEL ESTUDIO**

El estudio se realizará en un período de 12 semanas, comenzando hoy. El estudio incluirá una sesión de medición de valores iniciales. Luego realizará el ejercicio o la caminata 4 veces por semana. Le tomarán sus valores de nuevo en la 4ª semana, 8ª semana y 12ª semana. Su participación en el estudio culminará después de la sesión de medición en la 12ª semana.

El tiempo de medición de valores iniciales, en la 4ª semana, 8ª semana y 12ª semana será de aproximadamente 30 minutos. La educación y adiestramiento del programa de ejercicios en la primera sesión tomará unos 30 minutos adicionales. Cada vez que regrese a la clínica del higado, la revisión de los ejercicios y discusión de su progreso tomará aproximadamente 15 minutos.

Su programa de ejercicio y/o caminata en casa tomará aproximadamente 30 minutos diarios, por lo menos 4 veces por semana.

**PROCEDIMIENTOS**

 Después de que haya dado su consentimiento informado se harán las mediciones de sus valores iniciales en dos cuestionarios escritos a mano sobre la calidad de vida, se realizarán dos pruebas de fuerza de los miembros inferiores, y dos pruebas de rendimiento funcional de pie y caminando.

**Cuestionarios de calidad de vida**

El Formulario Corto 36 (SF-36) pedirá que califique sus respuestas en 36 renglones en relación con su estado de salud general, su capacidad para realizar actividades, su capacidad para realizar trabajo, su umbral de dolor, salud emocional y salud social. No debe tardar más de 5 minutos completar este formulario.

El Cuestionario Enfermedad Crónica del Hígado (CLDQ en inglés) consta de 29 preguntas sobre su salud en las últimas dos semanas. Se le preguntará sobre sus síntomas en relación con la enfermedad del hígado, cómo le ha afectado en la realización de sus actividades y sobre su estado de ánimo. No debe tardar más de 5 minutos completar este cuestionario.

Puede decidir dejar preguntas sin responder en los cuestionarios si no se siente cómodo respondiéndolas.
Mediciones de Fuerza
La Prueba de Elevación de Talón se realizará para medir la fuerza de su miembro inferior. Se mantendrá de pie apoyándose únicamente en su pierna dominante. Mantendrá el equilibrio colocando las puntas de los dedos de su mano sobre la mesa que se encuentra a su lado. Luego se elevará sobre los dedos de sus pies lo más alto que pueda, tantas veces como pueda, hasta que no pueda elevarse más. La velocidad con que se eleve y baje será medida con un metrónomo. Un investigador estará a su lado para asegurarse de su equilibrio y su seguridad.

La Prueba de Puente mide la fuerza de la cadera. Acostado de espaldas en la mesa de evaluación con sus piernas dobladas y sus pies sobre la mesa, elevará sus glúteos lo más alto que pueda, tantas veces como pueda, hasta que no pueda más. La velocidad con que se eleve y baje será medida con un metrónomo.

Mediciones de Rendimiento Funcional
La Prueba de Sentarse y Levantarse en 30 Segundos mide la fortaleza de sus piernas y la manera de ponerse de pie desde la silla. Desde la silla, con sus brazos doblados sobre su pecho, se levantará completamente y se sentará de nuevo completamente tantas veces como pueda en 30 segundos. El investigador del estudio estará al lado suyo para asegurar su equilibrio y seguridad.

La Prueba de la Caminata de Seis Minutos mide su resistencia y la fuerza de sus piernas. Caminará de un lado a otro en un pasillo de 100 metros tantas veces como pueda en 6 minutos. Se le permitirá detenerse a descansar en cualquier momento durante la prueba de caminata. Puede sentarse a descansar o permanecer de pie. Habrá sillas disponibles en el pasillo si las necesita. Se le notificará cuanto tiempo le queda a los 2 minutos, 4 minutos y 5 minutos. Se detendrá a los seis minutos. El investigador del estudio se encontrará cerca mientras dure su caminata para asegurar su equilibrio y seguridad.

Programas de caminata y ejercicio
Usted será designado al azar a uno de dos grupos de ejercicio.
Si queda en el grupo de caminata, caminará diariamente a su propio ritmo. Intentará cada día incrementar progresivamente la distancia y período de tiempo hasta lograr caminatas de 15 minutos cada una. Usted recibirá un podómetro que utilizará únicamente durante estas caminatas específicas. Asimismo se le entregará un paquete de libros de control diario, fáciles de completar, con el fin de documentar la distancia de sus caminatas. Inicialmente quizás sólo pueda caminar una sesión de 5 a 10 minutos. Luego incrementará sus caminatas para que eventualmente realice dos diarias de 15 minutos cada una y así cumplir el requisito de 30 minutos de caminata al día.

Si queda en el grupo de ejercicios de fortalecimiento en casa, realizará los ejercicios de resistencia de 3 a 4 días por semana. El programa de ejercicios es específico para los músculos de la pierna; aquellos músculos que se necesitan para ponerse en pie desde una silla, caminar y subir y bajar escaleras. El fortalecimiento se desarrollará desde la movilización de sus piernas en posición de cero resistencia hasta posiciones de movilización de sus piernas contra la gravedad, y luego moverá sus piernas contra la resistencia de una banda elástica. Las bandas elásticas
proveen un bajo nivel de resistencia, sin el riesgo de pesas sueltas que rueden o se caigan. Los ejercicios se pueden realizar fácilmente en su casa. Puede realizar todos los ejercicios en un mismo momento o los puede distribuir en varias sesiones durante el día. El tiempo para completar todos los ejercicios en una sesión es aproximadamente 15-20 minutos. Se le darán instrucciones para que realice los ejercicios de manera correcta y segura. Todas las posiciones de los ejercicios estabilizan su torso y evitan tensión sobre su abdomen o higado. Adicionalmente, en el grupo de fortalecimiento realizará una sesión de caminata diaria. Al principio quizás sólo pueda caminar entre 5 y 10 minutos. Luego incrementará sus caminatas hasta alcanzar 15 minutos. Usted recibirá un podómetro que utilizará únicamente durante las caminatas diarias específicas. Asimismo, se le entregará un paquete de libros de control diario, fáciles de completar, con el fin de documentar el número de repeticiones de cada ejercicio y el nivel de resistencia, y para documentar la distancia entre sus caminatas. Entre el tiempo de completar los ejercicios (15-20 minutos) y el tiempo de la caminata (15 minutos), el requisito de tiempo de este grupo es de 30-40 minutos diarios.

