Aerobic Exercises Improve Quality of Life, Psychological Wellbeing and Systemic Inflammation in Hepatitis C virus Patients

Shehab M. Abd El-Kader[1] and Mohammed H. Saiem Al-Dahr[2]

[1]Department of Physical Therapy, Faculty of Applied Medical Sciences, King Abdulaziz University.
[2]Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia.

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Globally, hepatitis C virus (HCV) adversely affects patients' function and their independent live. However, aerobic exercise may have disease modifying effects. Objective: The aim of this study was to detect the changes in quality of life, depression, mode and systemic inflammation in hepatitis C virus patients after aerobic exercises. Material and Methods: Eighty HCV patients (mean age 43.87 ± 4.65 year) participated in the study and were enrolled into two groups. Group (A) received aerobic exercise on treadmill where, group (B) received no intervention. Values of Rosenberg Self-Esteem Scale (RSES), Beck Depression Inventory (BDI), Profile of Mood States (POMS), tumor necrosis factor - alpha (TNF- α), Interleukin-6 (IL-6), C-reactive protein (CRP), and SF-36 HRQL were taken before and after the study. Results: There was a significant decrease in mean values of TNF- α, IL-6, CRP, BDI & POMS and increase in the mean values of SF-36 subscale scores, RSES in group (A) at the end of the study, but the changes in group (B) were not significant. Also, there were a significant differences between mean levels of the investigated parameters in group (A) and group (B) at the end of the study. Conclusion: Treadmill walking exercise training is an effective treatment policy to improve quality of life, systemic inflammation and psychological wellbeing in HCV patients.

Key words: Aerobic Exercise; Quality of Life; Psychological Wellbeing; Systemic Inflammation Hepatitis C virus.

Globally about many million population are affect with hepatitis C virus (HCV)[1, 2], which is the main cause for hepatic failure and cancer with their adverse psychiatric complications and poor quality of life in HCV patient[3]. Many psychiatric symptoms as depression affect about 21-59% of HCV patients[4], however the most commonly used anti-viral medications of HCV induced depression in about 17-44% of patients[5,6]. Moreover, this secondary depression adversely affects HCV patient's quality of life[7], and the effects of their antiviral medications[8].

Aerobic exercise training was proved to be effective and cost-efficient alternative treatment of anxiety and mood disorders[9]. Also, exercise training slow down the progression of cognitive decline[10, 11], improves performance on tests of cognition and psychological wellbeing[12], and enhance sleep quality[13]. However, the available previous studies involving the impact of exercise training upon the quality of life, psychological wellbeing along with systemic inflammation in HCV is limited in number[14].

Exercise is hypothesized to improve cognition, physical performance, functional ability and quality of life, but evidence is scarce, therefore, the aim of this study was to measure quality of life, systemic inflammation and psychological wellbeing response to aerobic exercises in hepatitis C virus patients.

* To whom all correspondence should be addressed.
Tel.: +966-569849276;
E-mail: salmuzain@kau.edu.sa

MATERIALS AND METHODS

Subjects

Eighty HCV patients were enrolled in the present study; their age ranged from 38-49 year and were selected from the Internal Medicine Department at King Abdul Aziz University Hospital and other Hospitals at Jeddah area. Exclusion criteria included smokers, subjects with pulmonary, cardiac, renal, metabolic and neurological diseases. Participants were enrolled in two groups; group (A) received treadmill aerobic exercise training. However, group (B) received no exercise training for three months. All participants signed an informed consent.

Measurements

Laboratory Analysis

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) levels were analyzed by "Immulite 2000" immunassay analyzer (Siemens Healthcare Diagnostics, Deerfield, USA). However, tumor necrosis factor- alpha (TNF-α) and C-reactive protein (CRP) levels were measured by using ELISA kits (R&D Systems, USA) in addition to ELISA microplate reader (ELX 808; BioTek Instruments, USA). All other parameters were perfomed using Hitachi (Elecsys 2010, Roche Company, Germany). For viral over load quantitation AmpliPrep/COBAS TaqMan (Roche Company, Germany).

Psychological well-being

Assessment of psychological wellbeing included measurement of self-esteem and depression. Self-esteem was evaluated using the Rosenberg Self-Esteem Scale (RSES), which included ten items to be answered on a four point Likert scale. Mood disturbance was measured by Profile of Mood States (POMS), it assessed the transient emotional state by 65 items on a 5-point Likert scale. This questionnaire evaluated 6 dimensions of mood in order to detect a Total Mood Disturbance score. However, depression was measured using the Beck Depression Inventory (BDI), a twenty-one item was covered to detect the total score for measuring the symptoms of depression[15].

