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Functional status, respiratory muscle strength, and quality of life in patients with cirrhosis

Condição funcional, força muscular respiratória e qualidade de vida em pacientes cirróticos

Lucas H. Galant[1], Luiz A. Forgiarini Junior[2], Alexandre S. Dias[3], Cláudio A. Marroni[1]

Abstract

Background: Liver diseases are responsible for metabolic disorders and loss of muscle mass and function that affect functional status and quality of life (QoL). **Objective:** To compare exercise capacity, respiratory muscle strength, and QoL in liver transplant candidates with cirrhosis of the following etiologies: hepatitis C virus (HCV), hepatitis B virus (HBV), and alcoholic cirrhosis (AC). **Methods:** Cross-sectional study comprising 86 patients divided into three groups: HCV (40 patients), HBV (14 patients), and AC (32 patients). Patients were evaluated using the Six-Minute Walk Test (6MWT), manometry, and the QoL questionnaire SF-36. **Results:** The AC group showed the lowest performance in the 6MWT (meters) compared to the HBV and HCV groups (373.50±50.48, 464.16±32, and 475.94±27.84, respectively, p=0.001). In the domains of the SF-36, the AC group had lower scores for functional capacity and physical limitations when compared to the HBV and HCV groups (p=0.001). In the comparison of respiratory muscle strength, the AC group had lower MIP (cmH_2O) compared to the HBV and HCV groups (-65.54±11.28, -71.61±6.96, -82.44±13.71, respectively, p=0.001). The MEP (cmH_2O) in the AC group was also lower than in the HBV and HCV groups (65.13±10.74, 82.44±13.87, 83.44±12.20, respectively, p=0.001). **Conclusion:** The AC group showed worse exercise capacity, respiratory muscle strength, and QoL compared to patients with HCV and HBV.

Keywords: liver transplantation; functional status; physical therapy; quality of life.

Resumo

Contextualização: As doenças hepáticas são responsáveis pelas alterações metabólicas, perda da massa e função muscular que interferem na condição funcional e na qualidade de vida (QV). **Objetivo:** Comparar a capacidade ao exercício, a força muscular respiratória e a QV entre os pacientes com cirrose hepática, candidatos ao transplante de fígado, com as seguintes etiologias: hepatite vírus C (HCV), hepatite vírus B (HBV) e cirrose alcoólica (CA). **Métodos:** Estudo transversal, composto por 86 pacientes, divididos em três grupos: HCV (40 pacientes), HBV (14 pacientes) e CA (32 pacientes). Os pacientes foram avaliados por meio do teste da caminhada de seis minutos (TC6min), manovacuometria e QV pelo questionário SF-36. **Resultados:** O grupo CA apresentou menor distância percorrida no TC6min (metros) quando comparado com os grupos HBV e HCV (373,50±50,48; 464,16±32 e 475,94±27,84, respectivamente, p=0,001). Nos domínios do SF-36, o grupo CA apresentou menores escores na capacidade funcional e limitações por aspectos físicos quando comparado com os grupos HBV e HCV (p=0,001). Na comparação da força dos músculos respiratórios, o grupo CA apresentou menor PImáx (cmH_2O) quando comparado com os grupos HBV e HCV (-65,54±11,28; -71,61±6,96; -82,44±13,71, respectivamente, p=0,001). A PEmáx (cmH_2O) no grupo CA foi menor do que nos grupos HBV e HCV (65,13±10,74; 82,44±13,87; 83,44±12,20, respectivamente, p=0,001). **Conclusão:** O grupo CA demonstrou pior capacidade ao exercício, força muscular respiratória e QV quando comparado aos pacientes com HCV e HBV.

Palavras-chave: transplante hepático; capacidade funcional; fisioterapia; qualidade de vida.