Antes de iniciar el primer procedimiento, calificará su nivel de fatiga utilizando la Escala Visual Análoga de Stanford. Descansará entre cada prueba y el investigador iniciará la próxima prueba después de que usted regrese a su nivel anterior de fatiga. Se le permitirá descansar todo el tiempo que sea necesario. Puede detenerse en cualquier momento durante las pruebas si siente dolor o molestia de cualquier tipo.

El proceso completo de medición tomará aproximadamente 30 minutos.

Usted será asignado al azar, así como lanzar la moneda, a uno de dos grupos de estudio. Los dos grupos recibirán distintos programas de actividad para determinar su beneficio para el fortalecimiento de los músculos después de un trasplante de hígado.

Al completar la medición de valores iniciales el investigador le dará instrucciones sobre su programa específico de actividades. La primera vez que se impartan las instrucciones en la clínica podría tomar aproximadamente 30 minutos. El investigador se comunicará con usted semanalmente por teléfono o se reunirá con usted durante la visita a la clínica de post-trasplante para supervisar y darle instrucciones sobre su programa de actividades y responder cualquier pregunta que usted pueda tener. Estas sesiones telefónicas no deben tomar más de 5 a 10 minutos.

Todo el estudio de investigación durará 12 semanas. Lo medirán de nuevo sobre las mismas medidas descritas anteriormente en la 4ª semana, 8ª semana y finalmente en la 12ª semana. Cada sesión de pruebas durará aproximadamente 30 minutos. Las sesiones de pruebas se realizarán en la clínica de post-trasplantes.

Si en algún momento siente que su salud está en riesgo debe contactar al Dr. Jang Moon MD, cirujano de trasplantes al número: (305) 355-5006.

Si tiene algunas preguntas o necesita instrucciones en relación con su programa de actividades,
proveen un bajo nivel de resistencia, sin el riesgo de pesas sueltas que rueden o se caigan. Los ejercicios se pueden realizar fácilmente en su casa. Puede realizar todos los ejercicios en un mismo momento o los puede distribuir en varias sesiones durante el día. El tiempo para completar todos los ejercicios en una sesión es aproximadamente 15-20 minutos. Se le darán instrucciones para que realice los ejercicios de manera correcta y segura. Todas las posiciones de los ejercicios estabilizan su torso y evitan tensión sobre su abdomen o hígado. Adicionalmente, en el grupo de fortalecimiento realizara una sesión de caminata diaria. Al principio quizás sólo pueda caminar entre 5 y 10 minutos. Luego incrementará sus caminatas hasta alcanzar 15 minutos. Usted recibirá un podómetro que utilizará únicamente durante las caminatas diarias específicas. Asimismo, se le entregará un paquete de libros de control diario, fáciles de completar, con el fin de documentar el número de repeticiones de cada ejercicio y el nivel de resistencia, y para documentar la distancia entre sus caminatas. Entre el tiempo de completar los ejercicios (15-20 minutos) y el tiempo de la caminata (15 minutos), el requisito de tiempo de este grupo es de 30-40 minutos diarios.

Antes de iniciar el primer procedimiento, calificará su nivel de fatiga utilizando la Escala Visual Análoga de Stanford. Descansará entre cada prueba y el investigador iniciará la próxima prueba después de que usted regrese a su nivel anterior de fatiga. Se le permitirá descansar todo el tiempo que sea necesario. Puede detenerse en cualquier momento durante las pruebas si siente dolor o molestia de cualquier tipo.

El proceso completo de medición tomará aproximadamente 30 minutos.

Usted será asignado al azar, así como lanzar la moneda, a uno de dos grupos de estudio. Los dos grupos recibirán distintos programas de actividad para determinar su beneficio para el fortalecimiento de los músculos después de un transplante de hígado.

Al completar la medición de valores iniciales el investigador le dará instrucciones sobre su programa específico de actividades. La primera vez que se impartan las instrucciones en la clínica podría tomar aproximadamente 30 minutos. El investigador se comunicará con usted semanalmente por teléfono o se reunirá con usted durante la visita a la clínica de post-transplante para supervisar y darle instrucciones sobre su programa de actividades y responder cualquier pregunta que usted pueda tener. Estas sesiones telefónicas no deben tomar más de 5 a 10 minutos.

Todo el estudio de investigación durará 12 semanas. Lo medirán de nuevo sobre las mismas medidas descritas anteriormente en la 4ª semana, 8ª semana y finalmente en la 12ª semana. Cada sesión de pruebas durará aproximadamente 30 minutos. Las sesiones de pruebas se realizarán en la clínica de post-transplantes.

Si en algún momento siente que su salud está en riesgo debe contactar al Dr. Jang Moon MD, cirujano de transplantes al número: (305) 355-5006.

Si tiene algunas preguntas o necesita instrucciones en relación con su programa de actividades,
COSTOS

Su participación en este estudio no tendrá costos para usted.

INCENTIVOS/PAGOS A PARTICIPANTES

No se le pagará por participar en este estudio.

