Advanced Research in Gastroenterology & Hepatology
ISSN: 2472-6400

Juniper Publishers
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Research Article
Volume 2 Issue 3 – January 2017
DOI: 10.19080/ARGH.2017.02.555587

Adv Res Gastroentero Hepatol

Impact of Aerobic Exercises on Fatigue Related to Systemic Inflammation in Patients with Hepatitis C Virus

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Submission: December 16, 2016; **Published:** January 03, 2017

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Abstract

Background: Chronic hepatitis C virus (HCV) infection is a major health problem with around 170 million people infected worldwide. Fatigue is one of the most frequent clinical symptoms in patients with chronic hepatitis C infection contributing significantly to the reduction of health-related quality of life and association between fatigue and elevation of inflammatory markers have been documented. At present, there is no widely accepted treatment for fatigue in HCV patients. The beneficial effects of aerobic exercise have been a matter of controversy in the field of hepatitis C virus patient's management.

Objective: As the available previous studies involving the impact of exercise training upon the fatigue related to systemic inflammation in HCV is limited in number; this study aims to measure the impact of aerobic exercise training on the fatigue related to systemic inflammation of HCV in Jeddah area.

Methods: non-hypertensive, non-cirrhotic Saudi patients with chronic HCV infection, their age ranged from 25- 40 years and was assigned to two subgroups; group (A) received aerobic exercise training for 12 weeks, however group (B) received no training intervention for 3 months. Measurements of fatigue symptoms and markers of systemic inflammation were assessed before and at the end of the study for all participants of both groups.

Results: The mean values of inflammatory markers interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNF-α) and multidimensional fatigue inventory (MFI) was significantly decreased in group (A), while changes were not significant in group (B). Also, there were significant differences between mean levels of the investigated parameters in group (A) and group (B) after treatment.

Conclusion: Treadmill walking exercise training is an effective treatment policy to improve ameliorates symptoms of fatigue related to inflammatory cytokines in patients with chronic HCV infection.

Keywords: Aerobic exercise; Inflammatory cytokines; Chronic hepatitis C; Fatigue syndrome.

Introduction

Chronic hepatitis C (CHC) is an important cause of chronic liver disease with substantial impact on mortality, morbidity, and resource utilization [1-3]. Hepatitis C virus (HCV) infected patients are known to be at risk of developing liver complications i.e. cirrhosis and liver cancer [3]. At the individual level, CHC is associated with fatigue leading to impairment in health-related quality of life, which can negatively impact not only patients' well-being but also their activity and work productivity [4,5].

Hepatitis C is an important cause of chronic liver disease worldwide with an estimated 170 million people infected [6,7]. Hepatitis C virus (HCV)-infected patients are physically and mentally impacted by fatigue. Fatigue is among the leading patient-reported symptoms in chronic HCV infection [8,9]. During interferon therapy, fatigue is the most common side effect and can lead to early termination of therapy and treatment failure [10].

Fatigue is a complex symptom that encompasses a range of complaints including malaise, exhaustion, lethargy, and loss of motivation and social interest. Chronic fatigue is common in the general population, affecting up to 20%. [11,12]. Fatigue is the most frequent symptom of liver disease and has a major effect on quality of life and daily activity in patients chronically infected with HCV [13,14].

Fatigue is one of the most common conditions associated with CHC infection, with up to 97% of patients reporting fatigue at one time or another during the course of their disease [15]. Fatigue related to CHC has been reported to adversely impact functional capacity and work performance and to result in an inability to work [16]. In patients undergoing antiviral therapy, fatigue is frequently reported to increase over the course of treatment and has led to premature discontinuation of therapy. Therefore, fatigue is a significant CHC-related morbidity that can result in disability and poor treatment outcome [17].

An expanding literature demonstrates that elevations of pro-inflammatory cytokines and chemokines are evidenced in patients diagnosed with a range of chronic psychiatric disorders including chronic fatigue syndrome [18]. However, during interferon (IFN), patients with HCV evidence significantly increased psychiatric symptoms, including symptoms of depression, anxiety, fatigue and pain. These psychiatric symptoms are generally short-term and remit following IFN termination, with increased benefit if viral clearance is achieved. However, IFN is not associated with significant declines in objective cognitive performance during or following IFN [19].