Health-related quality of life (SF-36 HRQL)

Health-related quality of life was assessed by SF-36 which includes eight subscales: Vitality, Bodily Pain, General Health, Physical Functioning, Social Functioning, Physical Role Functioning, Emotional Role Functioning, and Mental Health. The SF-36 is a questionnaire for detecting the amount of change in their general health over the past year [16].

Measurements of TNF-α, IL-6, CRP, RSES, BDI, POMS and SF-36 HRQL were done before the study (pre-test) and after the study (post-test).

Procedures

The training group (Group A)

Patients were submitted to the aerobic exercise training to complete a 12-week on a treadmill (Enraf Nonium, Model display panel Standard, NR 1475.801, Holland). Each session of physical exercise was divided in: 5 min of warm up, with stretching exercises and circling of members and body; 30 min of aerobic exercise divided into row ergometer (15 min) and bicycle ergometer (15 min).; and 5 min of cold down at the end, with stretching, flexibility and relaxation exercises, consisting of five sessions per week. The training program was performed at 70% of the individual age-predicted HR_{max} according to Tanaka *et al.*[17].

The control group (Group B)

Patients maintained their ordinary life style and received no exercise training.

Statistical analysis

All results are shown as means ± SD. The mean values of the investigated parameters obtained before and after training program 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

The two groups were considered homogeneous regarding the baseline characteristics (Table 1). There was a significant decrease in mean values of TNF-α, IL-6, CRP, Beck Depression Inventory (BDI) and Profile of Mood States (POMS) and increase in the mean values of SF-36 subscale scores, Rosenberg Self-Esteem Scale (RSES) in group (A) after treatments (Table 2), but the changes in group (B) were not significant (Table 3). Also, there were significant differences between mean levels of the investigated parameters in group (A) and group (B) at the end of the study (Table 4).

DISCUSSION

The results of the present study indicated that there was a significant decrease in mean values of Beck Depression Inventory (BDI) and Profile of Mood States (POMS) in response to aerobic exercise training in HVC patients. There is a growing body of evidence indicates that aerobic exercise is an effective and cost-efficient treatment alternative for a variety of anxiety and mood disorders, including panic disorder[18]. *Craft* found that a depressed group who undertook aerobic exercise for nine weeks had significantly higher coping efficacy than a non-exercise control[19]. In a sample

Table 1. This table illustrates the baseline characteristics for all the participants who volunteer to be involved in this study including age, BMI, renal liver and viral load for both groups

Characteristic	Group (A)	Group (B)	P-value
Age (year)	44.65 ± 5.12	43.93 ± 4.94	0.641
BMI (kg/m^2)	24.14 ± 3.97	23.78 ± 3.85	0.583
Body weight (kg)	69.21 ± 4.56	67.92 ± 5.17	0.164
Height (cm)	164.27 ± 5.18	163.84 ± 4.66	0.472
SBP (mm Hg)	125.58 ± 14.16	122.67 ± 12.88	0.074
DBP (mm Hg)	85.12 ± 8.36	83.94 ± 8.31	0.183
FPG (mg/dL)	114.22 ± 10.61	113.72 ± 10.25	0.711
Albumin (gm/dl)	3.47± 0.79	3.38± 0.68	0.186
ALT (U/L)	63.58 ± 6.84	61.14 ± 6.52	0.098
Hb (gm/dl)	12.23± 2.36	12.15± 2.18	0.826
HCV viral load (IU/mL)	7.47 ± 3.21 × 10^6	7.16 ± 3.11 × 10^6	0.168

BMI : Body Mass Index; Hb : Hemoglobin; FPG: Fasting Blood Glucose; ALT : Alanine aminotransferase ; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Table 2. This table shows the mean value and significance of SF-36 subscale scores, RSES, BDI, POMS, in only group (A) who were submitted to the aerobic exercise training for a complete 12-week on a treadmill before and at the end of the study

