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A Prospective Analysis of Factors Associated with Decreased Physical Activity in Patients with Cirrhosis Undergoing Transplant Evaluation

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Abstract

Background—Physical activity has been associated with improved recovery time after transplantation. Handgrip strength has been related to post-transplant outcomes.

Aim—To evaluate predictors of physical activity and grip strength in cirrhotic patients undergoing liver transplant evaluation.

Methods—Single center, prospective analysis.

Results—A hundred patients were evaluated (54% male, mean age 53 ± 9). Common etiologies of liver disease were non-alcoholic hepatitis (27%), hepatitis C (22%), and alcoholic liver disease (21%). Mean MELD score was 13.5. Forty one percent had a history of smoking. Ninety-three patients completed the International Physical Activity Questionnaire. The median total physical activity score of 33 MET-min/weeks. The mean total grip strength was 62.1 ± 22lb. Total grip strength was found to be an independent predictor of low-moderate physical activity (OR 4.7, 95% CI 1.4–16.2, p=0.038) and smoking was the only significant factor associated with reduced grip strength (OR 3.4, 95% CI 1.4–8, p=0.005).

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Conclusions—End-Stage Liver Disease patients undergoing liver transplant evaluation have reduced total physical activity by IPAQ. Total Grip Strength was found to be a significant predictor of low-moderate physical activity in patients with cirrhosis. Smoking is a risk factor for reduced grip strength, an important indicator of muscle wasting in cirrhotics.

Keywords

Cirrhosis; Physical Activity; Grip Strength; Liver Transplantation

Introduction

Physical activity (PA) plays a key role to better clinical outcomes and health-related quality of life in patients with chronic disease including those with End-Stage Renal Disease (ESRD)[1] and End-Stage Liver Disease (ESLD). The International Physical Activity Questionnaire (IPAQ) is a validated instrument to evaluate PA in the general population. This survey measures PA by assessing domestic, work-related, transport-related and leisure activities.

Malnutrition is a well-known prognostic factor in cirrhosis and has been validated before and after liver transplantation [2–4]. Nutritional assessment can be difficult in patients with ESLD because standard parameters currently utilized such as anthropometric and laboratory data, weight and albumin levels can be altered by the severity of the disease, particularly in the presence of ascites, edema, and inflammation [2, 3]. Sarcopenia, defined as loss of muscle mass, is a major component of malnutrition. In acute and chronic disease, many issues such as severity of illness, nutrition, comorbidities, medical treatment, and immobilization; influence muscle function.[5] Handgrip strength is a simple and validated method to assess nutritional status and a surrogate of muscle mass and function [5]. It has been reported a significant correlation between handgrip strength and malnutrition and complications of cirrhosis [6].

Previous studies indicated that transplanted patients have low levels of exercise capacity and are also frequently physically inactive[7, 8]. However, the impact of grip strength on physical activity in cirrhotic patients has not been investigated.

Our study aimed to evaluate predictors of physical activity in cirrhotic patients undergoing transplant evaluation.

Methods

Study Population

From January 2012 to October 2013, 100 adult cirrhotic patients undergoing liver transplantation evaluation at the Transplant Center of the University of Kentucky, Lexington, were analyzed prospectively. Informed consent was obtained after approval of the study protocol by the Institutional Review Board.

Clinical and Socio-Demographic Data

A complete medical history and physical examination were obtained in all patients. Demographic data included gender, age and race (Caucasian, Asian, African American, American Indian/Alaska native Native Hawaiian or other Pacific Islander), ethnicity (Hispanic/Latino, and not Hispanic/Latino).

Clinical data comprised comorbidities such as Diabetes Mellitus, Coronary Artery Disease, Chronic Obstructive Pulmonary Disease and malignancy [hepatocellular carcinoma (HCC), non-HCC]; indication for transplant evaluation, etiology of cirrhosis and presence of liver-related complications (ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis and hepatorenal syndrome).

Social history, which included smoking status (never, former, current usage of cigarettes, pack years), alcohol consumption and illicit drug use was obtained from the patient and caregiver or close family. Laboratory data included alanine aminotransferase (ALT), aspartate aminotransferase (ALT), total bilirubin, total protein, albumin, alkaline phosphatase, complete blood count, sodium, creatinine and prothrombin time. Laboratory Model for End-stage Liver Disease (MELD) scores was also recorded.

