REVIEW ARTICLE

Physical activity and chronic hepatitis C

Atividade física e hepatite C crônica

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ABSTRACT

Chronic hepatitis caused by hepatitis C virus (HCV) is relevant for the public health problem in the world. The infection associated with this virus is considered a significant cause of cirrhosis and its complications: portal hypertension, decompensation of the liver function and hepatocellular carcinoma. Physical activity is widely encouraged in the treatment of various chronic diseases. However, little has been done on the effect of physical activity on the evolutionary course of the HCV-related liver disease. It is known that individuals with chronic hepatitis C may develop other disorders due to physical inactivity that may interfere in the course of the viral disease. Therefore, the objective of the present study was to conduct a literature review on the relationship between physical activity and chronic hepatitis C.

Key words: *M*otor Activity; Hepatitis Viruses; Hepatitis C, Chronic; Liver Cirrhosis.

RESUMO

A hepatite crônica causada pelo vírus C (VHC) constitui problema relevante de saúde pública no mundo. A infecção associada a esse vírus é considerada causa significativa de cirrose e respectivas complicações: hipertensão portal, descompensação da função hepática e carcinoma hepatocelular. A atividade física é amplamente incentivada no tratamento de diversas doenças crônicas. Entretanto, pouco tem sido pesquisado sobre o efeito da atividade física no curso evolutivo da hepatopatia associada ao VHC. Ainda, sabe-se que indivíduos com hepatite C crônica podem desenvolver outras afecções devido à inatividade física que podem interferir no curso da doença viral. Portanto, o objetivo do presente estudo foi realizar revisão bibliográfica sobre a relação entre atividade física e hepatite C crônica.

Palavras-chave: *Atividade Física; Vírus da Hepatite; Hepatite C Crônica; Cirrose Hepática.*

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INTRODUCTION

Chronic hepatitis caused by the hepatitis C virus (HCV) is a worldwide relevant public health problem with an estimated number of 180 million carriers. In 2010, the Brazilian Ministry of Health released the National Viral Hepatitis Survey[1]: the prevalence of hepatitis C in Brazilian capitals was 1.38% and the frequency was relatively homogenous among regions, however, the northern region showed the highest prevalence.

The infection associated with this virus is considered a relevant cause of cirrhosis and its complications: liver cirrhosis, portal hypertension, and hepatocellular carcinoma. Lesions in hepatocytes can cause hypoglycemia, altered lipid metabolism, and interfere with the release of energy available for exercise.[2] In addition to the damage caused directly by HCVs, other diseases such as obesity[3], diabetes mellitus type 2

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(DM2),[4] and cardiovascular abnormalities[5] are factors that can influence the evolutionary course of chronic hepatitis C.

It is known that physical activity is important and should be recommended for the prevention, control, and treatment of chronic non-infectious diseases, especially those previously mentioned. On the other hand, the knowledge about the relationship between physical activity and chronic hepatitis caused by HCV is still scarce.

Physical activity can be defined as any body movement that significantly increases the expenditure of energy in relation to resting[6]. The term exercise means the systematic form.

Human evolution was influenced by physical activity.[6] It is observable in anthropometric characteristics that identify a close relationship with movement[7]. Therefore, the practice of physical activities is essential to the functioning of physiological systems and health maintenance.[6] Several studies have shown that physical activity exerts a protective effect against coronary heart disease, DM2, hypertension, obesity, depression, and some types of cancer.[8-10]

In view of the beneficial effects of movement in the human body and the impact of HCV infection in the world, the investigation on the influence of physical activity on the course of liver disease caused by HCV becomes relevant. Therefore, the objective of the present study was to conduct a literature review on the relationship between physical activity and chronic hepatitis C.