Systemic inflammatory diseases are commonly accompanied with alterations in behavior which result from changes in central neurotransmission. These changes in behavior, which include fatigue, increased anxiety, loss of appetite, sleep disturbances and loss of social interest, are collectively termed sickness behaviors. During acute systemic infections, sickness behaviors can serve an adaptive purpose. However, during chronic inflammation increased prevalence of sickness behaviors can greatly affect patient quality of life [20].

Patients living with CHC often experience many significant comorbidities. Depression and fatigue, in particular, have been shown to be as much as 3-4 times more prevalent in CHC patients compared to the general population [21]. However, higher levels of inflammatory markers, such as interleukin-1 and tumor necrosis factor [22] and lower levels of serum leptin have all been suggested as additional causes of depression and fatigue in HCV-infected patients [23]. Associations between fatigue and inflammatory markers have been documented in various medical conditions, including cancer, viral infections, chronic inflammation, autoimmunity, neurological diseases, and mood disorders [24-26]. Fatigue develops in a large proportion of patients with cancer who are receiving chemotherapy and/or radiation therapy. Fatigued patients with cancer have elevated circulating levels of biomarkers of inflammation, although this association is more consistently observed in longitudinal than in cross-sectional studies [27].

Serum leptin levels were found to be correlated to the severity of fatigue as assessed by multidimensional assessment of fatigue scale. Leptin dependent mechanism for fatigue was supported by several authors [28,29]. In patients with liver disease, a positive correlation between fatigue and circulating leptin level was found. It is suggested that leptin might play a role in the mediation of fatigue in patients with chronic hepatitis C infection [30]. Thus, our study was an attempt to assess the effects of aerobic exercise upon fatigue symptoms associated with markers of systemic inflammation in patients with chronic HCV infection.

Patients and Methods

Subjects

Eighty non-hypertensive, non-cirrhotic Saudi patients with chronic HCV infection, their age ranged from 25 to 40 years, will be studied on referral to Gastroenterology and Hepatology Department, King Abdulaziz University Teaching Hospital, Saudi Arabia. All these patients were anti HCV positive by enzyme-linked immunosorbent assay (ELISA). None of the patients included in this study had other potential causes of liver disease, such as alcoholism or autoimmune phenomena. Only patients diagnosed with chronic HCV mono-infection and had anti HCV antibodies by ELISA were selected to undergo Real-Time polymerase chain reaction (RT-PCR) and were treated with combined pegylatedinterferon-alfa (PEG-IFNα)-ribavirin therapy. Exclusion criteria included major depressive disorder, endocrine disorders, smokers, chronic inflammatory medical conditions, patients managed with psychiatric medications. Participants were included two groups; group (A) received treadmill aerobic exercise training on treadmill. However, group (B) received no exercise training. All participants signed the informed consent.

Measurements

Real-Time polymerase chain reaction (RT-PCR): Ten milliliter blood samples will be collected from each participant at study entry. The blood samples will be obtained using disposable needles and heparinized vacuum syringes and will be stored at –70°C until assayed. Serum samples of all participants will be tested for Real-Time polymerase chain reaction (RT-PCR) to detect serum HCV RNA levels by polymerase chain reaction using the COBAS TaqMan HCV test, v2.0 (Roche Diagnostics, Indianapolis, NJ, USA).

Anti-inflammatory cytokines assessment: Venous blood samples were drained from the antecubital vein after a 12-h fasting, the blood samples were centrifuged at + 4 °C (1000 = g for 10 min). Interleukin-6 (IL-6) level was analyzed by "Immulite 2000" immunassay analyzer (Siemens Healthcare Diagnostics, Deerfield, USA). However, TNF-α (tumor necrosis factor-alpha) and interleukin-8 (IL-8) levels were assessed by ELISA kits (ELX

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50) in addition to ELISA microplate reader (ELX 808; BioTek Instruments, USA). All analyses were done by Hitachi 7170 Autoanalyser (Tokyo, Japan) and kits (Randox).

Fatigue Assessment: Fatigue was measured by completion of the Multidimensional Fatigue Inventory (MFI). The MFI was used to capture five distinct dimensions of fatigue experienced "lately", including: general fatigue, physical fatigue, mental fatigue, and perceptions of reduced motivation and reduced activity. In each of the five subscales, scores range from 4 to 20, with higher scores indicating greater fatigue. In order to minimize confounding factors imposed by diurnal variation, this questionnaire was completed on the morning of the blood draw. Internal consistency for the MFI subscales was good (a = 0.82), suggesting the five domains adequately reflect a single construct [31].