Physical Activity Assessment

IPAQ questionnaire-long version was used as an instrument to determine levels of self-reported physical activity in our cohort. This survey was created for monitoring levels of PA of an adult population between 18 to 65 years. The IPAQ includes 7 questions that compute the Metabolic Equivalent (MET). In particular, 6 items concerning the number of days and minutes in the last week spent in vigorous activity (VA) or moderate activity (MA) and walking (W) were used. The item about sedentary habits was also considered. PA was classified in three levels: low, moderate and high based on the IPAQ scoring protocol[9].

Anthropometry and Handgrip Strength Measurement

Standard anthropometric data, which included weight, height, triceps skinfold thickness using a skinfold caliper and mid-arm circumference, were obtained for all patients. Body mass index (BMI) was calculated.

Skeletal muscle function was evaluated by measuring handgrip strength, which was obtained by using the Jamar grip strength dynamometer in both hands, taking the mean from 3 measurements. Handgrip strength was measured with the subject in the sitting position, with their shoulders adducted and their elbows flexed 90°, as proposed by the American Society of Hand therapists[11]. Handgrip strength was recorded in pounds. Reduced handgrip strength was defined in this study as having total grip strength (average of left and right grip) below the mean of the study population. Since age and gender are major factors affecting grip strength in healthy subjects[12], a subgroup analysis was performed in the male patients, age 35–60 years (group expected to have increased grip strength).

Statistical analysis

Continuous variables are presented as mean ± SD and using Student's t test. Chi-square test was used for categorical variables. A multivariable logistic regression analysis was performed to find predictors of PA.

Continuous indicators of PA are presented as median and inter-quartile range minutes/week or MET-minutes/week. METs are multiples of the resting metabolic rate and a MET-minute was computed by multiplying the MET score of an activity by the minutes performed. Statistical significance was set at $p<0.05$. Data were analyzed using IBM SPSS software, version 22.

Results

Demographic and Clinical Characteristics

Sixty four percent of our patients were male, and the mean age was 53.9 ± 9. The most common etiology of cirrhosis was NASH (27%), followed by Chronic Hepatitis C (22%), and Alcoholic Liver Disease (21%), combination of Hepatitis C and Alcoholic Liver Disease (13%), autoimmune liver disease (8%) and other etiologies of liver disease (8%). The mean MELD score was 13.5 ± 4. Among 100 patients, 7 were Child Pugh Class A, 52 were Child Pugh Class B, and 40 were Child Pugh Class C. Forty one percent were diabetics, 12% had COPD and 14% had CAD. Four patients (4%) had HCC. Other clinical and laboratory data are summarized in Table 1.

Forty one patients (41%) had a history of smoking, with mean pack-years of 21 ± 23. Eight of these patients (8%) were currently smoking at the time of evaluation. Thirty three patients (33%) reported previous alcohol use. Cocaine use was reported in 7% and marijuana use in 18% of the study patients.

Forty two patients (42%) had ascites and 48 (48%) had hepatic encephalopathy at the time of evaluation. The incidence of other significant complications from cirrhosis was much less frequent. Variceal bleeding was found in 22% of the patients and the incidence of hepatorenal syndrome and spontaneous peritonitis was 5% and 10%, respectively. Thirty one patients died during the 1-year follow up.

End-Stage Liver Disease patients have severely reduced physical activity compared to age-matched healthy population

Ninety-three patients completed the IPAQ. Sixty-two patients were categorized as low IPAQ score while 9 and 22 patients reported moderate and high scores, respectively. In the low category, 79% reported no physical activity on IPAQ. The median (inter-quartile range) total PA score for all ESLD patients was 33 (0–1914) MET-min/week.

Patients diagnosed with alcoholic cirrhosis, Hepatitis C, and NASH reported 173 (0–924), 0 (0–1387), and 0 (0–2031) MET-min/week, respectively. Median time spent sitting was 480 minutes (240–540) during a typical weekday, and 390 minutes (240–540) during a typical weekend day.