SF-36 subscale variables	Mean ±SD		P-value
	Before	After	
SF-36: Health transition	2.76 ± 0.73	1.84 ± 0.65	0.016*
SF-36: Physical functioning	75.52 8.76	82.91 8.41	0.007*
SF-36: Role functioning: Physical	79.42 10.15	85.23 10.83	0.008*
SF-36: Bodily pain	74.54 8.17	70.26 8.10	0.004*
SF-36: General health	72.12 11.23	77.88 10.65	0.013*
SF-36: Vitality	57.21 6.75	68.26 6.43	0.002*
SF-36: Social functioning	86.41 ± 9.32	92.11 ± 8.97	0.017*
SF-36: Role functioning: Emotional	92.18 ± 11.32	85.54 ± 10.71	0.005*
SF-36: Mental health	84.63 + 8.34	79.48+ 8.15	0.015*
Self-esteem (RSES)	22.47± 3.27	27.26 ± 3.13	0.023*
Depression (BDI)	7.92 ± 3.34	5.17 ± 3.16	0.007*
Total mood disturbance (POMS)	24.82 ± 4.72	18.26 ± 4.53	0.003*
TNF- α (pg/mL)	13.16 ± 2.85	8.23 ± 2.47	0.004*
IL-6 (pg/mL)	5.83 ± 1.75	3.12 ± 1.58	0.002*
CRP (mg/L)	4.25 ± 1.16	2.41 ± 0.95	0.006*

RSES: Rosenberg Self-Esteem Scale; BDI: Beck Depression Inventory; POMS: Profile of Mood States; IL-6:Interleukin-6; TNF-α: tumor necrosis factor-alpha; CRP : C-reactive protein; (*) indicates a significant difference between the two groups; P < 0.05.

of 101 healthy older adults randomized to four months of aerobic exercise, a yoga/flexibility control group, or wait list, assessment of scores from pre- to post-treatment revealed that depressive symptoms were reduced, especially in men[20]. Also, *Blumenthal* in his study on 156

Table 3. This table demnostrates mean value and significance of SF-36 subscale scores and TNF-α and IL-6 in group (B) before and at the end of the study

SF-36 subscale variables	Mean ±SD		P-value
	Before	After	
SF-36: Health transition	2.58 ± 0.73	2.71 ± 0.71	0.565
SF-36: Physical functioning	74.23 8.61	73.45 8.43	0.216
SF-36: Role functioning: Physical	80.16 10.47	80.48 10.21	0.581
SF-36: Bodily pain	73.88 8.18	74.42 8.11	0.431
SF-36: General health	72.64 10.46	72.36 10.53	0.312
SF-36: Vitality	56.37 6.19	56.44 6.12	0.272
SF-36: Social functioning	87.43 ± 10.17	88.14 ± 10.14	0.472
SF-36: Role functioning: Emotional	91.76 ± 9.83	90.81 ± 9.75	0.411
SF-36: Mental health	83.24+ 7.59	82.72+ 7.41	0.272
Self-esteem (RSES)	22.66 ± 3.31	23.18 ± 3.22	0.261
Depression (BDI)	7.62 ± 3.21	7.15 ± 3.01	0.283
Total mood disturbance (POMS)	24.17 ± 4.26	23.64 ± 4.15	0.211
TNF- α (pg/mL)	12.81± 2.44	12.32± 2.16	0.743
IL-6 (pg/mL)	5.47 ± 1.69	4.85 ± 1.47	0.654
CRP(mg/L)	4.31 ± 1.15	4.42 ± 1.13	0.518

RSES: Rosenberg Self-Esteem Scale; BDI: Beck Depression Inventory; POMS: Profile of Mood States; IL-6:Interleukin-6; TNF-α: tumor necrosis factor-alpha; CRP : C-reactive protein

Table 4. This table shows the mean value and significance of SF-36 subscale scores and TNF-α , IL-6 in both groups (A) and group (B) at the end of the study

SF-36 subscale variables	Mean ±SD		P-value
	Before	After	
SF-36: Health transition	1.84 ± 0.65	2.71 ± 0.71	0.017*
SF-36: Physical functioning	82.91 8.41	73.45 8.43	0.005*
SF-36: Role functioning: Physical	85.23 10.83	80.48 10.21	0.008*
SF-36: Bodily pain	70.26 8.10	74.42 8.11	0.015*
SF-36: General health	77.88 10.65	72.36 10.53	0.009*
SF-36: Vitality	68.26 6.43	56.44 6.12	0.007*
SF-36: Social functioning	92.11 ± 8.97	88.14 ± 10.14	0.008*
SF-36: Role functioning: Emotional	85.54 ± 10.71	90.81 ± 9.75	0.009*
SF-36: Mental health	79.48+ 8.15	82.72+ 7.41	0.028*
Self-esteem (RSES)	27.26 ± 3.13	23.18 ± 3.22	0.027*
Depression (BDI)	5.17 ± 3.16	7.15 ± 3.01	0.025*
Total mood disturbance (POMS)	18.26 ± 4.53	23.64 ± 4.15	0.026*
TNF- α (pg/mL)	8.23 ± 2.47	12.32± 2.16	0.008*
IL-6 (pg/mL)	3.12 ± 1.58	4.85 ± 1.47	0.013*
CRP(mg/L)	2.41 ± 0.95	4.42 ± 1.13	0.024*

