ISSN 0103-5150
Fisioter. Mov., Curitiba, v. 28, n. 3, p. 617-625, July/Sept. 2015
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DOI: http://dx.doi.org.10.1590/0103-5150.028.003.AR02

The influence that hepatic cirrhosis provides in exercise capacity and muscle strength: a review

Influência da cirrose hepática na potência aeróbia e força muscular: uma revisão

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Abstract

Introduction: Hepatic cirrhosis leads to a series of physiological changes, among which stand out cardiorespiratory and muscle impairments. These changes determine a negative impact on quality of life and may cause physical inactivity. **Objective**: The objective of this study was to review, in the most current scientific literature, the influence that hepatic cirrhosis provides in exercise capacity and muscle strength, and the effect of exercise when applied to this situation. **Materials and methods**: For this review, research on original studies was carried out on Medical Literature Analysis and Retrieval System Online (assessed by PubMed), Scopus and Web of Science between the years 1990 to 2015. In order to be included, studies had to meet the following criteria: a) be from original articles; b) evaluate exercise capacity or muscle strength; and c) provide relevant results. **Results and Discussion**: The majority of studies concluded that the exercise capacity and muscle strength are decreased in individuals with cirrhosis when compared to control subjects.

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Final considerations: Hepatic cirrhosis has negative effect on cardiorespiratory and neuromuscular capacity during physical exercise in individuals with liver disease.

Keywords: Cirrhosis. Exercise. Exercise capacity. Strength.

Resumo

Introdução*: A cirrose hepática acarreta uma série de alterações fisiológicas, dentre as quais se destacam as alterações cardiorrespiratórias e neuromusculares. Estas determinam um impacto negativo na qualidade de vida dos pacientes, induzindo a inatividade física.* ***Objetivo****: O objetivo deste estudo foi revisar, na literatura científica, a influência que a cirrose hepática tem na potência aeróbia e na força muscular esquelética, bem como o efeito do exercício físico aplicado nessa situação.* ***Materiais e métodos****: Foram investigadas as principais revistas que compõem as bases de dados Medical Literature Analysis and Retrieval System Online (MEDLINE) (acessada via PubMed), Scopus e Web of Science publicados entre 1990 e 2015. Para serem incluídos, os estudos deveriam preencher os seguintes critérios: a) ser oriundo de artigos originais; b) avaliar potência aeróbia ou força muscular; e c) apresentar resultados relevantes.* ***Resultados e discussão****: A maioria dos estudos concluiu que a potência aeróbia e a força muscular encontram-se diminuídas em indivíduos com cirrose quando comparadas com as de sujeitos não portadores da doença.* ***Considerações finais****: A cirrose hepática tem efeito negativo nas capacidades cardiorrespiratórias e neuromusculares durante o exercício físico em indivíduos acometidos pela doença.*

Palavras-chave*: Cirrose. Exercício físico. Potência aeróbia. Força muscular.*

Introduction

Hepatic cirrhosis is the most severe outcome resulting from progressive and chronic hepatic injury. It is frequently an indolent, asymptomatic and unsuspected disease until complications start to emerge (1). Hepatic cirrhosis is identified by hepatocytes dysfunction, and it leads to accelerated hepatic fibrosis and distortion of vasculature on the hepatic tissue (2). Consequently, a hemodynamic disturbance occurs, which results in increased hepatic outflow and intrahepatic vasculature resistance. These alterations result in an increase in the portal blood flow, which gives rise to the hyperdynamic circulation (3). Due to these circulatory alterations, chronic hepatic disease induces several physiological alterations, especially in cardiovascular and neuromuscular functions (4).

