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Exercise in the physical rehabilitation of cirrotics: a randomized pilot study

Danusa **ROSSI**[1], André Ferreira **D'AVILA**[1], Lucas Homercher **GALANT**[1] and Claudio Augusto **MARRONI**[1,2]

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ABSTRACT – Background – Physical exercise delays the sarcopenic process and can reverse the loss of muscle strength, improve quality of life and prognosis in cirrhotic patients. **Objective –** The aim was to verify the effects of face-to-face versus home aerobic exercise on the variables fatigue, respiratory and peripheral muscle strength, functional capacity and quality of life in patients with compensated cirrhosis. **Methods –** Patients were selected by convenience, stratified and randomized into supervised face-to-face exercise (n=13) and home exercise without daily supervision (n=12). Patients were submitted to a program of aerobic physical exercises, with progressive duration of 30 to 50 minutes, twice a week for twelve weeks. Before starting the program and every four weeks, all patients in both groups were assessed for fatigue (fatigue severity scale), respiratory (Pimáx and Pemáx) and peripheral (concentric quadriceps peak torque) muscle strength, functional capacity (6-minute walking distance) and quality of life (Short Form-36 Health Survey questionnaire). **Results –** The face-to-face group showed reduced fatigue (P<0.001), increased inspiratory (P<0.001), expiratory (P<0.001) and peripheral (P<0.001) muscle strength of the 6MWD (P<0.001) and improved quality of life. The home group showed no significant improvement in these variables. **Conclusion –** A face-to-face program of moderate aerobic exercise in patients with compensated cirrhosis reduces fatigue, improves functional capacity and quality of life and increases respiratory and peripheral muscle strength. Home physical exercises do not cause the same adaptive effects in this population.

Keywords – Physical exercise; sarcopenia; rehabilitation; cirrhosis.

INTRODUCTION

Cirrhosis is the final stage of progressive liver fibrosis and represents the 14th leading cause of death worldwide[1,2]. The disease modifies liver function and affects, among others, muscle tissue, causing significant muscle mass loss, which reaches pathological levels characterizing sarcopenia[3].

Sarcopenia is a progressive and generalized syndrome of loss of skeletal muscle and muscle strength, and results from the imbalance between protein synthesis and degradation due to nutritional, metabolic and biochemical abnormalities, and increases patient morbidity and mortality[4,5]. In addition, it causes damage to body composition, aerobic capacity, muscle strength and power production, resulting in impairments in functionality and quality of life. It is an independent mortality factor, which implies a worse clinical outcome[6].

Cirrhotic patients have a high prevalence of sarcopenia and physical inactivity, which, added to aging, malnutrition, decreased hepatic protein synthesis, hypermetabolism, increased inflammatory cytokines, hyperammonemia and low testosterone levels, allow muscle deconditioning, resulting in reduced cardiovascular reserve, increased physical fragility and decreased strength and quality of life[7, 8].

There is no effective treatment to reverse cirrhosis and management focuses on treating the primary disease, managing complications and liver transplantation. However, a poor physical condition, even after the transplant, has a negative impact on the success of the procedure, resulting in lower survival[9-11].

Research on the benefits of physical activity in cirrhotic patients is at an early stage, but suggests that physical exercise is essential as it delays the sarcopenic process[12], increases muscle mass and strength[13-15], improves functionality[16,17], reduces the risk of falls[18] and fatigue[19], promotes glycemic control[20], increases protein synthesis[21] and provides better quality of life[19, 22] enabling a better prognosis.

This study aimed to verify the effects of moderate aerobic exercise in person versus at home on fatigue, respiratory and peripheral muscle strength, functional capacity and quality of life in patients with compensated cirrhosis.

METHODS

This study is a randomized controlled, parallel, open-label, 2-arm clinical trial approved by the Research Ethics Committee (CEP) of the Federal University of Health Sciences of Porto Alegre (UFCSPA) and the Santa Casa de Misericordia Hospital Complex (n° 3805918 and 3938979, respectively) and was registered in the ReBec Clinical Trials registry database (n. RBR-3gtcvjU111112367585). All patients gave their informed consent before being included in the study.