HEPATITIS C

The main form of HCV transmission is through contact with contaminated blood.[11] The acquisition of infection occurs predominantly by parenteral transmission, representing about 30.0 to 70.0% of the means of infection acquisition.[12]

The natural history of hepatitis C is variable and dependent on the degree of liver inflammation and fibrosis associated with HCV[13]. The natural course of hepatitis C is slow and progressive in most cases, and approximately 80.0% of those infected become chronic HCV carriers. Of these, approximately 20.0% develop advanced forms of liver disease after 10 to 20 years of infection: cirrhosis and its complications.[13] Several studies in patients with chronic hepatitis C have demonstrated a significant reduction of health-related quality of life (HRQOL) compared to healthy patients, regardless of the stage of liver disease.[14,15] The HCV infection primarily affects functions of social interaction, physical activity, and vitality.[16]

The treatment of chronic hepatitis C has been achieving relevant results over time. The combination of pegylated interferon (PegIFN) plus ribavirin (RBV) for 24 to 48 weeks is considered the conventional treatment of hepatitis C. The therapeutic response depends on the HCV genotype, viral load, and disease stage determined by liver biopsy. The rates of sustained virologic response (SVR) to treatment with the association of PegIFN alpha-2a or 2b and RBV revolve around 40.0% and 50.0% in patients infected with genotype 1, and 80.0% or more in those infected with HCV genotype 2 or 3. SVR is associated with long-term viral clearance or "virologic cure" that is associated with reduced morbidity and mortality rates.[17,18]

It is worth mentioning that at present, with the use of direct antiviral agents (DAAs), a significant increase in the chances of SVR in patients with genotype 1 is observed. These are HCV protease inhibitors: boceprevir and telaprevir. Although PegIFN and RBV continue to be the essential scheme for the treatment of hepatitis C, the emergence of these two DAAs, approved in the US, Europe, and Brazil in 2011, resulted in a substantial increase of 30.0% in the chances of SVR and the possibility of shortening treatment time in a significant portion of patients infected with genotype 1.[18-20] Telaprevir along with PegIFN and RBV comprise the threefold scheme, currently already prescribed for the treatment of patients with genotype 1.

PHYSICAL ACTIVITY AND CHRONIC HEPATITIS C

Chronic hepatitis is characterized by the persistence of liver disease with evidence of cellular inflammation and/or necrosis by more than six months. In this type of HCV-related liver disease, there is a shortage of studies that have evaluated the effects of physical activity and its various forms and intensities in the biochemical, physiological and psychosocial parameters in individuals infected with this virus.

It is known that alterations in liver function predispose to alterations in the metabolism of glucose, lipids, and proteins in addition to alterations in hormone homeostasis.[2,21] These abnormalities determine the reduction in metabolic capacity of muscles and en-

ergy release, resulting in decreased aerobic capacity. Still, alterations in the ability of homeostasis recovery after exercise are observed.[2,22]

Ritland et al.[23], submitted 22 patients (active chronic hepatitis, n = 17; portal vein shunt, n = 5) to a submaximal ergometric test with the purpose of analyzing the effects of physical activity in individuals with chronic active hepatitis. Low oxygen consumption (VO_2) was observed in most individuals as well as alterations in serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, creatine kinase (CPK), Gama glutamyl transferase, and pre-albumin, which are markers of hepatocyte lesions. It should be noted that ALT is almost exclusively found in these cells and considered a sensitive marker for identifying liver damage.[2] Based on that study, the authors concluded that the clinical condition was not influenced by the physical exercise. Thus, physical activity in moderate intensity and short duration was well tolerated by patients with chronic active hepatitis. However, the number of evaluated patients was reduced limiting the expansion of the study's results.

It is known that other factors may aggravate the course of liver diseases such as lifestyle and nutritional status. Among these factors, obesity is highlighted, which is recognized as an independent factor in the progression of hepatic fibrosis in various liver chronic diseases. Hickman et al.[24] in Australia, investigated the influence of body mass loss achieved through diet and physical exercise in 31 individuals [infected by HCV (n = 18); non-alcoholic fatty liver disease (n = 13)]. The following parameters were analyzed: liver biochemistry, serum levels of insulin, and HRQOL.