COMPENSACIÓN POR LESIÓN RELACIONADA CON EL ESTUDIO

Aunque existe poca posibilidad de riesgos, si ocurriera alguna lesión, en la mayoría de los casos habrá tratamiento disponible. Si usted tiene seguro, su compañía de seguro puede pagar o no pagar estos costos. Si no tiene seguro o si su compañía de seguros se niega a pagar, usted debe pagar. No hay fondos disponibles para compensar por dolor, gastos, salarios caídos y demás daños que surjan de una lesión.

PARTICIPACIÓN VOLUNTARIA/RETIRO DEL ESTUDIO

Su participación en este estudio es voluntaria. Puede rehusarse a participar o retirarse del estudio en cualquier momento, sin penalidades ni pérdida de los beneficios que de otra manera le correspondan. Esto no afectará el cuidado médico que reciba del doctor del estudio o de UM/Jackson Memorial Hospital. Usted debe informar al investigador o investigadores del estudio si desea retirarse del estudio. El investigador del estudio podría interrumpir su participación en el estudio, sin su consentimiento, en cualquier momento si éste considera que su participación en el estudio ya no es beneficiosa para usted. Asimismo, la Junta de Revisión Institucional (Institutional Review Board-IRB) o autoridades reguladoras podrían suspender su participación en el estudio.

Si cancela su consentimiento después de haber comenzado el estudio, el personal del estudio y el investigador(es) del estudio suspenderán la recolección de información sobre su salud. Aunque no recogerán nueva información sobre usted, podría ser necesario que utilicen la información que han recopilado para evaluar los resultados del estudio. Si comienza el estudio y luego cancela su consentimiento, no podrá continuar su participación en el estudio debido a que el personal del estudio y/o el investigador del estudio no podrán recoger la información necesaria.

CONFIDENCIALIDAD

Al firmar este consentimiento, usted autoriza a los Investigadores y al personal a tener acceso a su historia médica e información relacionada según sea necesario para los fines del estudio. Su historia médica y resultados no serán identificados como suyos en ninguna publicación sin su consentimiento expreso. Los Investigadores y el personal tratarán sus registros de manera confidencial en la medida permitida por ley. La Administracion de Drogas y Alimentos (Food and Drug Administration-FDA) y el Departamento de Salud y Servicios Humanos (Department of Health and Human Services-DHHS) pueden revisar estos registros de investigación. Su
historia médica podría ser revisada con fines de auditoría por parte de empleados autorizados de la Universidad de Miami y otros agentes quienes estarán sometidos a las mismas disposiciones de confidencialidad.

Su información será almacenada en un archivo seguro en una oficina del Instituto de Transplantes de Miami (Miami Transplant Institute). Sólo los investigadores del estudio podrán tener acceso a su información. Se asignará un código numérico a su nombre y su información sólo se identificará a través del código numérico.

Los investigadores utilizarán su información para llamar a su casa y supervisar sus actividades relacionadas con el estudio y para recordarle cualquier cita relacionada con las pruebas del estudio.

A QUIÉN CONTACTAR

Si en algún momento surge alguna pregunta sobre el estudio, puede contactar a David Mandel PT al (954) 540-0048.

En caso de alguna lesión relacionada con el estudio, por favor contacte al Dr. Jang Moon MD al (305) 355-5006 y David Mandel PT al (954) 540-0048.

Si tiene alguna pregunta en relación con sus derechos en calidad de sujeto de una investigación, por favor comuníquese con la OFICINA DE INVESTIGACIONES CON SUJETOS HUMANOS de la Universidad de Miami (University of Miami's HUMAN SUBJECTS RESEARCH OFFICE/HSRO), al 305-243-3195.
ACUERDO DE DECISIÓN DE PARTICIPAR

Usted recibirá una copia de este formulario de consentimiento informado firmado.

He leído este consentimiento, el cual está impreso en castellano (lenguaje que leo y entiendo). Me han explicado el estudio a mi completa satisfacción y han respondido todas mis preguntas en relación con los procedimientos del estudio, riesgos y molestias, y efectos secundarios. Si surge alguna pregunta en relación con el estudio o en el caso de una lesión relacionada con el estudio, debo contactar a la persona apropiada mencionada anteriormente. Sobre la base de esta información, yo otorgo voluntariamente mi permiso (consentimiento) para participar en este estudio.

Firma del participante ________________________________________________________________________________
Fecha _____________________________________________________________________________________________

Nombre del participante (letra de molde) _______________________________________________________________________

Firma de la persona que obtiene el consentimiento __________________________________________________________________________
Fecha _____________________________________________________________________________________________

Nombre de la persona que obtiene el consentimiento (letra de molde) ___________________________________________________________________________
APPENDIX XVIII

Consent (Permission) to Participate in a Research Study

Title of Study: Comparison of Targeted Lower Extremity Strengthening and Usual Care Progressive Ambulation in Subjects Post-Liver Transplant: A Randomized Controlled Trial

Principal Investigator: KATHRYN ROACH, PhD, PT
Department: Physical Therapy
Phone Number: (305) 284-4535
Email Address: kroach@miami.edu

Study Contact Name: DAVID MANDEL, MSPT
Study Contact Telephone Number: (954) 540-0048
Study Contact Email: d.mandl@umiami.edu

READ THE FOLLOWING CAREFULLY

This consent form contains important information, so that you can decide if you wish to take part in this study. If you have any questions that remain unanswered, please ask the study doctor or one of his/her research study personnel before signing this form.

You are being asked to give permission for you to volunteer to participate in a research study. Before you give your consent (permission) for you to be part of this study, please read the following and ask as many questions as necessary to be sure that you understand what your participation will involve.

PURPOSE

You are being asked to be in the study because you recently underwent a liver transplantation. Many individuals with liver disease develop muscle wasting and weakness. Their muscle wasting and weakness remain after liver transplantation and lead to difficulty with performing daily activities such as walking, getting up and down from chairs, and interacting in the community. After individuals have a transplant, there is no standard rehabilitation program for increasing muscle strength and improving mobility. The purpose of this research study is to compare a program of resistance strengthening exercise to a program of walking to improve strength and function in individuals after liver transplantation.