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[1] Department of Hepatology, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS, Brazil
[2] Department of Respiratory Airways, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil
[3] School of Physical Education, UFRGS, Porto Alegre, RS, Brazil
Correspondence to: Lucas Homercher Galant, Avenida Osvaldo Aranha, 522/42, Bom Fim, CEP 90035-190, Porto Alegre, RS, Brasil, e-mail: lucasgalant@hotmail.com

Introduction

Cirrhosis is a pathological clinical disorder responsible for systemic and metabolic changes in the affected individuals. Clinical studies demonstrate various complications related to this pathological process, such as compromised pulmonary function, ascites, hepatic encephalopathy, jaundice, loss of muscle mass and function, changes in portal venous pressure, and cardiac changes with consequent reduction in quality of life (QoL)[1,2]. Among the complications caused by liver diseases are metabolic changes associated with patients' malnutrition, given that they lose a large quantity of muscle mass leading to negative repercussions in the musculoskeletal system[3,4].

Chronic hepatic patients develop a clinical condition of malnutrition due to the decrease in food intake, deficits in absorption and transport of nutrients, and increased energy expenditure during rest[5,6]. According to Merli et al.[7], there is no direct relationship between the degree of reduction in levels of serum albumin and the severity of liver disease. Studies suggest that persistent muscle fatigue causes a deficit in the functional condition and QoL of these patients. A possible explanation for this fatigue could be the loss of muscle mass, but it could also be related to the reduction in mitochondrial oxidative capacity, which results in persistent physical deconditioning and cachexia[8,9].

Therefore, we aimed to evaluate and compare the functional condition, respiratory muscle strength, and QoL of candidates for orthotopic liver transplantation with cirrhosis of the following etiologies: hepatitis C virus (HCV), hepatitis B virus (HBV), and alcoholic cirrhosis (AC). Another aim was to correlate the severity score in the Model for End Stage Liver Disease (MELD) with the distance covered in the Six-Minute Walk Test (6MWT) of chronic hepatic patients.

Methods

The present study is characterized by a cross-sectional design with a convenience sample. The analyzed sample consisted of 86 adult patients with a medical diagnosis of HCV, HBV, and AC who were being followed-up by the Hepatic Transplantation Service of Complexo Hospitalar Santa Casa de Porto Alegre (Rio Grande do Sul, Brazil) in the period of August 2009 to December 2010. The study included all individuals who were clinically able to perform the proposed procedures and who were in the pre-operative period of liver transplantation.

All patients had periodic medical monitoring and were able to execute the recommended tests. They could not present factors that would interfere with the data collection: non-cooperation, hemodynamic instability, difficulty in locomotion, neuromuscular diseases, and being listed for organ re-transplant). The 86 cirrhotic patients were divided into three distinct groups: 40 were in the HCV group, 14 in the HBV group, and 32 in the AC group. A signed informed consent form was obtained from each patient, and the work was approved by the Ethics Committees of Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) and Complexo Hospitalar Santa Casa de Porto Alegre, RS, Brazil (Report 110/05, Protocol 1036/05).

The selected patients were subjected, on the same occasion, to the application of the self-administered QoL questionnaire "Short-Form 36" (SF-36), manometry, and the 6MWT. Prior to the performance of the tests, the data concerning sample characteristics were recorded on a specific assessment form, and all the measurements were performed by the same evaluator. To evaluate the functional capacity, that is, the functional level of daily physical activities, the 6MWT was performed. This test requires the patient to cover a maximum distance during six minutes of walking as fast as possible, and it took place in a straight 30-meter hallway without obstacles or inclinations[10]. Before and after the test, the patient would rate the sensation of dyspnea and lower limb fatigue by means of the modified Borg Scale (0 to 10). Cardiac and respiratory rates as well as peripheral oxygen saturation (SpO_2) were also recorded at that time.

The QoL of patients was evaluated using the self-administered questionnaire SF-36, which describes and assesses the health condition of individuals by means of several domains (functional capacity – $SF\text{-}36_1$; limitation due to physical aspects – $SF\text{-}36_2$; pain – $SF\text{-}36_3$; general health status – $SF\text{-}36_4$; vitality – $SF\text{-}36_5$; social aspects – $SF\text{-}36_6$; mental health – $SF\text{-}36_7$; limitation by emotional aspects – $SF\text{-}36_8$). The scores in each domain are obtained by adding up the responses for that item and transforming these raw scores into a scale in which 0 represents impaired health and 100, good health status[11].