It has been described that one of the main cardiorespiratory consequences of hepatic cirrhosis is the decrease in gas exchange, leading to arterial deoxygenation, which along with intrapulmonary vasodilation increases alveolar perfusion (5, 6). In addition, decreased mitochondrial oxidative capacity and reduced number of mitochondria in the muscle tissue may occur, which play a role on loss of muscle mass and oxidative muscle metabolism alteration by the skeletal muscle. This event anticipates the beginning of the anaerobic metabolism, which gives rise to muscle power decline following maximal oxygen consumption reduction (7). However, previous research in the scientific literature have found conflicting results regarding strength and muscle mass loss in patients who have hepatic cirrhosis. While few authors have proposed that metabolic alterations and oxidative stress are the main causes for neuromuscular dysfunction (8-10), others have suggested that a low caloric intake may be related to loss of muscle mass (11, 12).

These physiological alterations induce a negative impact on quality of life of patients and on their capacity of accomplishing daily activities (13). For this reason, the possibility of replacing an insufficient liver through hepatic transplantation when the hepatic disease is in an advanced level may be used as a treatment.

Liver transplantations provide improvement on survival rates, gas exchanges, and functional gains (14). Unfortunately, many patients have to wait on liver transplantation waiting lists, and the number of patients awaiting transplants is greater than the ones receiving (15). Therefore, a relevant alternative to these patients might be to begin physical training and multidisciplinary rehabilitation programs (16, 17). Physical exercise may reduce cardiovascular and neuromuscular variable impairments, improving both life quality and expectancy of these patients (18-20).

In order for this to be possible, it is necessary to understand hepatic cirrhosis effects on cardiorespiratory and neuromuscular capacities during physical activity performance, as well as the real benefits of this treatment. The aim of this study was to review in the scientific literature the influence of hepatic cirrhosis on exercise capacity and skeletal muscle strength, and the effect of physical exercise when applied to this situation.

Methods

In this review the most recent studies related to hepatic cirrhosis, physical aerobic exercise capacity and muscle strength were linked together. The main journals published between the years 1990 to 2015 were searched on Medical Literature Analysis and Retrieval System Online (MEDLINE) (accessed via PubMed), Scopus, and Web of Science databases. The following English terms were interconnected: cirrhosis, exercise, exercise/aerobic capacity, and strength.

The studies should complete the following including criteria: a) be from original articles (randomized clinical trials); b) evaluate "exercise capacity" and "muscle strength"; and c) have found pertinent relevant results. Articles about subjects with other clinical complications and diseases other than hepatic cirrhosis were excluded.

Our searches identified 2,545 original articles that presented the words "cirrhosis" and "physical exercise", of which only 240 were randomized clinical trials. For "exercise capacity", only 25 studies were found. Of those, only 15 studies were included, due to their common goal to identify the effect of hepatic cirrhosis on exercise capacity and other 4 on "muscle strength". Figure 1 presents an organogram with the manual searching results on electronic databases.