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[1] Universidade Federal de Ciências da Saúde de Porto Alegre, Programa de Pós-Graduação em Hepatologia, Porto Alegre, RS, Brasil. [2] Santa Casa de Misericórdia em Porto Alegre, Serviço de Transplante de Fígado, Porto Alegre, RS, Brasil.
Corresponding author: Danusa Rossi. E-mail: danusafisio@gmail.com

Cirrhotic patients from 18 to 75 years old, of both genders, with cirrhosis of any etiology, in outpatient follow-up, were included. Due to the risk of increased portal pressure and bleeding from esophageal varices, patients with decompensated liver disease, characterized by Class C of the Child-Turcotte-Pugh score, with manifestations of portal hypertension (splenomegaly, grade III esophageal varices, increased portal vein or collateral circulation) were excluded. Patients with dietary supplementation with amino acids, recent hospitalization, neuromuscular diseases or orthopedic alterations that compromised the performance of tests or physical exercises, or with contraindications for the same were also excluded.

Patients were selected by convenience, stratified according to age and gender and randomized by the researchers, using the Microsoft Excel® program, into two groups: Face -to-face group (FG) and home group (HG). A trained researcher (P1) performed all assessments of patients in both groups and a second trained researcher (P2) supervised physical activity in the FG and guided exercises to the HG. The face-to-face assessments and interventions were performed simultaneously by the researchers in the same laboratory. Thus, blinding was only possible for the professional who performed the analysis statistic.

In-person exercise protocol

Patients filled out an evaluation form, prepared by the researchers, with demographic and clinical characteristics. Subsequently, they were evaluated by P1, regarding respiratory and peripheral muscle strength, functional capacity, quality of life and fatigue. In the following session, supervised by P2, they performed aerobic exercises twice a week, for 12 weeks. The first session consisted of 5 minutes of warm-up, followed by 30 minutes of treadmill walk, at the maximum speed tolerated by the patient, according to the Borg scale[23]. Two minutes of walking were added to each session, up to a limit of 50 minutes of walking, time maintained until the end of the protocol. All patients were reassessed at the 4th, 8th and 12th weeks of exercise.

Home exercise protocol

Patients were evaluated in the same way as the face-to-face group by P1 and then instructed by P2 to perform a 5-minute warm-up period followed by walking on level ground, twice a week, for 12 weeks. As in the face-to-face group, each day, they added 2 minutes of walking, until reaching 50 minutes, at the maximum tolerated speed. Patients were instructed to discontinue exercise in the event of malaise, arrhythmias, dizziness, shortness of breath and to seek medical attention as soon as possible. All patients were reassessed in person at the 4th, 8th and 12th weeks of exercise.

Variables analyzed

Fatigue was assessed using the Fatigue Severity Scale (FSS), where a score equal to or greater than four indicates severe fatigue[24] Respiratory muscle strength was measured through maximal inspiratory (Pimáx) and expiratory (Pemáx) pressure, using the Globalmed® MVD 500 digital manovacuometer. To assess peripheral muscle strength, concentric isokinetic peak torque (PT) values were used, in Newton/Meters (Nm), generated by the knee extensor muscles of the dominant limb in the Biodex System 3 Isokinetic Dynamometer with the Biodex Advantage software version 3.0 (Biodex Medical Systems, Inc., Shirley, New York, USA). We evaluated the functional condition through the distance covered in the 6-minute walk test (6MWD), according to the American Thoracic Society guidelines[25] and the quality of life through the Medical Outcomes Study, Short Form-36 Health Survey questionnaire (SF-36)[26].

Data analysis

Quantitative variables were described by average and standard deviation and categorical, by absolute and relative frequencies. The comparison of averages was performed by the *t*-student test. Comparison of proportions was performed using Pearson's chi-square or Fisher's exact tests. Simultaneous intra- and inter-group comparisons were performed using the generalized estimating equations (GEE) model, complemented by the Least Significant Difference Test. The significance level adopted was 5% ($P<0.05$) and the analyzes were performed using the Statistical Program Package for the Social Sciences (SPSS) version 21.0.

RESULTS

This study was carried out between 2020 and 2021. FIGURE 1 shows the flow of patients in the study, according to the standards of CONSORT.