Smoking is independently associated with reduced grip strength in cirrhosis

The mean total grip strength was 62.1 ± 22 lb. The average left grip strength was 60.8 + 23 lb. and the average right grip strength was 63.7+22 lb (Table 2). This reflects almost 40% reduction in patients with ESLD compared to age-matched norms. Table 3 compares values[13] for grip strength in normal adults and in cirrhotic patients in our cohort by gender and age. The normative reference values were consolidated in a meta-analysis from 12 studies involving 3317 subjects[13].

Total, right and left grip strength were found to correlate significantly with the presence of ascites and encephalopathy ($p<0.005$). However, there was no correlation between grip strength and hepatorenal syndrome, variceal bleeding and spontaneous bacterial peritonitis.

Age and smoking were associated with reduced grip strength ($p=0.003$ and $p=0.005$). Alcohol use, sex, BMI, MELD >15, comorbidities such as DM, COPD and CAD did not predict reduced grip strength. We have evaluated the relationship between sex by grip strength using right, left and total grip strength separately as a continuous variable, as well as Chi-squared analysis and these further analyses demonstrated again that there was no correlation between gender and grip strength.

On logistic regression analysis, smoking was found to be the only independent predictor of reduced grip strength (OR 3.4, 95% CI 1.4–8, $p=0.005$) after controlling for age, gender, and MELD score (Table 4). In a subgroup analysis among males between 35 and 60 years old, smoking remained as a significant factor correlated with reduced grip strength.

Total grip strength is an independent predictor of low-moderate physical activity

On multivariate analysis, after controlling for age, gender, diagnosis, obesity and encephalopathy; reduced total grip strength was found to be an independent predictor of low-moderate PA (OR = 4.7, 95% CI 1.4–16.2, $p= 0.038$) (Table 5).

Out of the patients who completed the IPAQ, 10 presented at least one episode of spontaneous bacterial peritonitis (SBP) and reported low or moderate score of PA. Other portal hypertension complications including ascites, encephalopathy, hepatorenal syndrome and variceal bleeding were not found to correlate with PA measurements.

Discussion

Liver transplantation has become the treatment of choice for patients with End-Stage Liver Disease with overall good long-term outcomes. Several studies have reported positive effects of physical activity and exercise in the prevention of cardiovascular disease, and in the management of chronic diseases[14, 15]. In some instances cirrhosis is associated with muscle wasting and malnutrition which could impact patient's exercise capacity and overall PA. There is limited objective clinical data evaluating the impact of physical activity in patients with cirrhosis[7, 8].

The International Physical Activity Questionnaire (IPAQ) is one of the most widely used questionnaires to assess physical activity (PA) in the general population. In the IPAQ,

participants report the frequency and duration of vigorous, moderate, and walking activities as well as the time spent sitting during the last 7 days. This survey has previously been used as a valid instrument to assess physical activity in patients with chronic disease. Amaral-Figueroa et al. analyzed 31 patients with ESRD using IPAQ and found that the total physical activity is significantly reduced in this patient population. The authors reported a significant inverse relationship between total physical activity and years on hemodialysis, regardless of age[16].

To our knowledge, this is the first report of a prospective study evaluating predictors of physical activity in cirrhotic patients undergoing liver transplant evaluation using the self-reported IPAQ questionnaire. Our findings demonstrated that End-Stage Liver Disease patients have reduced total physical activity compared to the general population. Median total PA for this population is 33 MET-min/weeks and sitting time between 6–8 hours a day measured by IPAQ. Interestingly, 79% of patients in the low PA group reported very minimal or no physical activity. Moreover, we found lower PA levels in patients with diagnosis of Hepatitis C and NASH compared to those with alcoholic cirrhosis (median of 0, 0 and 173 MET-min/weeks, respectively). Masala et al. used IPAQ and the SF-36 questionnaire to evaluate physical activity and quality of life, respectively. They concluded that liver transplant recipients have a significantly lower physical function than the general population (p=0.001) [7, 8]

There is increasing body of evidence showing the association between malnutrition and sarcopenia with morbidity and mortality before and after liver transplantation [2–4, 17–19]. Handgrip strength has been found to be a simple and valid method in the assessment of malnutrition in the general population and in patients with cirrhosis[5, 6]. The severity of malnutrition has been reported to be associated with reduced grip strength in patients with cirrhosis. Lower pre-operative grip strength has been associated with longer ICU length of stay and higher likelihood of post-transplant infections [4].