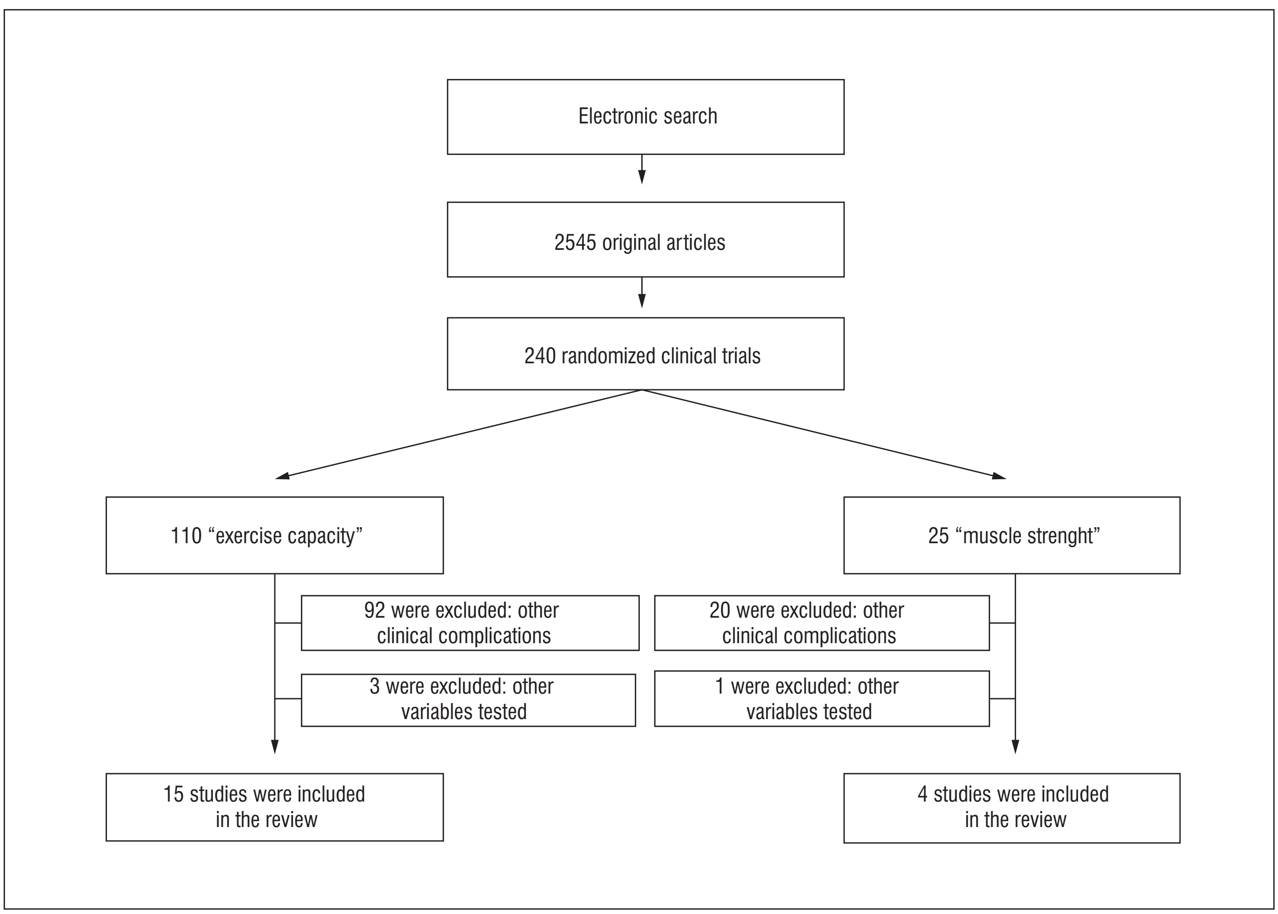

Figure 1 – Organogram of electronic search

Exercise capacity assessment in patients with hepatic cirrhosis

The exercise capacity of subjects with hepatic cirrhosis was assessed using oxygen consumption on maximum cardiopulmonary tests on fifteen different articles (21-35). These studies are described on table 1. In only two studies (21, 23) oxygen maximum consumption (VO_{2max}) was tested. In most studies, authors used peak of VO_2 (VO_{2peak}), which considers the maximum value achieved in an exhaustion moment. This was used because patients with chronic diseases usually are not able to achieve a plateau in VO_{2max} (36). However, three studies (26-28) used anaerobic threshold (VO_{2AT}), which measures the energy production supply via anaerobic pathway (37). Wiesinger (27) concluded that there is an increased risk on the occurrence of adverse effects on patients with hepatic cirrhosis that present complications, such as esophageal varices, when performing maximal effort on physical exercises.

Patients with hepatic cirrhosis have previously presented lower values of maximal oxygen consumption when compared to subjects not affected with the disease (21, 23, 24, 26, 32). One of these studies (23) did not find any significant difference on VO_{2max} when patients were compared to healthy subjects. This physical exercise intolerance may be due to a decrease on oxygen delivery on peripheral muscles, which might be caused by a disordered peripheral distribution of blood flow to skeletal muscles, or by a peripheral muscle dysfunction. Either way, the lower capacity of these subjects to perform exercises should be related to physiological complications induced by hepatic cirrhosis (24).