To participate in this study you must be at least 6 weeks, but no more than 12 weeks, out from undergoing liver transplantation for liver disease. You must be able to walk without the help of another person. You may use a cane or walker. If you currently are being treated for cancer, severe cardiac disease, chronic obstructive
pulmonary disease (COPD), severe osteoarthritis, or a neurological disorder such as Parkinson’s disease or a prior stroke you cannot participate in the study.

NUMBER OF STUDY PARTICIPANTS

If you decide to be in this study, you will be one of approximately 70 people in this research study.

DURATION OF STUDY

The study will last 12 weeks starting from today. The study will include a baseline measurement session. You will then perform either the exercise or the walking intervention 4 days a week. You will then be re-measured at the 4th week, the 8th week, and the 12th week. After the 12th week measurement session, your participation in the study will end.

Measurement time at baseline, 4th week, 8th week, and 12th week will take approximately 30 minutes. Education and training of the exercise program at the first session will take an additional 30 minutes. Each time you come back to the liver clinic, review of the exercises and discussion of your progress will take approximately 15 minutes.

Your exercise and/or walking program at home will take approximately 30 minutes each day, at least 4 days a week.

PROCEDURES

After you have given informed consent your baseline measurements will be taken on two handwritten quality of life questionnaires, two lower leg strength tests, and two functional performance tests of standing and walking.

Quality of Life Questionnaires:
The Short Form 36 (SF-36) will ask you to rate your answers on 36 items related to your general health status, your ability to perform activities, your ability to perform work, your pain level, your emotional health, and your social health. This questionnaire should take less than 5 minutes to complete.

The Chronic Liver Disease Questionnaire (CLDQ) will ask you 29 questions on how you have been feeling the last two weeks. You will be asked about your symptoms related to liver disease, how you have been affected in doing activities, and how your mood has been. This survey should take less than 5 minutes to complete.

You may choose to skip questions on the surveys if you feel uncomfortable answering them.
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Strength Measurements
The Heel Rise test will be performed to measure your lower leg strength. You will stand on the foot of your dominant leg only. You will balance yourself by placing your fingertips on the tabletop next to you. You will then rise up on your toes as high as you can, for as many times as you can, until you cannot rise any more. The speed at which you rise up and down will be paced with a metronome. An experienced investigator will be standing next to you to ensure your balance and safety.

The Bridging Test measures your hip strength. While lying on your back on an assessment table with your legs bent and your feet on the table, you will raise your buttocks off the table as high as you can, for as many times as you can, until you cannot rise any more. The speed at which you rise up and down will be paced with a metronome.

Functional Performance Measurements
The 30-Second Chair-Rise test measures your leg strength and how well you can get out of a chair. From the chair, with your arms folded across your chest, you will stand up fully and sit back down completely as many times as you can over 30 seconds. The study investigator will be standing next to you to ensure your balance and safety.

The Six Minute Walk Test measures your endurance and your leg strength. You will walk back and forth along a 100-meter hallway as many times as you can for 6 minutes. You are allowed to stop and rest at any time during the walking test. You may sit to rest or remain standing. Chairs will be available in the hallway if needed. The study investigator will be standing nearby as you walk to ensure your balance and safety.

Walking and Exercise Programs
You will be randomly assigned to one of two exercise groups. If you are selected to be in the walking group, you will walk daily at your own pace. Each day, you will try to gradually increase your distance and length of time walked up to 15 minutes each week. You will be issued a pedometer that you will wear only during these specific walks. You will be provided with a packet of easy-to-complete daily logs to document the distance of your walking. When you first begin you may only be able to walk one session for 5 or 10 minutes. Then you will progress your walking to eventually perform two walks a day for 15 minutes each walk for a total time requirement of 30 minutes each day.

If you are selected to the home strengthening exercise group, you will perform resistance exercises 3 to 4 days a week. The exercise program targets the leg muscles; those muscles needed for standing from a chair, walking, and going up and down stairs. Strengthening will progress from moving your legs in positions of no resistance, to positions of moving your legs against gravity, and then progressing to moving your legs against resistance of an elastic band. The elastic bands provide a low level of resistance, without the risk of loose weights rolling off.

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around or dropping. The exercises are easy to perform in your own home. You can perform all the exercises at one time or spread them out over a few sessions of the day. The time to complete all the exercises in one session is approximately 15-20 minutes. You will be instructed how to perform each exercise properly and safely. All the exercise positions stabilize your trunk to prevent any stress on your abdomen or liver.

Additionally, in the strengthening group you will also perform one session of daily walking. When you first begin you may only be able to walk for 5 or 10 minutes. Then you will progress your walking to eventually reach 15 minutes. You will also be issued a pedometer that you will wear only during the specific daily walk activity. You will be provided with a packet of easy to complete daily logs to document the amount of repetitions of each exercise and the resistance level, and to document the distance of your walks. Between the time to complete the exercises (15-20 minutes) and the time of walking (15) minutes, the time requirement of this group is 30-40 minutes daily.

Prior to beginning the first procedure, you will rate your level of fatigue using the Stanford Visual Analog Scale. You will rest between tests and the investigator will begin the next test after you return to your prior level of fatigue. You will be allowed to rest as long as you need too. You may stop at any time during the tests if you feel pain or discomfort of any kind.

The entire measurement process will take approximately 30 minutes to complete.

You will be assigned by chance, like flipping a coin, to one of two study groups. The two groups will receive different activity programs to determine their benefit on muscle strengthening after liver transplantation.