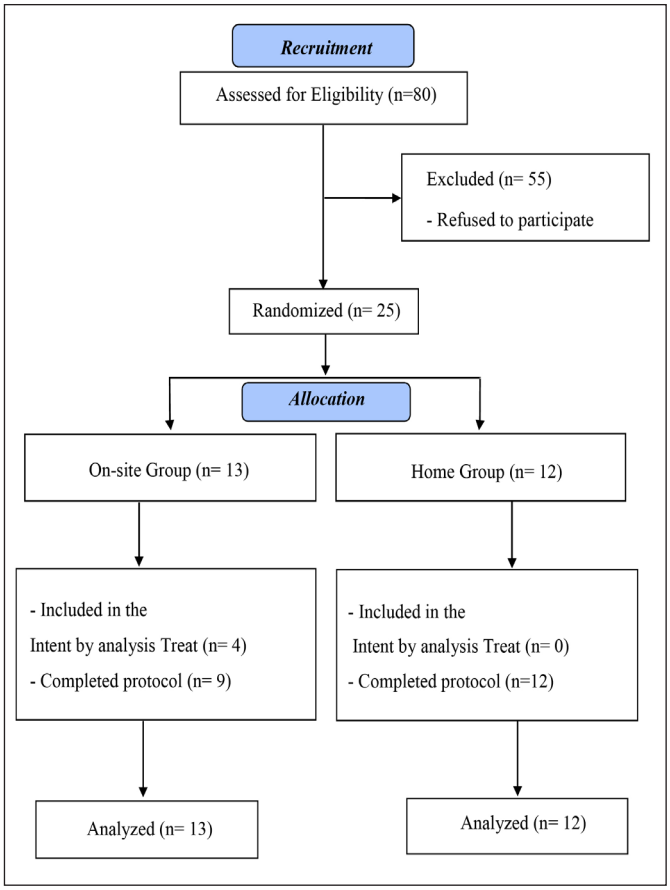

FIGURE 1. Flow diagram of study participants according to CONSORT.

Descriptive analysis of demographic characteristics of the patients analyzed in the study is shown in TABLE 1.

The behavior of the variables Fatigue, Pi and Pemáx, Extension PT and 6MWD between the groups throughout the exercise program is shown in TABLE 2. Regarding fatigue, in the intragroup

TABLE 1. Sample characterization.

Variables	FG (n=13)	HG (n=12)	*P*
Age (years) - mean ± SD	56.5±8.8	58.7±7.7	0.512
Gender - n (%) masculine	8 (61.5)	6 (50.0)	0.859
BMI (kg/m^2) – mean ± SD	28.4±4.9	27.8±3.9	0.730
Years of study - mean ± SD	7.8±3.3	6.9±2.5	0.481
Etiology - n (%)			0.301
HCV	5 (38.5)	7 (58.3)	
Alcohol	2 (15.4)	0 (0.0)	
HCC	1 (7.7)	0 (0.0)	
NASH	2 (15.4)	1 (8.3)	
Alpha1 deficiency	1 (7.7)	0 (0.0)	
PBC	1 (7.7)	0 (0.0)	
HCV + CHC	0 (0.0)	1 (8.3)	
HCV + alcohol	0 (0.0)	1 (8.3)	
VHC+ CHC+ alcohol	0 (0.0)	2 (16.7)	
HBV + alcohol	1 (7.7)	0 (0.0)	
MELD – mean ± SD	11.0±4.2	12.3±4.4	0.446
CHILD - n (%)			0.593
A	12 (92.3)	10 (83.3)	
B	1 (7.7)	2 (16.7)	
No physical activity - n (%)	10 (76.9)	9 (75.0)	1,000

FG: face-to-face group; HG: home group; SD: standard deviation; BMI: body mass index; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; NASH: Non-alcoholic steatohepatitis; PBC: primary biliary cirrhosis; HBV: hepatitis B virus; MELD: *Model* For End-Stage liver Disease.

comparison, the FG showed a significant reduction at each evaluated moment, with significantly lower values from the 8th week and reduced by 1.86 points, on average, during the total follow-up period, while the HG increased by 0.10 points on average, this difference being statistically significant.

The behavior of quality of life is shown in TABLE 3. The FG showed a statistically significant increase in the scores of almost all the SF-36 domains in relation to the HG. This increase was not significant in the mental health, social aspects and pain domains.