There is limited data evaluating the factors affecting handgrip strength in pre-transplant cirrhotic patients. Although gender has been a determinant of grip strength in healthy individuals[12], we did not find a significant correlation between gender and grip strength in our analysis. Similarly, gender was not found to predict physical activity in our cohort. Peng et al. reported that protein depletion was more prevalent in cirrhotic men than women (51% vs. 28%, p<0.0001) and that grip strength was significantly lower in patients with protein depletion than in those without[21]. The expectation that males would have increased grip strength and the observation that cirrhotic women have greater protein conservation than their male counterparts[21] may possibly explain the lack of gender differences in grip strength in our cirrhotic patients. We also speculate that overall illness in patients with cirrhosis may reduce differences seen in grip strength and physical activity between males and females.

Grip strength did not correlate with the severity of liver disease (MELD score) in our study. Data is conflicting regarding the association of grip strength with the severity of liver disease. Huisman et al.[20] found that malnutrition defined by handgrip strength was

associated with higher Child Pugh Clas, while several authors reported that grip strength does not correlate with the degree of liver dysfunction [22, 23].

Our results demonstrated that smoking is an independent predictor of reduced grip strength in patients with cirrhosis undergoing liver transplant evaluation. These findings correlate with prior studies that have reported decreased grip strength in healthy[24] and elderly[26] smokers. The exact mechanism of how smoking reduces grip strength is not well defined, especially in patients with cirrhosis. However, some authors have suggested a possible effect of cigarette smoke on muscle protein breakdown based on in vivo and in vitro studies. Components of cigarette smoke have been shown to initiate muscle protein breakdown by causing a cascade of processes causing increased intracellular oxidative stress, which then activates other pathways leading to loss of muscle mass such as mitogen-activated protein kinase p38, nuclear factor κB, and E3 ligases[27].

The influence of smoking on reduced grip strength may have significant implications in the management of cirrhotic patients undergoing liver transplant evaluation. Smoking has been previously reported to be associated with long-term post-operative morbidity[28], increased incidence of wound complications, infections [29–32] and prolonged ICU stay[31] in liver transplant recipients. On further sub-group analysis performed in male patients between 35 to 60 years of age (with expected better grip strength), smoking remains as the only independent predictor for reduced grip strength.

Although the quality of life and physical function improve after transplantation, a proportion of cases remain with limitations such as fatigue, difficulty in walking and inability to perform daily activities. It has been reported that among transplant recipients, those who had regular physical activity before the intervention had a much better quality of life [33–35]. There is a significant correlation between malnutrition defined by grip strength and complications of cirrhosis [6, 20]. Our univariate analysis showed a significant correlation between reduced grip strength and the presence of ascites and hepatic encephalopathy.

We have also demonstrated a strong association between reduced total, right and left grip strength; and self-reported low-moderate physical activity in cirrhotic patients undergoing liver transplant evaluation, after controlling for age, sex, the presence of morbid obesity and encephalopathy in this patient population (OR = 4.7, 95% CI 1.4–16.2, p= 0.038).

This study has a few limitations that must be considered. Data was obtained from a single-center experience. There is not a well-accepted definition of reduced grip-strength in this patient population. Therefore the total grip strength below the mean was arbitrarily assigned to observe reduction in grip strength in our patients. In addition, the self-reported nature of the measures collected for physical activity through the IPAQ could lead to inaccurate information leading to over or under estimation of the patient's overall PA [36]. Future studies would benefit from more detailed quantification of physical activity in cirrhotics patients.

In summary, patients diagnosed with cirrhosis undergoing liver transplant evaluation have reduced total physical activity compared to respective general norm. Median total PA for this population is 33 MET-min/weeks and sitting time between 6–8 hours a day measured by IPAQ.