After the baseline measurements are completed the investigator will instruct you in your specific activity program. The first time the instruction is provided in the clinic it may take approximately 30 minutes. Every week the investigator will call you on the telephone or meet with you at a post-transplant clinic visit to monitor and provide direction with your activity program and answer any questions you may have. These telephone sessions should take only 5-10 minutes.

The entire research study will be 12 weeks long. You will be re-tested on the same measurements described above at the 4th week, the 8th week, and finally on the 12th week. Each testing session will take approximately 30 minutes. The testing sessions will be performed at the post-transplant clinic.

If at any time you feel your health is at risk you should contact Dr. Jang Moon MD, transplant surgeon at: (305) 355-5006.

If you have any questions or need direction with your activity program please contact David Mandel PT, investigator at: (954) 540-0048.

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Revised 2/1/07
RISKS AND DISCOMFORTS

Even though the tests in this study are very similar to your normal everyday activities, you should be aware there are risks associated with your participation in the study:

• You may experience fatigue or shortness of breath when performing the functional or strength tests and the activity program. You will be allowed to rest as needed during testing and you are encouraged to take rest breaks at home if you become fatigued during your activity program.
• You may fall during the walking, chair-rise, and heel-rise tests. During these activities, the investigator will stand beside you to minimize your chances of falling.
• You may develop muscle soreness after the activity programs. This is normal and you will be instructed to rest between days you perform the activity.

You will be asked to complete questionnaires that ask questions about your feelings and behaviors. Some questions may discuss issues that might make you feel uncomfortable or cause you stress.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to Dr. Jang Moon, David Mandel, and/or your transplant nurse.

You have the right to ask any questions about the potential and/or known hazards of this study at any time. You will be asked to tell the study investigator about any possible side effects you might have at any time during the study.

BENEFITS

Research is designed to benefit society by gaining new knowledge. The exercise and walking programs post-transplantation are theorized to increase your strength and improve your ability to perform activities of daily living; however, no direct benefits can be promised to you for your participation in this study.

ALTERNATIVES

You have the alternative not to participate in this study. You can decide to stop participating in this study at any time. Not participating in this study will not affect your medical care.
COSTS

There are no costs to you for participating in this study.

INCENTIVES/PAYMENTS TO PARTICIPANTS

You will not be paid for taking part in this study.

COMPENSATION FOR STUDY-RELATED INJURY

Although risks are unlikely, if injury should occur, treatment will in most cases be available. If you have insurance, your insurance company may or may not pay for these costs. If you do not have insurance, or if your insurance company refuses to pay, you will be expected to pay. Funds to compensate for pain, expenses, lost wages and other damages caused by injury are not available.

VOLUNTARY PARTICIPATION / WITHDRAWAL FROM STUDY

Your participation in this study is voluntary. You may refuse to participate, or withdraw from the study at any time, without penalty or loss of benefits to which you are otherwise entitled. This will not affect the medical care you receive from the study doctor or UM/Jackson Memorial Hospital. You must tell the study investigator(s) if you wish to stop taking part in the study. Your participation in this study may be discontinued, without your consent, at any time by the study investigator, if he/she believes that participation in the study is no longer in your best interest. The Institutional Review Board (IRB) or regulatory authorities may also discontinue your participation in the study.

If you cancel your permission after you have started in the study, the study staff and the study investigator(s) will stop collecting your health information. Although they will stop collecting new information about you, they may need to use the information they have already collected to evaluate the study results. If you start the study and then you cancel your permission, you will not be able to continue to participate in the study. This is because the study staff and or the Study investigator would not be able to collect the information needed.

CONFIDENTIALITY

By signing this consent, you authorize the Investigators and staff to access your medical records and associated information as may be necessary for purposes of this study. Your records and results will not be identified as pertaining to you in any publication without your expressed permission. The Investigators and staff will consider your records confidential to the extent permitted by law. The Food and Drug Administration (FDA) and Department of Health and Human Services (DHHHS) may review these research records. Your records may...
also be reviewed for audit purposes by authorized University of Miami employees or other agents who will be bound by the same provisions of confidentiality.

Your information will be kept in a secured file in an office at the Miami Transplant Institute. Only study investigators will have access to your information. Your name will be assigned a number code and all your information will only be identifiable through the number code. The investigators will use your information to call you at home to monitor your study related activity and remind you of any study related testing appointments.

WHOM TO CONTACT

If at any time you have any questions about the study, you may contact David Mandel PT at (954) 540-0048.

In case of study-related injury, please contact Dr. Jang Moon MD at (305) 355-5006 and David Mandel PT at (954) 540-0048.

If you have any questions relating to your rights as a research subject, please contact the University of Miami’s HUMAN SUBJECTS RESEARCH OFFICE (HSRO), at 305-243-3185.

AGREEMENT OF DECISION TO PARTICIPATE

You will receive a copy of this signed informed consent form.

I have read this consent, which is printed in English (a language which you read and understand). This study has been explained to my satisfaction and all of my questions relating to the study procedures, risks and discomforts, and side effects have been answered. If I have any further questions regarding this study, or in the event of a study-related injury, I should contact the appropriate person named above. Based on this information, I voluntarily agree to give permission (consent) for me to take part in this study.

Signature of Participant ____________________ Date ________________

Printed Name of Participant ____________________

Signature of Person Obtaining Consent ____________________ Date ________________

Printed Name of Person Obtaining Consent ____________________

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APPENDIX XIX

Informed Consent Form

Consentimiento (Permiso) para Participar en un Estudio de Investigación

Título del Estudio: Comparación entre el fortalecimiento de extremidad inferior específica y la ambulación progresiva con la atención usual en sujetos post-transplante hepático: Ensayo controlado aleatorio.