To measure the strength of the respiratory muscles, we used a digital manometer (MVD 500, Globalmed®) and, to assess maximal inspiratory pressure (MIP), we asked the patient to perform maximal expiration to residual volume followed by forced inspiration to total lung capacity. To evaluate the maximal expiratory pressure (MEP), we asked the patient to begin the maneuver from total lung capacity followed by forced maximal expiration. To carry out the maneuvers, the equipment had to be properly positioned in the patient's mouth to avoid a test failure. The results were obtained after the completion of five maneuvers, including a minimum of three acceptable maneuvers, with the values not differing from the highest value by more than 10%. The highest pressure in centimeters of water (cmH_2O) was recorded, and normality values were used[12].

Lung function (forced vital capacity – FVC; forced expiratory volume in the first second – FEV_1) was measured using a microspirometer (Micromedical/Microplus) according to the Guidelines for Pulmonary Function Tests prescribed by

the Brazilian Society of Pneumology and Phthisiology[13]. The spirometry test was applied to obtain three acceptable maneuvers, including two reproducible maneuvers. The reproducibility criteria involved the difference between the two highest FEV_1 values and FVC below 0.2 liters, which indicates that the maximum value was probably obtained.

To measure the severity of liver patients, we used the MELD severity score, which was calculated using the formula below (available at http://www.unos.org/docs/MELD_PELD_Calculator_Documentation.pdf):

$\{0.957 \times Log_e [creatinine (mg/dL)] + 0.378 \times Log_e [bilirubin (mg/dL)] + 1.120 \times Log_e (INR) + 0.643\}$[14].

To check sample normality, we used the Kolmogorov-Smirnov test. To compare groups in relation to performance in the 6MWT, respiratory muscle strength, and SF-36 scores, we used analysis of variance (ANOVA) with a Tukey post-hoc test and, to correlate the MELD with the 6MWT, we used Pearson's correlation. The data were analyzed in the statistical program SPSS version 16.0, and the significance level was 5%, with $p<0.05$ being considered significant.

Results

Table 1 shows the anthropometric and clinical characteristics of the studied sample. Similar results were observed in the assessed groups, with no statistical differences between the participants. The main diagnoses of liver disease were: type C cirrhosis, type B cirrhosis, and alcohol-induced cirrhosis. The MELD severity score did not differ statistically between groups.

In the comparison of the ability to exercise, the AC group obtained a lower performance in the 6MWT compared to the HBV and HCV groups (p=0.001). In the AC group, the heart rate (HR) at the end of the 6MWT was significantly higher than in the HCV and HBV groups (p=0.03). The Borg scores for lower limb fatigue immediately after the 6MWT were higher in the AC group compared to the HCV and HBV groups (p=0.01). The AC group had lower MIP and MEP compared to the HBV and HCV groups (p=0.001) as shown in Table 2.

In relation to the domains of the QoL questionnaire SF-36 (Table 3), the AC group had lower scores in all domains compared to the HBV and HCV groups. However, it only showed statistically significant differences in functional capacity (p=0.001) and limitations due to physical aspects (p=0.001). In the analysis of the correlation of MELD with the distance covered in the 6MWT (Figure 1), a moderate negative correlation was found (r=-0.56; p=0.001).

Table 1. Anthropometric and clinical characteristics of patients.

	HCV (n=40)	HBV (n=14)	AC (n=32)	p
Age (years)	56.3±8.1	52.3±6.4	54.3±9.7	0.9
Sex (no.) - M/F	30/10	14/4	20/8	0.8
Weight (Kg)	67.34±8.62	69.23±10.62	71.00±8.50	0.8
Height (m/cm)	1.67±0.83	1.69±0.73	1.70±0.91	0.9
MELD	16±2	17±3	19±3	0.6
FVC(%)	95.0±19.5	97.0±17.4	93.2±30.5	0.7
FEV_1 (%)	90.9±16.9	88.7±18.0	87.1±14	0.8

The variables age, weight, height are described as mean and standard deviation, respectively. M/F=male/female; HCV=hepatitis C virus group; HBV=hepatitis B virus group; CA=alcoholic cirrhosis group; MELD=Model for End Stage Liver Disease; FVC (%)=Forced vital capacity; FEV_1 (%)=Forced expiratory volume in the first second.

Table 2. Comparison between groups of variables in the Six-Minute Walk Test and respiratory muscle strength.