Total Grip Strength, an indicator of malnutrition and muscle-wasting state, was found to be an independent predictor of low-moderate physical activity. SBP, a complication with high mortality in this patient population, is associated with a trend towards lower PA score on IPAQ. Smokers were found to have a 3-fold higher likelihood of having reduced grip strength in this population. Future studies are needed to evaluate the implications of reduced physical activity, malnutrition, weakness and muscle wasting in cirrhotic patients undergoing transplant evaluation and the role of possible therapeutic interventions in transplant outcomes.

Acknowledgments

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Abbreviations

ESLD	End-Stage Liver Disease
IPAQ	International Physical Activity Questionnaire
MELD	Model of End-Stage Liver Disease
MET	Metabolic Equivalent
NASH	Non-alcoholic steatohepatitis
PA	Physical Activity
SBP	Spontaneous Bacterial Peritonitis
SF-36	Short-Form General Health Survey

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Table 1

Baseline Demographic and Clinical Characteristics

Parameter	n=100	Percentage or Range
Age (years)	53.9 ± 9	30–68
Male	64	64%
Etiology of cirrhosis		
Alcohol	21	21%
HCV	22	22%
HCV + ETOH	13	13%
NASH	27	27%
Autoimmune liver disease [a]	8	8%
Others [b]	8	8%
MELD score	13.5 ± 4	6–28
Child Pugh Class		
A	7	
B	53	
C	40	
Albumin	2.7 ± 0.45 g/dl	1.8–3.7
Creatinine	1.2 ± 0.9 mg/dl	0.5–5.2
Bilirubin	2.8 ± 1.99 mg/dl	0.2–9.7
Sodium	136.8 ± 4.3 mEq/L	124–144
Liver-related complications		
Ascites	42	
Variceal Bleed	23	
Hepatic Encephalopathy	48	
Spontaneous Bacterial Peritonitis	10	
Hepatorenal syndrome	5	

Table 2

Baseline Anthropometric Data

Parameter	Mean ± SD
BMI	31.7 ± 6.4
Triceps skinfold thickness (mm)	
Left	21.2 ± 13
Right	22.4 ± 13.2
Arm circumference (cm)	
Left	31.8 ± 5.2
Right	32.5 ± 5.3
L grip strength average (lb)	60.8 ± 22.6
R grip strength average (lb)	63.7 ± 22.2
Total grip strength average (lb)	62.1 ± 21.9

Table 3

Grip strength of cirrhotic subjects in comparison with reference values in healthy individuals

Age range (years)	Left grip strength mean (lb)	Reference values for left grip strength (lb), mean	Right grip strength mean (lb)	Reference values for right grip strength (lb), mean
Male				
20–24	-	104.6	-	117.6
25–29	-	110.2	-	119
30–34	54.82	108.4	58.31	116.4
35–39	42.61	113.7	45.28	117.6
40–44	57.07	109.7	69.38	119.4
45–49	79.86	107.4	77.10	111.1
50–54	79.86	99.7	64.82	111.4
55–59	56.66	90.4	60.28	97.2
60–64	53.29	85.4	53.74	92
65–69	57.34	84.3	63.95	91.9
70–74	-	79.9	-	84.3
75+	-	65.6	-	61.7
Female				
20–24	-	61.4	-	67.4
25–29	-	68	-	74.5
30–34	-	70	-	74.5
35–39	37.33	66.5	72.04	73.1
40–44	57.70	64.5	63.14	72.3
45–49	56.95	67.8	62.53	74.8
50–54	67.61	63.4	74.43	68.2
55–59	76.82	60	81.32	66
60–64	52.18	50.6	56.58	57.1
65–69	40.35	50.4	41.38	56.5
70–74	-	49.5	-	53.4
75+	36.1	36.1	-	39.6

Table 4

Factors Associated with Reduced Grip Strength

	Odds Ratio	95% CI	p-value
Smoking	**3.4**	**1.4–8**	**0.005**
Sex	0.87	0.3–2.5	0.79
Age	0.96	0.9–1.02	0.14
MELD score	1.032	0.92–1.16	0.59

Table 5

Predictors of Low-Moderate Physical Activity

	Odds Ratio	p-value
Age	0.99	0.95
Sex	0.75	0.58
NASH	0.66	0.50
Obesity Class 3 (BMI±34)	1.88	0.99
Encephalopathy	0.45	0.11
Total Grip Strength	**4.7**	**0.03**