DISCUSSION

There are still few studies that analyze the benefits and effects of physical exercise in cirrhotic patients, evaluating different patient profiles and physical activity modalities.

The physical exercise protocols proposed for this population are still quite heterogeneous with very restrictive inclusion criteria. In the studies carried out to date, these exercises had different modalities, ranging from 6 weeks to 12 months, with sessions from 1 to 3 times a week, lasting up to 1 hour. Most studies have found positive and significant results with exercise in this population, although little is known about its clinical repercussions on the disease.

TABLE 2. Comparison of Fatigue, MIP, Pemax, 6MWT and Peak Torque intra and intergroups.

Variables	FG (n=13)	HG (n=12)	*P*
	Mean±EP	Mean±EP	
Fatigue			
Pre exercise	3.43±0.29^{d}	3.76±0.44^{a}	0.529
4th week	2.69±0.27^{c}	3.73±0.49^{a}	0.063
8th week	1.97±0.24^{b}	3.80±0.48^{a}	0.001
12th week	1.56±0.19^{a}	3.86±0.44^{a}	<0.001
Pre-12th week difference	-1.86 (-2.42 to -1.31)	0.10 (-0.36 to 0.56)	<0.001
Pimáx (cmH_2O)			
Pre exercise	-72.9±6.0^{a}	-53.7±6.2 ^{a}	0.026
4th week	-76.0±7.4^{a}	-58.5±6.2 ^{a}	0.072
8th week	-88.6±6.3^{b}	-55.5±6.3 ^{a}	<0.001
12th week	-95.9±5.2^{c}	-56.2±5.3 ^{a}	<0.001
Pre-12th week difference	-23.0 (16.8 to 29.1)	-2.5 (-3.5 to 8.5)	<0.001
Pemáx (cmH_2O)			
Pre exercise	108.8±6.7^{a}	88.8±7.8^{a}	0.052
4th week	118.6±8.9^{b}	88.4±7.2^{a}	0.008
8th week	125.9±8.2^{c}	87.1±6.5^{a}	<0.001
12th week	137.3±8.1^{d}	88.2±5.7^{a}	<0.001
Pre-12th week difference	28.5 (20.8 to 36.2)	-0.65 (-10.3 to 9.0)	<0.001
6MWT (m)			
Pre exercise	457.2±18.9^{a}	389.2±13.9^{a}	0.004
4th week	503.0±17.7^{b}	411.8±15.1^{b}	<0.001
8th week	539.2±15.2^{c}	407.7±15.4^{b}	<0.001
12th week	555.0±15.3^{d}	400.9±14.7^{ab}	<0.001
Pre-12th week difference	97.8 (63.8 to 131.9)	11.7 (-1.3 to 24.7)	<0.001
Extension PT (N)			
Pre exercise	126.3±11.9^{a}	106.7±12.0^{a}	0.246
4th week	154.9±14.4^{b}	106.7±10.7^{a}	0.007
8th week	159.5±15.6^{b}	107.7±12.9^{a}	0.010
12th week	167.3±16.6^{c}	105.7±12.8^{a}	0.003
Pre-12th week difference	41.0 (21.8 to 60.2)	-1.03 (-8.78 to 6.72)	<0.001

FG: face-to-face group; HG: home group; EP: standard error; ^{a,b} ^{,c,d} equal letters do not differ by the least test significant difference (LSD) at 5% significance; Pimáx: maximum inspiratory pressure; Pemáx: maximum expiratory pressure; 6MWT: 6-Minute Walk Test; m: meters; PT: peak torque; N: Newton.

TABLE 3. Comparison of intra and inter group quality of Life (SF-36).