	HCV (n=40)	HBV (n=14)	AC (n=32)	p
6MWT (m)	475.94±27.84*	464.16±32.00*	373.50±50.48*	0.001
HR (initial	72±16	77±11	74±13	0.9
HR(final)	87±22 *	91±15*	102±20*	0.02
RR (initial)		15±3	16±5	0.8
RR (final)	23±2	21±3	25±8	0.7
SpO_2 (initial %)	97±2	98±1	97±3	0.9
SpO_2 (final %)	96±4	97±1	95±2	0.8
Borg score (initial)		1±0.6	2±0.4	0.7
Borg score (final)	2±1*	2±1*	4±1.5*	0.01
MIP (cmH_2O)	-82.44±13.71*	-71.61±6.96*	-65.54±11.28*	0.001
MEP (cmH_2O)	83.44±12.20*	82.44±13.87*	63±10.74*	0.001
6MWT Pred (m)	703±95	654±101	701±78	0.8
MIP Pred (cmH_2O)	-165±54	-154±62	-162±57	0.9
MEP Pred (cmH_2O)	259±34	247±41	254±51	0.7

The variables are described as mean and standard deviation. HCV=hepatitis C virus group; HBV=hepatitis B virus group; AC=alcoholic cirrhosis group; 6MWT=Six-Minute Walk Test; HR=heart rate; RR=respiratory rate; SpO_2=peripheral oxygen saturation; MIP=Maximal Inspiratory Pressure; MEP=Maximal Expiratory Pressure; 6MWT Pred=Six-Minute Walk Test predicted; MIP Pred=Maximal Inspiratory Pressure predicted; MEP Pred=Maximal Expiratory Pressure predicted. *Significant difference between groups AC and HBV and between groups AC and HCV. The statistical analysis used was ANOVA with Tukey post-hoc.

Table 3. Comparison of quality of life between groups.

	HCV (n=40)	HBV (n=14)	AC (n=32)	p
SF-36$_1$	67.08±24.96*	64.60±22.22*	46.59±14.75*	0.001
SF-36$_2$	69.02±11.00*	64.80±21.40*	40.00±12.61*	0.001
SF-36$_3$	56.05±13.97	61.44±25.58	52.66±19.13	0.07
SF-36$_4$	48.87±16.45	51.96±17.50	47.00± 15.41	0.08
SF-36$_5$	56.14±11.07	63.20±26.45	51.52±17.50	0.1
SF-36$_6$	67.89±19.71	71.04±25.40	63.55±24.75	0.08
SF-36$_7$	48.32±12.04	51.61±15.12	44.29±10.95	0.07
SF-36$_8$	66.12±20.05	68.08±16.07	63.00±13.04	0.6

The variables are described as mean and standard deviation. HCV=hepatitis C virus; HBV=hepatitis B virus; AC=alcoholic cirrhosis; SF-36=Short Form 36; SF-36$_1$=functional capacity; SF-36$_2$=limited by the physical aspect; SF-36$_3$=pain; SF-36$_4$=general health; SF-36$_5$=vitality; SF-36$_6$=social; SF-36$_7$=mental health; SF-36$_8$=limitation by emotional aspects.*Significant difference between groups AC and HBV and between groups AC and HCV. The statistical analysis used was ANOVA with Tukey post hoc.

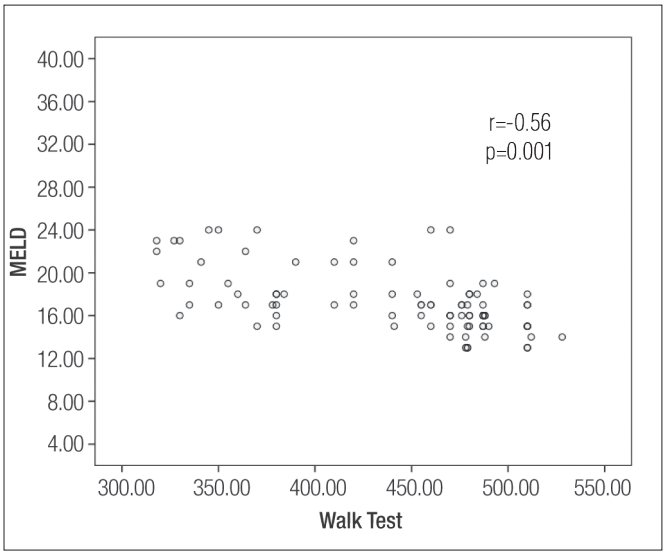

Figure 1. Correlation between the MELD with the Six-Minute Walk Test.