The nutritional analysis showed that all individuals included in the study were overweight. These patients underwent a lifestyle intervention during 15 months through the prescription of diet and physical exercise. Out of all individuals, 21 (68.0%) lost weight and managed to maintain control over body mass. The increase in serum ALT was correlated to the amount of lost body mass ($r = 0.35$, $p = 0.04$). Other alterations were also associated with body mass loss: increased serum insulin ($r = 0.46$, $p = 0.04$) and improvement in HRQOL. The increase in ALT should be evaluated with caution because it can be associated with lesions in hepatocytes.[2] The hypothesis that the body mass loss may have had an undesired effect on hepatocytes is considered, however, this effect could be related to the training load (not adequately explained in the article), which could be non-adjusted to the individuals with liver disease.

In contrast, Vandyck et al.[4] found no increases in serum ALT in patients with chronic liver disease submitted to physical activity. In a study conducted in Mexico, these authors evaluated 17 individuals infected with HCV, who were not in treatment. Anthropometric patterns, metabolic state, and immune response were investigated in these patients who were subjected to a walking protocol for six months. The findings showed that 70.0% of them were obese or overweight, and 77.0% had peripheral resistance to insulin. Alterations were observed in several evaluated parameters, particularly after the 6th month of the intervention. Reductions in plasma levels of ALT (106 ± 93 U/L vs. 59 ± 32 U/L, $p < 0.01$),ALT/AST ratio (1.04 vs. 0.70, $p < 0.01$), triglycerides (165 ± 86 mg/dL vs. 124 ± 49 mg/dL), and peripheral resistance to insulin (4.0 vs. 2.7) were observed. Yet, at the end of six months, 88.0% of individuals reported feeling better in their overall health conditions. Another relevant finding of this study was the reduction in viral load detected in four individuals (viral load was measured in only seven individuals).

A study conducted in Romania by Rusu et al.[25] evaluated the combined effect of dieting and physical activity (30 minutes of moderate activity – e.g. hiking, lightweight race, and cycling-three to seven times per week) during 12 months. They found benefits of low calorie and hypolipidemic diets associated with exercise on body mass and lipid and liver profile. In addition, reduction in insulin resistance and reduced prevalence and severity of steatosis and fibrosis were observed.

Corroborating some of these results, Patullo et al.[26] stressed that 24 weeks of physical activity intervention, based on steps per day (minimum of 10,000 steps), in obese patients with HCV was sufficient to reduce body mass index. Furthermore, after this intervention, 50% of the volunteers were no longer resistant to insulin. It is important to stress that in this study, patients with cirrhosis and non-cirrhotic patients performed the physical activity intervention.

These findings are similar to those found by Konishi et al.[27]. The authors recruited 15 individuals with chronic hepatitis C who were evaluated before and after six months of walking (at least 8,000 steps a day) with the aim of clarifying how much aerobic exercise reduces insulin resistance and body fat. Significant reductions of some parameters were identified after the intervention, that is, with the adoption of aerobic

physical activity: fat, body mass index, plasma levels of ALT and leptin, and insulin resistance.

It is likely that the benefits of physical exercise occur even when the frequency of training (days a week) is low as shown by McKenna et al.[28]. The results indicated the feasibility of the exercising in 12 sessions during six weeks during treatment of hepatitis C. The protocol consisted of stretching, strength, and aerobic endurance exercises (70.0% to 85.0% of maximum heart rate). Patients who performed the exercise protocol improved aerobic capacity, manual grip strength, and HRQOL.

In addition to biochemical markers and data that evaluate the immune response and HRQOL, knowledge about the amount of physical activity performed by patients with chronic viral hepatitis become necessary. White et al.[29], aiming to evaluate the association between physical activity, diet, and advanced HCV-related liver disease, led a study with 91 war veterans with chronic hepatitis C. The individuals completed the Block Food Frequency Questionnaire (BFF) and International Physical Activity Questionnaire (IPAQ) and were divided into groups according to the degree of hepatic involvement: fibrosis (advanced = F3-F4 vs. moderate = F1-F2), inflammation (acute = A2-A3 vs. moderate = A1), and steatosis (pronounced vs. moderate).

The dietary intake and physical activity of veterans with advanced liver disease were compared to those in veterans with the incipient liver disease. The MET-minute by weekly walk (energy expenditure inferred from IPAQ) was negatively associated with the degree of liver steatosis, that is, physical activity was identified with greater frequency in individuals with light steatosis than in those with severe steatosis. Based on these findings, it appears that lifestyle, especially eating habits and physical activity, are determined by the stage of the disease.