Variables	FG (n=13)	HG (n=12)	*P*
	Mean ± EP	Mean ± EP	
Functional capacity			
Pre exercise	73.8±4.7[a]	62.1±6.7[a]	0.149
12th week	93.5±4.7[c]	60.9±5.8[a]	<0.001
Pre-12th week difference	19.7 (9.0 to 30.3)	-1.17 (-9.32 to 6.97)	0.002
Physical aspects			
Pre exercise	51.9±11.4[a]	22.9±9.5 [a]	0.051
12th week	86.5±9.4[c]	30.0±9.0[a]	<0.001
Pre-12th week difference	34.6 (15.0 to 54.2)	7.08 (-2.06 to 16.2)	0.013
Emotional aspects			
Pre exercise	48.7±10.0[a]	19.5±8.3[ab]	0.024
12th week	64.2±12.9[ab]	16.3±7.0[a]	0.001
Pre-12th week difference	15.4 (-4.64 to 35.5)	-3.11 (-23.6 to 17.3)	0.017
Vitality			
Pre exercise	63.8±4.4[a]	57.1±6.0[a]	0.363
12th week	84.0±3.6[c]	55.5±6.1[a]	<0.001
Pre-12th week difference	20.2 (12.6 to 27.7)	-1.63 (-8.49 to 5.23)	<0.001
Mental health			
Pre exercise	72.9±4.6[a]	64.0±6.4[b]	0.258
12th week	80.7±4.3[a]	59.6±5.5[ab]	0.003
Pre-12th week difference	7.73 (-5.94 to 21.4)	-4.36 (-9.20 to 0.48)	0.102
Social aspects			
Pre exercise	69.3±6.0[a]	55.3±8.4[a]	0.174
12th week	81.3±6.6[a]	57.5±7.3[a]	0.016
Pre-12th week difference	12.0 (-2.76 to 26.7)	2.25 (-6.27 to 10.8)	0.263
Pain			
Pre exercise	61.2±5.7[a]	64.8±8.6[a]	0.727
12th week	75.3±8.5[a]	65.0±6.5[a]	0.339
Pre-12th week difference	14.1 (-8.07 to 36.2)	0.21 (-9.98 to 10.4)	0.265
General health			
Pre exercise	61.9±4.8[a]	52.1±5.7[a]	0.186
12th week	84.0±4.1[c]	56.4±5.0[ab]	<0.001
Pre-12th week difference	22.1 (11.7 to 32.5)	4.28 (-1.76 to 10.3)	0.004

FG: face-to-face group; HG: home group; EP: standard error; [a,b c,d] Equal letters do not differ by the least test significant difference (LSD) at 5% significance.

In this study, we observed that patients in the FG did not show a significant improvement in the variables studied, when compared to patients in the HG. Professional supervision could contribute to better results[27, 28].

Although fatigue is frequently reported by patients with cirrhosis, few studies have evaluated the symptom as an outcome with physical activity as an intervention. In our study, fatigue decreased in the FG and increased in the HG. A randomized clinical trial by Zenith et al showed that patients who performed supervised home exercise 3 times a week for 8 weeks also had symptom reduction[19].

In the FG, Pi and Pemáx reached an increase of 23 cmH2O and 28.5 cmH2O, respectively. We did not find studies that evaluated respiratory muscle strength as an outcome after exercise or physical activity in this population.

We observed an increase in the 6MWD by 97 meters in the FG patients, a result corroborated by other studies[14-17]. The literature shows increments of 34 to 80 meters in patients who performed supervised face-to-face exercise similar to that performed in this study. A 30.5 m increase in 6MWD has been suggested as the minimum improvement needed to confer any clinical benefit, but this has not yet been validated in patients with cirrhosis[28] The greatest increase in 6MWD was reported by Chen et al.[17], of 151 meters, after intervention guided by a pedometer (P=0.03).

FG patients showed a significant increase in PT. Aamann et al. obtained similar results when cirrhotic patients performed strength physical exercise three times a week[15]. Hiraoka et al. demonstrated a 5.6% increase in muscle strength after 12 weeks of aerobic exercise with daily step count goals (P<0.01). An 11% increase in lower limb strength was also reported over the same time period (P<0.01). However, patients received amino acid supplementation concurrently with exercise[29].

Despite being recommended, the application of physical exercise in cirrhotic patients is far behind other chronic diseases, possibly due to the chance of increased portal pressure. Garcia-Pagan et al. demonstrated that moderate exercise increases portal pressure in patients with portal hypertension and therefore, theoretically increases the risk of variceal bleeding[30]. Other barriers are the lack of specific supervised exercise programs available for this group of patients and the lack of evidence for safely and effectively prescribing and evaluating exercise[31]. Therefore, the results of current studies may not be easily generalizable to patients with more advanced liver disease, Child-Turcotte-Pugh C or very high MELD. However, recent controlled studies have shown safety, improvements in physical fitness, muscle mass and QOL[32-34].