Discussion

The present study is the first to compare functional status, respiratory muscle strength, and QoL in Brazilian liver transplant candidates with cirrhosis of different etiologies. When we measured the distance covered in the 6MWT in the different groups, we found a decrease in the functional status of the AC group compared to the HCV and HBV groups, indicating a possible deterioration of the musculoskeletal system as a result of the combination of the pathological process and the use of alcohol. In the study by Alameri et al.[15], the functional status of liver transplant candidates was evaluated. The results showed that individuals with Child-Pugh class C liver cirrhosis had lower functional capacity and survival rate than patients with Child-Pugh class A and B, demonstrating that the severity of the disease affects functional aspects before transplantation.

The existence of moderate inverse association between the MELD variables and the distance in the 6MWT has been previously described by our group[16]. The considerable sample size of the present study strengthens the idea that the MELD severity score shows interference with the performance of functional analysis in patients with hepatic disease.

The AC group showed greater fatigue compared to the other groups at the end of the 6MWT. A possible explanation relies on aspects of adaptation that the type I muscle fibers (slow contractions/oxidative) can suffer, becoming fast-twitch fibers (type IIA/glycolytic) as a result of physical inactivity[17]. This glycolytic mechanism is characterized by the non-use of aerobic metabolic routes for the formation of energy substrate with a predominance of anaerobic metabolism, which physiologically produces lactate. The accumulation of lactic acid is responsible for the depletion of the glycogen reserves in the muscle fibers, thus interfering with anatomical-functional aspects of the muscular system, causing fatigue and limiting the activities of daily living of these patients. According to this concept, the rates of adenosine triphosphate (ATP), phosphocreatine (PCr), and total magnesium (Mg^{2+}) are lower in the skeletal muscle of cirrhotic patients. This concept was demonstrated by Jacobsen et al.[18], who found higher rates of PCr and mitochondrial ATP in individuals with better clinical conditions.

As a result of changes in functional capacity, these individuals will have negative consequences in the aspects related to QoL. In our study, the patients of the AC group had lower scores in all of the domains of the SF-36, but only the functional status and limitations due to physical aspects differed statistically from the HCV and HBV groups. Such results are limited in relation to the discussion because there are few studies that compare QoL among these respective groups. However, van den Berg-Emons et al.[19] compared the QoL of patients undergoing liver transplantation and healthy individuals and found that the transplant patients had lower scores in the functional capacity domain than the control group[20].

Although the liver transplant patients show improvement in their social aspects, the vast majority does not return to the social tasks previously carried out. Employment status is often decreased as a result of emotional and physical changes. According to Ratcliffe et al.[21], 45% of the individuals in their sample did not return to their employment duties after the transplant. This factor has a direct impact on social aspects and may interfere with QoL.

Multidisciplinary rehabilitation programs prior to liver transplantation may be a relevant option for these patients, specifically those with AC, who in the present study showed

further deterioration in functional status, QoL, and respiratory muscle strength. However, there are few studies that measured the effectiveness of rehabilitation programs in patients with chronic hepatic disease[22].

The present study has some limitations. The small sample size of the HBV group, due to the low prevalence of HBV in our region, restricts the comparisons of variables between groups. Another limiting aspect is the inclusion of a single walking test, as it is recognized that learning influences performance. The use of the generic instrument SF-36 to measure QoL may limit the assessment of the influence of liver disease on QoL, given that there are validated instruments specific for liver diseases.

In light of these considerations, it can be concluded that the AC group showed lower functional status, respiratory muscle strength, and QoL when compared to the patients of the HCV and HBV groups. There was also an inverse correlation between the MELD severity score and the distance in the 6MWT in patients who were on the waiting list for liver transplantation. Therefore, further studies are needed to evaluate the influence of the respective variables on the different groups investigated here.

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