Investigadora Principal: KATHRYN ROACH, PhD, PT
Departamento: Fisioterapia
Teléfono: (305) 284-4535
Correo electrónico: keroach@miami.edu

Nombre del Contacto del Estudio: DAVID MANDEL, MSPT
Teléfono del Contacto del Estudio: (954) 540-0048
Correo electrónico del Contacto del Estudio: d.mandel@umiami.edu

LEA CUIDADOSAMENTE LO SIGUIENTE

El presente documento de consentimiento contiene información importante, con el fin de que usted decida si desea tomar parte en el estudio. Si aún tiene preguntas sin responder, por favor solicite al doctor del estudio o al personal del estudio de investigación que se las aclaren antes de firmar el formulario.

Se le está pidiendo permiso para que participe en calidad de voluntario en un estudio de investigación. Antes de dar su consentimiento (permiso) con el fin de participar en el estudio, por favor lea lo siguiente y formule todas las preguntas que considere necesarias para que no tenga dudas sobre lo que implica su participación.

OBJETO

Se le ha solicitado que participe en el estudio porque recientemente se sometió a un transplante de hígado. Un gran número de individuos con el hígado enfermo desarrollan desgaste y debilidad muscular. Este desgaste y debilidad muscular permanecen después del transplante de hígado y conduce a dificultades en la realización de actividades diarias tales como caminar, incorporarse o sentarse en sillas, e interactuar en la comunidad. Después de someterse a un transplante, no existe un programa estándar de rehabilitación para fortalecer los músculos y mejorar la movilidad. El objeto del presente estudio de investigación es comparar un programa de ejercicio para aumentar la resistencia con un programa de caminatas para incrementar la fortaleza y la función en individuos después de un transplante de hígado.

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Con el fin de participar en el estudio, usted debe tener por lo menos 6 semanas, pero no más de 12 semanas, de haberse sometido a un trasplante de hígado debido a enfermedad del hígado. Debe ser capaz de caminar sin ayuda de otra persona. Puede utilizar un bastón o una caminadora. Si actualmente está sometido a un tratamiento de cáncer, enfermedad cardíaca grave, enfermedad pulmonar obstructiva crónica (EPOC), osteoartritis severa, o enfermedad neurológica tal como el mal de Parkinson o haya sufrido un derrame cerebral no podrá participar en el presente estudio.

**NÚMERO DE PARTICIPANTES EN EL ESTUDIO**

Si decide participar en el estudio, será uno entre aproximadamente 70 personas que participarán en el estudio de investigación.

**DURACIÓN DEL ESTUDIO**

El estudio se realizará en un periodo de 12 semanas, comenzando hoy. El estudio incluirá una sesión de medición de valores iniciales. Luego realizará el ejercicio o la caminata 4 veces por semana. Le tomarán sus valores de nuevo en la 4ª semana, 8ª semana y 12ª semana. Su participación en el estudio culminará después de la sesión de medición en la 12ª semana.

El tiempo de medición de valores iniciales, en la 4ª semana, 8ª semana y 12ª semana será de aproximadamente 30 minutos. La educación y adiestramiento del programa de ejercicios en la primera sesión tomará unos 30 minutos adicionales. Cada vez que regrese a la clínica del hígado, la revisión de los ejercicios y discusión de su progreso tomará aproximadamente 15 minutos.

Su programa de ejercicio y/o caminata en casa tomará aproximadamente 30 minutos diarios, por lo menos 4 veces por semana.

**PROCEDIMIENTOS**

Después de que haya dado su consentimiento informado se harán las mediciones de sus valores iniciales en dos cuestionarios escritos a mano sobre la calidad de vida, se realizarán dos pruebas de fuerza de los miembros inferiores, y dos pruebas de rendimiento funcional de pie y caminando.

**Cuestionarios de calidad de vida**

El Formulario Corto 36 (SF-36) pedirá que califique sus respuestas en 36 renglones en relación con su estado de salud general, su capacidad para realizar actividades, su capacidad para realizar...
trabajo, su umbral de dolor, salud emocional y salud social. No debe tardar más de 5 minutos completar este formulario.

El Cuestionario Enfermedad Crónica del Hígado (CLDQ en inglés) consta de 29 preguntas sobre su salud en las últimas dos semanas. Se le preguntará sobre sus síntomas en relación con la enfermedad del hígado, cómo le ha afectado en la realización de sus actividades y sobre su estado de ánimo. No debe tardar más de 5 minutos completar este cuestionario.

Puede decidir dejar preguntas sin responder en los cuestionarios si no se siente cómodo respondiéndolas.

Mediciones de Fuerza
La Prueba de Elevación de Talón se realizará para medir la fuerza de su miembro inferior. Se mantendrá de pie apoyándose únicamente en su pierna dominante. Mantendrá el equilibrio colocando las puntas de los dedos de su mano sobre la mesa que se encuentra a su lado. Luego se elevará sobre los dedos de sus pies lo más alto que pueda, tantas veces como pueda, hasta que no pueda elevarse más. La velocidad con que se eleve y baje será medida con un metrónomo. Un investigador estará a su lado para asegurarse de su equilibrio y su seguridad.

La Prueba de Puente mide la fuerza de la cadera. Acostado de espalda en la mesa de evaluación con sus piernas dobladas y sus pies sobre la mesa, elevará sus glúteos lo más alto que pueda, tantas veces como pueda, hasta que no pueda más. La velocidad con que se eleve y baje será medida con un metrónomo.

Mediciones de Rendimiento Funcional
La Prueba de Sentarse y Levantarse en 30 Segundos mide la fortaleza de sus piernas y la manera de ponerse de pie desde la silla. Desde la silla, con sus brazos doblados sobre su pecho, se levantará completamente y se sentará de nuevo completamente tantas veces como pueda en 30 segundos. El investigador del estudio estará al lado suyo para asegurar su equilibrio y seguridad.