All measurements of TNF-α, Il-6, IL-8 and MFI were done at the beginning of the study and will be repeated after 3 months.

Procedures

Following the previous evaluation, all patients were divided randomly into the following groups:

i. Group A

participated in a treadmill aerobic exercise which was conducted according to recommendation of aerobic exercise application approved by the American College of Sports Medicine [32]. Training program included 5 minutes for warming –up in the form of range motion and stretching exercises, 10-30 minutes of aerobic exercise training (60-70% of maximum heart rate) and 10 minutes of cooling down (on treadmill with low speed and without inclination). Participants had 3 sessions /week for 3 months with close supervision of physical therapist.

ii. Group B

received no exercise training.

Statistical analysis

The mean values of the investigated parameters obtained before and after three months in both groups were compared using paired "t" test. Independent "t" test was used for the comparison between the two groups (P<0.05).

Results

Table 1: Baseline and anthropometric data between HCV patients in both groups.

	Group (A)	Group (B)
Age (year)	32.42 ± 7.61	31.92 ± 6.48
Height (cm)	165.13 ± 4.12	164.73 ± 4.95
Body weight (kg)	64.26 ± 3.88	63.75 ± 3.62
BMI (kg/m2)	22.43 ± 2.97	21.69 ± 2.56
Waist circumference (cm)	75.12 ± 4.25	74.18 ± 4.32
Fat mass (kg)	14.85 ± 2.87	13.94 ± 2.66
ALT (U/L)	35.49 ± 5.93	34.12 ± 6.11
Albumin (gm/dl)	3.71 ± 0.85	3.64 ± 0.73
FBG (mg/dl)	113.47 ± 11.25	111.36 ± 10.17
Hb (gm/dl)	12.32 ± 1.71	12.15 ± 1.46
Total Bilirubin (mg/dl)	1.38 ± 0.74	1.27 ± 0.81
SBP (mm Hg)	124.56 ± 11.22	122.18 ± 10.87
DBP (mm Hg)	79.41 ± 7.35	76.92 ± 6.58
HCV viral load (IU/mL)	1.85 ± 3.51 × 106	1.71 ± 3.48 × 106

The baseline and anthropometric characteristics of the subjects are shown in Table 1. There was no significant differences in the mean value of the age, height, body weight, body mass index (BMI), waist circumference, fat mass, alanine aminotransferase (ALT), albumin, fasting blood glucose (FBG), hemoglobin (HB), total bilirubin, systolic blood pressure (SBP), diastolic blood pressure (DBP) and HCV viral load between both groups.

BMI: Body Mass Index; Hb: Hemoglobin; FBG: Fasting Blood Glucose; ALT: Alanine aminotransferase; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; (*) indicates a significant difference between the two groups, P < 0.05.

Table 2: Mean value and significance of TNF- α, IL-6, IL-8, MFI total score and fatigue symptom dimensions in group (A) before and after treatment. TNF-α: tumor necrosis factor – alpha; IL-6:Interleukin-6; IL-8: Interleukin-8; MFI: Multidimensional Fatigue Inventory; (*) indicates a significant difference between the two groups, P < 0.05.

	Mean + SD		t- value	Significance
	Pre	Post		
TNF-α (pg/mL)	5.92 ± 1.51*	4.26 ± 1.32	5.73	P <0.05
IL-6 (pg/mL)	6.71 ± 2.11*	5.21 ± 1.63	6.32	P <0.05
IL-8 (pg/mL)	14.25 ± 3.27*	12.13 ± 2.88	6.49	P <0.05
MFI total score	53.16 ±10.42*	40.85 ± 9.17	7.13	P <0.05
Fatigue Symptom Dimensions				
General fatigue	12.18 ± 3.21*	9.76 ± 2.82	6.17	P <0.05
Physical fatigue	11.74 ± 2.76*	8.45 ± 2.61	5.83	P <0.05
Reduced activity	10.85 ± 2.53*	8.12± 2.32	6.11	P <0.05
Mental fatigue	8.92 ± 2.81*	7.26 ± 2.55	5.94	P <0.05
Reduced motivation	8.78 ± 2.42*	7.15 ± 2.18	6.15	P <0.05

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There was a 28.04 %, 22.35 %, 14.88% and 23.16 % reduction in mean values of TNF- α, IL-6, IL-8 and MFI total score respectively in the training group (Table 2). While, there was a 5.67% , 2.42 %, 1.49 % and 2.38 % increase in mean values of TNF-α, IL-6, IL-8 and MFI total score respectively in the control group. The mean values of TNF- α, IL-6, IL-8 and MFI total score were decreased significantly in the training group; however the results of the control group were not significant (Table 3). Also, there were significant differences between both groups at the end of the study (Table 4).