Although the study of White et al.[29] have defined the stages of liver disease, studies about the relationship between physical activity and chronic hepatitis C have, in general, the limitation of not clearly describing the stage of liver disease, therefore, not controlling this variable for participation in the research.

PHYSICAL ACTIVITY, CHRONIC HEPATITIS C, AND DRUG TREATMENT

It turns out that physical exercise is recommended for the treatment of various chronic diseases such as diabetes[30], multiple sclerosis[31], and after myocardial infarction[32]. Based on these findings and considerations on chronic hepatitis C, the possibility that individuals who are in treatment for chronic viral hepatitis could continue or start the practice of physical activities is suggested.

It is possible that the treatment with interferon-alpha (IFN-α) can limit exercise tolerance due to lesions on the endothelial function. It is known that the endothelial function can be partially involved in exercise-induced hyperemia in humans.[33] Takase et al.[33] recruited ten individuals who received subcutaneous injections of IFN-α, seven days a week, for four weeks. This drug interferes with the endothelium-dependent vasodilation, and this event was correlated to exercise maximum tolerance in patients with HCV ($r = 0.86$, $p < 0.001$). These results are relevant to the understanding of the body's physiological adjustments during exercise simultaneous to drug treatment.

In a study conducted in France, Payen et al.[34] assessed the influence of a program of physical activity (conducted five days a week) on the HRQOL of 11 individuals infected with HCV who were in treatment with IFN-α and ribavirin for a period of 12 weeks. Maximum oxygen consumption (VO_{2MaX}), ventilatory threshold, and heart rate were measured. The SF-36 questionnaire for the assessment of HRQOL was also applied. The weekly exercise program was divided into four categories: individual physical activity (walking, running, swimming) 1:30 h; team physical activity (frisbee, racquet sports, badminton, volleyball) 1:30 h; recreational activity (dancing, archery) 1:30, and lectures. The authors observed an increasing trend in HRQOL scores one month after the start of the program.

On the other hand, physiological adaptations and biochemical responses during and after the exercise program were not analyzed. It was concluded that physical activity should be indicated and performed on a regular basis; however, studies with more consistent data are needed.

Other findings that are favorable to the practice of physical activity by HCV-infected patients in treatment can be observed in the study of Zucker[35]. This investigation included patients with chronic hepatitis C, and in treatment, to assess their perception of fatigue undergoing an exercise protocol. At the end of the intervention, the perception of fatigue by these individuals was reduced. This finding corroborates the study of Arias-Vásquez and Lucatero-Lecona[21] in which 18 patients with chronic hepatitis C in treatment with PegIFN and RBV were distributed in two groups: experimental and control.

The experimental group performed an exercise protocol for eight weeks (five times a week), which consisted of 10 min of flexibility exercises and 30 min of aerobic exercise at 50.0% of the maximum working load. Physical capacity and HRQOL improvement and decreased fatigue in individuals undergoing this exercise protocol were recorded. It is likely that aerobic exercise can promote hormone regulation and therefore, decrease fatigue.[36]

Although these studies show favorable results to the practice of physical activity by individuals subjected to antiviral treatment, prospective studies are needed to assess the physiological and biochemical effects of exercise on patients with liver disease, especially in patients with chronic hepatitis C and in treatment.

CONCLUSIONS

It was concluded that physical activity with restrictions is well tolerated by patients with chronic hepatitis C and associated with the reduction of circulating liver enzymes, body fat, and insulin resistance. Physical activity appears to be well tolerated, even by patients with cirrhosis. Conversely, if the training load (intensity, volume, frequency, and density) is not adequate, negative effects may occur. In addition, factors such as HRQOL and fatigue can be improved with the practice of physical exercises.

It must be still considered that the degree of liver disease may influence physical activity habits and vice versa. However, studies are still scarce and further research to investigate the physiological and psychosocial effects of physical activity (acute and chronic) in the course of chronic hepatitis C, are necessary.

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