A recent review showed that several studies investigated the effect of exercise on quality of life using different instruments with positive results[35]. We observed that the HG achieved lower scores in relation to the FG in all domains. Studies report that the lack of direct supervision can result in a loss of exercise effectiveness. This could be an explanation for our result[36, 37].

The limitations of this study are mainly related to the lack of nutritional control of patients in both groups. In addition, restrictions imposed by the pandemic, such as the reduction in the number of professionals and patients with access to the institutions involved in this study and transport difficulties, lack of supplies for the acquisition of technologies, led to the impossibility of four patients from the FG to continue participating in the study. This scenario only made it possible to supervise the HG in the 4th, 8th and 12th weeks and not on a daily basis like the HG. Many of our patients did not have access to technology

that supported applications that would allow us to do this follow-up, even virtually.

However, this study produced statistically significant results, which makes us suppose that moderate aerobic physical exercise cannot be underestimated. In addition, it reinforces the importance of a trained professional supervision for this population. The challenge will be the development of studies with a representative sample, which may involve patients with decompensated disease, to assess the benefits of aerobic physical exercise, minimizing the risks imposed by physical activity with load. In the end, these activities could clarify the effects of exercise on the clinical evolution of these patients.

CONCLUSION

This study showed that 12 weeks of face-to-face sessions of moderate-intensity aerobic exercise, were able to reduce fatigue, strengthen respiratory and peripheral muscles, improve functional capacity and quality of life in cirrhotic patients with compensated disease. Physical activity at home did not have the same effects in these patients.

Authors' contribution

Rossi D and D'avila AF: data acquisition; preparation of the article and final approval of the version to be published. Galant LH: conception and design, writing of the article and final approval of the version to be published. Marroni CA: Design and supervision, final approval of the version to be published.

Orcid

Danusa Rossi: 0000-0001-6787-4915.
André Ferreira D'Avila: 0000-0002-2028-0180.
Lucas Homercher Galant: 0000-000-4333-1403.
Claudio Augusto Marroni: 0000-0002-1718-6548.

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RESUMO – Contexto – O exercício físico retarda o processo sarcopênico e pode reverter a perda de força muscular, melhorar a qualidade de vida e prognóstico em cirróticos. **Objetivo –** O objetivo foi verificar os efeitos do exercício aeróbico presencial versus domiciliar sobre variáveis fadiga, força muscular respiratória e periférica, capacidade funcional e qualidade de vida em pacientes com cirrose compensada. **Métodos –** Os pacientes foram selecionados por conveniência, estratificados e randomizados em exercício presencial supervisionado (n=13) e exercício domiciliar sem supervisão diária (n=12). Os pacientes foram submetidos a um programa de exercícios físicos aeróbicos, com duração progressiva de 30 minutos a 1 hora, duas vezes por semana durante 12 semanas. Antes de iniciar o programa e a cada 4 semanas, todos os pacientes de ambos os grupos foram avaliados quanto à fadiga (escala de gravidade da fadiga), força muscular respiratória (Pimáx e Pemáx) e periférica (pico de torque do quadríceps concêntrico), capacidade funcional (distância caminhada de 6 minutos) e qualidade de vida (questionário Short Form-36 Health Survey). **Resultados –** O grupo presencial apresentou redução da fadiga (P<0,001), aumento da força muscular inspiratória (P<0,001), expiratória (P<0,001), e periférica (P<0,001), da DTC6 (P<0,001) e melhora da qualidade de vida. O grupo domiciliar não apresentou melhora significativa nessas variáveis. **Conclusão –** Um programa presencial de exercícios aeróbicos moderados em pacientes com cirrose compensada reduz a fadiga, melhora a capacidade funcional e qualidade de vida, aumenta força muscular respiratória e periférica. Os exercícios físicos domiciliares não provocam os mesmos efeitos adaptativos nesta população.

Palavras-chave – Exercício físico; sarcopenia; reabilitação; cirrose.

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