Most of the studies (21, 22, 24, 25, 27, 28, 30, 32) assessed the relationship between exercise capacity and the Child-Pugh scoring – this model was created to predict life mortality and expectancy in patients with hepatic cirrhosis (38, 39). Even though some studies did not find a negative correlation between exercise capacity and Child-Pugh scoring (21, 22, 34, 35), it has been suggested that hepatic cirrhosis can affect cardiorespiratory capacity during exercise (24, 25, 27, 28, 30, 32).

Only two studies (21-23) assessed exercise sessions on patients with hepatic cirrhosis. Each exercise session was performed on a treadmill during 32 minutes (21) and 90 minutes (23), respectively, at 50% of VO_{2max}. Both studies concluded that patients with hepatic cirrhosis have a high tolerance to exercise.

Not much is known about training effects on people who have severe hepatic disease (22, 34, 35). Campillo et al. (22) was the first study to perform aerobic training on 4 patients. The results demonstrated increase on VO_{2max} and muscle mass on half of the sample and improvements on Child-Pugh for the other half, which lead them to conclude that aerobic training can improve cardiorespiratory capacity and life expectancy for these patients. Only after a few decades a second study about training on this population was done. Zenith et al. (34) concluded that this paucity of data may be mostly related to extreme concerns about safety precautions of training intervention applied to this population. In agreement to the findings of this study, other two investigations, (34, 35) with a larger sample demonstrated a significant increase in VO_{2peak} after aerobic training. Interestingly, exercise improved also muscle mass, besides cardiorespiratory capacity.

When both resting and testing spirometry variables were assessed (21, 24, 25, 28, 30-32), divergent ventilatory values during maximal cardiopulmonary exercise testing were pointed out. Three case-control studies (21, 25, 30) found that values of this variable were greater in subjects with hepatic cirrhosis. Contrary to these findings, two other studies (24, 32) found greater ventilatory results on control groups, and only one investigation (28) did not find any significant differences on ventilatory results, when survival and non-survival patients that underwent hepatic transplantations were compared.

Other ventilatory variables have been previously investigated, such as dead space and tidal volume ratio (VD/VT), alveolar-arterial oxygen gradient ($P(A-a)O_2$), and partial arterial pressure of oxygen. (PaO_2). There may be a relationship between increases in $P(A-a) O_2$ and VD/VT, which supports the hypothesis that perfusion increases, through ventilation-perfusion mismatch decrease, could determine the hypoxemia presented by patients with hepatic cirrhosis (30). This was analyzed by two studies (25, 30), in which the authors found increased VD/VT during physical exercise, as well as decreased PaO_2 values and increased $P(A-a) O_2$, when patients with high level of hypoxemia were compared with normoxemic individuals.

Exercise capacity before and after hepatic transplantation

Taking together the studies that have assessed patients with hepatic cirrhosis before and after transplantation, two of them (28, 29) found a positive association between increases in aerobic capacity and chance of survival post transplantation. On the other hand, in another study (31) it was concluded that patients that who underwent hepatic transplantation presented greater exercise capacity after the surgery. Therefore, exercise capacity testing may be a valuable tool to improve allocation of patients in transplantation waiting lists (28). Additionally, cardiopulmonary rehabilitation programs focusing on exercise capacity improvements could be an important approach for these patients after surgery, improving mortality rates (31).

It is not possible to state that there is an actual relationship between increase in exercise capacity and chance of surviving during the post transplantation period. Recently, in a study (40) it was found that there is a positive association between muscle strength, exercise capacity measured by oxygen maximum consumption, and MELD score (Model for End-stage Liver Disease). This model is intended to predict mortality and chances of survival of patients on hepatic transplantation waiting lists (41). Moreover, individuals before liver transplantation have low scores on the quality of life questionnaire, especially regarding functional capacity, pain, health and vitality.