La Prueba de la Caminata de Seis Minutos mide su resistencia y la fuerza de sus piernas. Caminará de un lado a otro en un pasillo de 100 metros tantas veces como pueda en 6 minutos. Se le permite detenerse a descansar en cualquier momento durante la prueba de caminata. Puede sentarse a descansar o permanecer de pie. Habrá sillas disponibles en el pasillo si las necesita. Se le notificará cuánto tiempo le queda a los 2 minutos, 4 minutos y 5 minutos. Se detendrá a los seis minutos. El investigador del estudio se encontrará cerca mientras dure su caminata para asegurar su equilibrio y seguridad.
Programas de caminata y ejercicio

Usted será designado al azar a uno de los grupos de ejercicio. Si queda en el grupo de caminata, caminará diariamente a su propio ritmo. Intentará cada día incrementar progresivamente la distancia y periodo de tiempo hasta lograr caminatas de 15 minutos cada una. Usted recibirá un podómetro que utilizará únicamente durante estas caminatas específicas. Asimismo se le entregará un paquete de libros de control diario, fáciles de completar, con el fin de documentar la distancia de sus caminatas. Inicialmente quizás sólo pueda caminar una sesión de 5 a 10 minutos. Luego incrementará sus caminatas para que eventualmente realicen dos diarias de 15 minutos cada una y así cumplir el requisito de 30 minutos de caminata al día.

Si queda en el grupo de ejercicios de fortalecimiento en casa, realizará los ejercicios de resistencia de 3 a 4 días por semana. El programa de ejercicios es específico para los músculos de la pierna; aquellos músculos que se necesitan para ponerse en pie desde una silla, caminar y subir y bajar escaleras. El fortalecimiento se desarrollará desde la movilización de sus piernas en posición de cero resistencia hasta posiciones de movilización de sus piernas contra la gravedad, y luego moverá sus piernas contra la resistencia de una banda elástica. Las bandas elásticas proveen un bajo nivel de resistencia, sin el riesgo de pesas sueltas que rueden o se caigan. Los ejercicios se pueden realizar fácilmente en su casa. Puede realizar todos los ejercicios en un mismo momento o los puede distribuir en varias sesiones durante el día. El tiempo para completar todos los ejercicios en una sesión es aproximadamente 15-20 minutos. Se le darán instrucciones para que realice los ejercicios de manera correcta y segura. Todas las posiciones de los ejercicios estabilizan su torso y evitan tensión sobre su abdomen o hígado. Adicionalmente, en el grupo de fortalecimiento realizará una sesión de caminata diaria. Al principio quizás sólo pueda caminar entre 5 y 10 minutos. Luego incrementará sus caminatas hasta alcanzar 15 minutos. Usted recibirá un podómetro que utilizará únicamente durante las caminatas diarias específicas. Asimismo, se le entregará un paquete de libros de control diario, fáciles de completar, con el fin de documentar el número de repeticiones de cada ejercicio y el nivel de resistencia, y para documentar la distancia entre sus caminatas. Entre el tiempo de completar los ejercicios (15-20 minutos) y el tiempo de la caminata (15 minutos), el requisito de tiempo de este grupo es de 30-40 minutos diarios.

Antes de iniciar el primer procedimiento, calificará su nivel de fatiga utilizando la Escala Visual Analógica de Stanford. Descansará entre cada prueba y el investigador iniciará la próxima prueba después de que usted regrese a su nivel anterior de fatiga. Se le permitirá descansar todo el tiempo que sea necesario. Puede detenerse en cualquier momento durante las pruebas si siente dolor o molestia de cualquier tipo.

El proceso completo de medición tomará aproximadamente 30 minutos.
Usted será asignado al azar, así como lanzar la moneda, a uno de dos grupos de estudio. Los dos grupos recibirán distintos programas de actividad para determinar su beneficio para el fortalecimiento de los músculos después de un trasplante de hígado.

Al completar la medición de valores iniciales el investigador le dará instrucciones sobre su programa específico de actividades. La primera vez que se impartan las instrucciones en la clínica podría tomar aproximadamente 30 minutos. El investigador se comunicará con usted semanales por teléfono o se reunirá con usted durante la visita a la clínica de post-trasplante para supervisar y darle instrucciones sobre su programa de actividades y responder cualquier pregunta que usted pueda tener. Estas sesiones telefónicas no deben tomar más de 5 a 10 minutos.

Todo el estudio de investigación durará 12 semanas. Se medirán de nuevo sobre las mismas medidas descritas anteriormente en la 4ª semana, 8ª semana y finalmente en la 12ª semana. Cada sesión de pruebas durará aproximadamente 30 minutos. Las sesiones de pruebas se realizarán en la clínica de post-trasplantes.

Si en algún momento siente que su salud está en riesgo debe contactar al Dr. Jang Moon MD, cirujano de trasplantes al número: (305) 355-5006.

Si tiene alguna pregunta o necesita instrucciones en relación con su programa de actividades, por favor contacte al investigador David Mandel PT, al número: (954) 640-0948.

RIESGOS Y MOLESTIAS

Aunque las pruebas en este estudio son similares a sus actividades normales diarias, debe estar consciente que existen riesgos relacionados con su participación en el estudio:

- Puede experimentar fatiga o dificultad para respirar cuando realice pruebas funcionales o de resistencia así como el programa de actividad. Se le permitirá descansar según sea necesario durante las pruebas y se le aconseja que tome descansos en casa si se cansa durante el programa de actividad.

- Podría caerse durante las pruebas de caminata, silla y elevación de talón. Durante estas actividades, el investigador se quedará a su lado para minimizar la posibilidad de caídas.
• Podría presentarse sensibilidad dolorosa en los músculos después de los programas de actividad. Esto es normal y se le instruirá descansar entre los días que realice la actividad.

Se le pedirá que complete cuestionarios que formulan preguntas sobre sus sentimientos y comportamiento. Algunas preguntas podrían plantear asuntos que posiblemente le incomoden o causen estrés.