Table 3: Mean value and significance of TNF- α, IL-6, IL-8, MFI total score and fatigue symptom dimensions in group (B) before and at the end of the study. TNF-α: tumor necrosis factor – alpha; IL-6:Interleukin-6; IL-8: Interleukin-8; MFI: Multidimensional Fatigue Inventory.

	Mean + SD		t- value	Significance
	Pre	Post		
TNF-α (pg/mL)	5.83 ± 1.37	6.16 ± 1.41	0.91	P >0.05
IL-6 (pg/mL)	6.62 ± 2.13	6.78 ± 2.26	0.78	P >0.05
IL-8 (pg/mL)	14.10 ± 3.12	14.31 ± 3.24	0.62	P >0.05
MFI total score	52.85 ± 9.73	54.11 ± 9.86	1.14	P >0.05
Fatigue Symptom Dimensions				
General fatigue	12.74 ± 3.32	13.14 ± 3.43	0.86	P >0.05
Physical fatigue	12.17 ± 2.82	12.26 ± 2.97	0.81	P >0.05
Reduced activity	11.13 ± 2.41	11.35 ± 2.61	0.63	P >0.05
Mental fatigue	9.16 ± 2.95	9.23 ± 3.12	0.82	P >0.05
Reduced motivation	8.91 ± 2.58	9.16 ± 2.71	0.79	P >0.05

Table 4: Mean value and significance of TNF- α, IL-6, IL-8, MFI total score and fatigue symptom dimensions in group (A) and group (B) at the end of the study. TNF- α: tumor necrosis factor – alpha; IL-6: Interleukin-6; BMI: Body Mass Index; IL-8: Interleukin-8; MFI: Multidimensional Fatigue Inventory; (*) indicates a significant difference between the two groups, P < 0.05.

	Mean + SD		t- value	Significance
	Group (A)	Group (B)		
TNF-α (pg/mL)	4.26 ± 1.32*	6.16 ± 1.41	5.61	P <0.05
IL-6 (pg/mL)	5.21 ± 1.63*	6.78 ± 2.26	6.28	P <0.05
IL-8 (pg/mL)	12.13 ± 2.88*	14.31 ± 3.24	6.57	P <0.05
MFI total score	40.85 ± 9.17*	54.11 ± 9.86	7.18	P <0.05
Fatigue Symptom Dimensions				
General fatigue	9.76 ± 2.82*	13.14 ± 3.43	6.32	P <0.05
Physical fatigue	8.45 ± 2.61*	12.26 ± 2.97	5.92	P <0.05
Reduced activity	8.12± 2.32*	11.35 ± 2.61	6.27	P <0.05
Mental fatigue	7.26 ± 2.55*	9.23 ± 3.12	5.81	P <0.05
Reduced motivation	7.15 ± 2.18*	9.16 ± 2.71	6.25	P <0.05

Discussion

Hepatitis C virus (HCV) causes chronic, insidious liver infection in 2.2% of adults around the world [33], and approximately 10-15% of these cases progress to advanced liver disease resulting in decompensated liver cirrhosis, hepatocellular carcinoma, liver transplantation, or death [34]. Until recently, standard of care for HCV was combination therapy including both PEGylated interferon-alpha and ribavirin [35]. However, during IFN, patients with HCV evidence significantly increased psychiatric symptoms, including symptoms of depression, anxiety, fatigue and pain [36]. Fatigue is among the leading patient-reported symptoms in chronic HCV infection [37]. To our knowledge, this is the first study addressing fatigue symptoms associated with markers of systemic inflammation parameters of patients with chronic HCV infection after 12 weeks of concurrent training. We observed reduction of markers of systemic inflammation and fatigue symptoms.