Muscle strength assessment in patients with hepatic cirrhosis

Four scientific articles (27, 35, 42, 43) investigated neuromuscular capacity during maximal strength tests on isokinetic dynamometers in subjects with hepatic cirrhosis. The description of these studies is presented on Table 1.

The study of Tarter et al. (42) was the first to measure concentric and eccentric strength of lower and upper limbs in alcoholic cirrhotics, nonalcoholic cirrhotics and healthy controls. The authors did not find significant differences between groups, however the two cirrhotic groups presented lower muscle strength scores when compared to healthy subjects. When a neuropsychological assessment was tested no association between cognitive factors and muscle strength was found. Patients with hepatic cirrhosis presented significant differences compared to the control group only for psychomotor factors.

Table 1 - Description of included studies

(To be continued)

Authors	Sample characterization	Variables tested	Results
Campillo et al. (21)	Alcoholic Cirrhosis Group (ACG): 10; Control Group (CG): 6	VO_{2max} and muscle mass. Child-Pugh classification. Physical exercise intervention in a treadmill during 32 minutes.	CG presented greater VO_{2max} and muscle mass. A negative correlation was found between VO_{2max} and Child-Pugh, ACG had a good tolerance to physical exercise.
Campillo et al. (22)	Cirrhosis Group: 24	VO_{2peak} and muscle mass. Child-Pugh classification. Aerobic training.	Predicted VO_{2max} value was greater than accurate value. A negative correlation was found between VO_{2max} and Child-Pugh. Increases in VO_{2max} and muscle mass were found in 2 subjects. Increase in Child-Pugh classification was found in other 2 subjects.
Delissio et al. (23)	Cirrhosis Group (CIG): 4; Control Group (CG): 4	VO_{2max}. Physical exercise intervention on a treadmill for 90 minutes at 50% of VO_{2max}.	No significant differences were found between groups.

Table 1 - Description of included studies

(Conclusion)

Authors	Sample characterization	Variables tested	Results
Tarter et al. (42)	Alcoholic Cirrhosis Group (ACG): 49; Nonalcoholic Cirrhosis Group (NCG): 45; Control Group (CG): 50	Concentric and eccentric muscle strength of lower and upper limbs. Psychomotor tests.	CG demonstrated greater muscle strength and psychomotor test results. No significant differences were found between ACG and NCG.
Andersen et al. (43)	Alcoholic Cirrhosis Group (ACG): 24; Control Group: 24	Knee, hip, elbow and wrist extensors and flexors muscle strength, shoulder adductors and abductors, muscle mass, triceps skinfold thickness, and mid-arm circumference. Child-Pugh classification.	ACG presented less muscle mass for all variables, except for wrist extension. No significant differences were found between Child-Pugh classifications. Anthropometric assessment represented nutritional state.
Epstein et al. (25)	Cirrhosis and Hepatopulmonary Sindrome Group (HPS): 5; Cirrhosis and Hypoxemia Group (CHG): 9; Cirrhosis Group (CG): 10	$VO_{2\ peak}$. Child-Pugh Classification.	CG presented greater VO_{2peak}. No significant differences were found between Child-Pugh classifications.
Epstein et al. (24)	Cirrhosis Group (CIG): 19; Control Group (CG): 12	VO_{2peak}. Child-Pugh Classification.	CG presented Greater VO_{2peak}. No significant differences were found between Child-Pugh classifications.
Wong et al.(26)	Cirrhosis Group (CIG): 18; Ascites Cirrhosis Group (ACG): 21; Control Group (CG): 12	VO_{2peak}. and VO_{2AT}.	GC presented greater VO_{2peak} and VO_{2AT}.
Wiesinger et al. (27)	Cirrhosis Group: 26; Child-Pugh Class A: 3, B: 7 and C: 9	VO_{2AT}, knee extensors and hand-grip muscle strength.	Groups B and C presented the lowest VO_{2AT}. Group C presented less muscle strength compared to A. There was a negative correlation between hand-grip strength and Child-Pugh.
Epstein et al. (28)	Transplantation Survival Group: 53; Nonsurvivals Group: 6	VO_{2peak} and VO_{2AT}. Child-Pugh and MELD Classifications.	Survivals had greater VO_{2peak} and VO_{2AT}.
Dharancy et al. (29)	Cirrhosis Group before Transplantation: 135	VO_{2peak}. MELD Classification.	Patients with low VO_{2peak} have less chances of surviving after transplantation. There was a negative correlation between VO_{2peak} and MELD.
Terziyski et al. (32)	Cirrhosis Group (CIG): 19; Control Group (CG): 19	VO_{2peak}. Child-Pugh Classification.	CG presented greater VO_{2peak}. There was a negative correlation between VO_{2peak} and Child-Pugh.
Lemyze et al. (31)	Pre- and Post- Cirrhosis Transplantation Group: 20	VO_{2peak}. MELD Classification.	There was an increase on VO_{2peak} after transplantation. There were no significant differences between MELD classifications.
Galant et al. (33)	Alcoholic Cirrhosis Group (ACG): 27	VO_{2max}. MELD.	There was a negative correlation between VO_{2max} and MELD.
Zenith et al. (34)	Cirrhosis Training Group (CTG): 9; Cirrhosis Control Group (CCG): 10	VO_{2peak}. Child-Pugh Classification. Aerobic Training.	CTG presented greater VO_{2peak}.
Debette-Gratien et al (35)	Cirrhosis post-transplantation group (CIG): 8	VO_{2peak} and knee extensors muscle strength. Child-Pugh Child-Pugh and MELD classifications. Aerobic training.	VO_{2peak} and muscle strength increases.