Asimismo, podrían existir riesgos poco comunes o desconocidos. Debe informar cualquier problema que surja al Dr. Jang Moon, David Mandel, y/o su enfermera de transplante.

Tiene derecho a formular preguntas sobre posibles riesgos posibles y/o conocidos en relación con este estudio en cualquier momento. Se le pedirá que diga al investigador del estudio cualquier posible efecto secundario que pueda experimentar en cualquier momento durante el estudio.

**BENEFICIOS**

La investigación está diseñada para el beneficio de la comunidad al obtener nuevos conocimientos. En teoría, los programas de ejercicio y caminatas post-transplante deben incrementar su fuerza y mejorar su capacidad para realizar sus actividades diarias; sin embargo, no podemos prometerle beneficios directos por participar en este estudio.

**ALTERNATIVAS**

Tiene la alternativa de no participar en este estudio. Puede detener su participación en cualquier momento. El hecho de no participar en este estudio no afectará su cuidado médico.

**COSTOS**

Su participación en este estudio no tendrá costos para usted.

**INCENTIVOS/PAGOS A PARTICIPANTES**

No se le pagará por participar en este estudio.
COMPENSACIÓN POR LESIÓN RELACIONADA CON EL ESTUDIO

Aunque exista poca posibilidad de riesgos, si ocurriera alguna lesión, en la mayoría de los casos habrá tratamiento disponible. Si usted tiene seguro, su compañía de seguro puede pagar o no pagar estos costos. Si no tiene seguro o si su compañía de seguros se niega a pagar, usted debe pagar. No hay fondos disponibles para compensar por dolor, gastos, salarios caídos y demás daños que surjan de una lesión.

PARTICIPACIÓN VOLUNTARIA/RETIRO DEL ESTUDIO

Su participación en este estudio es voluntaria. Puede rehusarse a participar o retirarse del estudio en cualquier momento, sin penalidades ni pérdida de los beneficios que de otra manera le correspondan. Esto no afectará el cuidado médico que reciba del doctor del estudio o de UM/Jackson Memorial Hospital. Usted debe informar al investigador o investigadores del estudio si desea retirarse del estudio. El investigador del estudio podría interrumpir su participación en el estudio, sin su consentimiento, en cualquier momento si éste considera que su participación en el estudio ya no es beneficiosa para usted. Asimismo, la Junta de Revisión Institucional (Institutional Review Board-IRB) o autoridades reguladoras podrían suspender su participación en el estudio.

Si cancela su consentimiento después de haber comenzado el estudio, el personal del estudio y el investigador(es) del estudio suspenderán la recolección de información sobre su salud. Aunque no recogerán nueva información sobre usted, podría ser necesario que utilicen la información que han recopilado para evaluar los resultados del estudio. Si comienza el estudio y luego cancela su consentimiento, no podrá continuar su participación en el estudio debido a que el personal del estudio y/o el investigador del estudio no podrán recoger la información necesaria.

CONFIDENCIALIDAD

Al firmar este consentimiento, usted autoriza a los Investigadores y al personal a tener acceso a su historia médica e información relacionada según sea necesario para los fines del estudio. Su historia médica y resultados no serán identificados como suyos en ninguna publicación sin su consentimiento expreso. Los Investigadores y el personal tratarán sus registros de manera confidencial en la medida permitida por ley. La Administración de Drogas y Alimentos (Food and Drug Administration-FDA) y el Departamento de Salud y Servicios Humanos (Department of Health and Human Services-DHHS) pueden revisar estos registros de investigación. Su historia médica podría ser revisada con fines de auditoría por parte de empleados autorizados de la Universidad de Miami u otros agentes quienes estarán sometidos a las mismas disposiciones de confidencialidad.

Jackson Memorial Hospital
Miami, Florida

C-640 CLINICAL RESEARCH CONSENT FORM

Revised 2/1/07
Su información será almacenada en un archivo seguro en una oficina del Instituto de Transplantes de Miami (Miami Transplant Institute). Sólo los investigadores del estudio podrán tener acceso a su información. Se asignará un código numérico a su nombre y su información sólo se identificará a través del código numérico.

Los investigadores utilizarán su información para llamar a su casa y supervisar sus actividades relacionadas con el estudio y para recordarle cualquier cita relacionada con las pruebas del estudio.

A QUIÉN CONTACTAR

Si en algún momento surge alguna pregunta sobre el estudio, puede contactar a David Mandel PT al (954) 540-0048.

En caso de alguna lesión relacionada con el estudio, por favor contacte al Dr. Jang Moon MD al (305) 355-5006 y David Mandel PT al (954) 540-0048.

Si tiene alguna pregunta en relación con sus derechos en calidad de sujeto de una investigación, por favor comuníquese con la OFICINA DE INVESTIGACIONES CON SUJETOS HUMANOS de la Universidad de Miami (University of Miami’s HUMAN SUBJECTS RESEARCH OFFICE-HSRO), al 305-243-3198.
ACUERDO DE DECISIÓN DE PARTICIPAR

Usted recibirá una copia de este formulario de consentimiento informado firmado.
He leído este consentimiento, el cual está impreso en castellano (lenguaje que leo y entiendo). Me han explicado el estudio a mi completa satisfacción y han respondido todas mis preguntas en relación con los procedimientos del estudio, riesgos y molestias, y efectos secundarios. Si surge alguna pregunta en relación con el estudio o en el caso de una lesión relacionada con el estudio, debo contactar a la persona apropiada mencionada anteriormente. Sobre la base de esta información, yo otorgo voluntariamente mi permiso (consentimiento) para participar en este estudio.

Firma del participante

Fecha

Nombre del participante (letra de molde)

Firma de la persona que obtiene el consentimiento

Fecha

Nombre de la persona que obtiene el consentimiento (letra de molde)