Regarding inflammatory cytokines, the results of our study agreed with several previous studies suggesting 12-weeks aerobic exercise training program promotes the modulation of systemic inflammation as Zenith et al. [38-41] conducted a controlled prospective pilot trial of supervised exercise was performed on a cycle ergometer 3 days/week for 8 weeks at 60%–80% of baseline peak VO2 for patients with cirrhosis. At week 8, peak VO2 was 5.3mL/kg/min higher in the exercise group compared with controls (P=0.001) and fatigue subscores of the Chronic Liver Disease Questionnaires were lower in the exercise group compared with controls (P=0.01). However, Rosety-Rodriguez et al. [38] conducted a 12-week arm cranking exercise program for spinal cord injury patients at a moderate work intensity of 50% to 65% of heart rate reserve for of 3 sessions per week. Their results proved that arm cranking exercise improved low-grade systemic inflammation by decreasing plasma levels of inflammatory cytokines.While, Trøseid et al. [39] Stated that 12 weeks exercise training program reduces plasma levels of chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8) in subjects with the metabolic syndrome.In addition, Valentine et al. [40] Study represented an examination of the relations among adiposity, physical activity, and systemic inflammation on fatigue, controlling for the well-established psychosocial influences on fatigue (sleep quality, depression, and perceived stress) in One

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hundred eighty-two community-dwelling older adults. Results suggest that increasing the physical activity levels of older adults may have important implications for reducing their levels of fatigue and markers of systemic inflammation [serum C-reactive protein (CRP) and interleukin-6 (IL-6)] even in the presence of obesity [41].

Regarding fatigue symptoms, the results of our study agree with several previous studies suggesting 12-weeks aerobic exercise training program promotes the modulation of fatigue symptoms as Learmonth et al. [42-49] conducted a pilot study to determine whether a 15-minute bout of moderate-intensity aerobic cycling exercise would affect symptoms (pain and fatigue) and function (Timed 25-Foot Walk test and Timed Up and Go test) in people with multiple sclerosis (MS) or chronic fatigue syn¬drome (CFS), their results suggest that people with MS or CFS may undertake 15 minutes of cycling as moderate aerobic exercise with no expected negative impact on pain, fatigue or function. In addition, Sangelaji et al. [42] conducted a randomized controlled clinical trial on 59 multiple sclerosis patients who received 10 weeks of combination therapy including aerobic, strengthening, balancing and stretching exercises. Exercise has significant effect on improving balance, fatigue and quality of life in multiple sclerosis patients. While, Maniam et al. [43] Conducted an exercise program for hemodialysis patients, three times a week for 12 weeks and concluded that low-to-moderate-intensity exercise is effective for improving fatigue, sleep disorders and the overall quality of life among hemodialysis patients [44]. However, Smith et al. [45] conducted a study on Sixty subjects completed a 12-week supervised exercise program conclude that supervised aerobic exercise training safely decreases fatigue, weight, BMI, subcutaneous fat and abdominal girth (central fat) in HIV-1- infected individuals. Also, Yang et al. [46] proved that a mild- to moderate-intensity aerobic exercise program for six weeks reduces the fatigue of Taiwanese women with breast cancer undergoing radiotherapy. Moreover, Durcan et al. [47] conducted a 12-week exercise training program on forty rheumatoid arthritis patients. They concluded that exercise program resulted in significant improvement in sleep quality and fatigue. Finally, Taso et al. [48] proved that an eight week yoga exercise program developed in this study effectively reduced fatigue in 60 patients with breast cancer but did not reduce depression or anxiety. The physiological mechanisms underlying these effects were not elucidated; however, both cancer and chronic hepatitis C virus infection are associated with higher levels of inflammatory cytokines and exercise may have anti-inflammatory properties [28,41,49,50].

Conclusion

The current study provides evidence that treadmill walking exercise training is an effective treatment policy to improve ameliorates symptoms of fatigue related to inflammatory cytokines in patients with chronic HCV infection.

Acknowledgment

This project was funded by the Deanship of Scientific Research (DSR), King Abdulaziz University, Jeddah, under grant no. (40-142-1437-G) The authors, therefore, acknowledge with thanks DSR technical and financial support.

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How to cite this article: Shehab M A E, Osama H A. Impact of Aerobic Exercises on Fatigue Related to Systemic Inflammation in Patients with Hepatitis C Virus. Adv Res Gastroentero Hepatol 2017; 2(3): 555587. DOI: 10.19080/ARGH.2017.02.555587

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