Andersen et al. (43) found lower strength results on knee, hips, and elbow flexion and extension, wrist flexion, and shoulder abduction and adduction strength when patients with hepatic cirrhosis were compared to healthy subjects. No differences were found for wrist extension strength between groups. Only on this study anthropometric characteristics were assessed, demonstrating nutritional and malnutrition state of subjects, which presented a positive correlation to muscle weakness. These findings are not in agreement to another study (12), in which no association was found between nutritional state and loss of skeletal muscle function of patients with hepatic cirrhosis. Contrary to this, Wiesinger et al. (27) assessed only muscle strength of knee extensors of the right and left limbs. This was also the first study to test hand-grip strength in patients with hepatic cirrhosis, who did not present any significant difference when dominant and non-dominant hands were compared. However, a negative correlation between this variable and Child-Pugh classification was found, demonstrating that subjects that were class C in this classification had lower values of muscle strength when compared to subjects class A.

Knee extensors muscle strength before and after an adapted physical activity program for patients with severe hepatic cirrhosis was recently assessed in patients awaiting for hepatic transplantation (35). After 12 weeks of personalized training, patients improved their strength significantly, which indicates that physical activity program can have a positive impact during the post transplantation period, decreasing time duration of hospitalization.

Final considerations

It appears evident that hepatic cirrhosis affects on cardiorespiratory and neuromuscular capacities during physical exercise in individuals who have this disease. Overall, both oxygen consumption and muscle strength are decreased in patients with cirrhosis when compared to healthy controls. Additionally, the studies searched here demonstrate that there is a negative relationship between exercise capacity and strength production, depending on the severity of hepatic cirrhosis. Therefore, the more advanced is the clinical state the more complications may give rise, decreasing performance on physical tests.

Due to the reduced number of studies that have investigated hepatic transplantation and physical training, as well as cardiorespiratory and neuromuscular capacity of patients with hepatic cirrhosis, more studies on this field are needed to determine the real influence of hepatic cirrhosis on these variables.

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Received: 05/09/2013
Recebido: 09/05/2013

Approved: 04/07/2015
Aprovado: 07/04/2015