RSES: Rosenberg Self-Esteem Scale; BDI: Beck Depression Inventory; POMS: Profile of Mood States; IL-6:Interleukin-6; TNF-α: tumor necrosis factor-alpha; CRP : C-reactive protein; (*) indicates a significant difference between the two groups; $P < 0.05$.

community dwellers diagnosed with major depression were randomized to supervised exercise, medication, or a combination of exercise and medication. The 16-week exercise treatment consisted of three weekly sessions of aerobic activity. By the end of the treatment period, each of the three treatment groups experienced a significant reduction in their levels of depression. The treatments did not differ significantly from one another in efficacy. These results suggest that exercise may be a viable alternative to medication in the treatment of depression in older adults[21]. However, *Mota-Pereira and colleagues* conducted a study a 12 week, home-based exercise program of 30-45 min/day walks, 5 days/week on 150 individuals with treatment-resistant major depression, results showed improved depression and functioning parameters and contributed to remission of 26% of these patients. Moderate intensity exercise may be a helpful and effective adjuvant therapy for treatment-resistant major depression[22].

A number of potential mechanisms may be responsible for the reductions in depression associated with physical exercise e.g. physiological mechanisms hypothesized include the central monoamine theory (i.e., exercise corrects dysregulation of the central monoamines believed to lead to depression), as well as consideration of the role of the hypothalamic–pituitary–adrenal (HPA) axis (i.e., some depressed individuals exhibit HPA hyperactivity in response to stress and exercise may regulate this activity)[23,24].

The results in this study revealed that serum IL-6 and TNF- α were significantly decreased in response to aerobic exercise training in HCV patients. These findings were consistent with *Goldhammer and colleagues* found large (48%; 7.5 to 3.9 mg/L) reductions in serum CRP in 28 elderly coronary heart disease patients in response to 12 weeks of aerobic exercise training as offered in typical Phase II cardiac rehabilitation programs[25]. In a study by *Kohut and colleagues* sedentary, low fit older adults aged >64 years were randomized to moderate aerobic exercise training (65-80% heart rate reserve, 3times per week, 30-45min/day) or flexibility control group for 10 months. Exercisers had a significant reduction in serum CRP, IL-6 , IL-18 and TNF- α when compared to the flexibility group[26]. Also, *Nicklas and colleagues* examined the effects of 12 months of moderate walking training on plasma CRP and IL-6. Four hundred and twenty four sedentary, over weight/obese (BMI >28), community-dwelling elderly (70-89 years) were randomized to treatment. The exercise intervention resulted in a significant 16% reduction in IL-6. CRP was 32% lower after exercise[27]. Moreover, *Ogawa and colleagues* found that 12 week of strength training significantly reduced serum CRP despite having no effect on body weight or waist circumference[28].

The potential mechanisms of exercise training-induced reductions in inflammation in HCV patients include loss of adipose tissue which induced reductions in serum markers of inflammation[29,30]. Exercise training also increases vagal tone[31], which according to the cholinergic anti-inflammatory reflex espoused by Tracy, could lead to reductions in systemic inflammation[32]. Acute exercise activates the hypothalamic-pituitary-adrenal axis and sympathetic nervous systems. Cortisol is known to have potent anti-inflammatory effects[33] and catecholamines can inhibit pro-inflammatory cytokine production[34]. Several studies have demonstrated that exercise training can down regulate toll-like receptor 4, ligation of which activates pro-inflammatory cascades[35,36].

Furthermore, on analyzing the quality of life changes in response aerobic exercise training HCV patients. This study has shown a significant improvement in the mean values of SF-36 subscale scores. These findings were consistent with several studies have shown that exercise intervention might enhance health-related quality of life and psychological well-being[37-39]. *Mahendra* conducted a randomised controlled trial for 3 months follow-up, percentage of participants exercising ≤ 60 min per week increased in the exercise group compared with routine care. Exercise improved levels of physical functioning (SF-36 score) and depression compared with people in routine care (whose levels worsened). At 24 months, longitudinal analyses of all follow-up data revealed improvements in exercise group physical functioning (SF-36) and mobility compared with routine care[40]. Also, *Schmitz and colleagues* conducted the German National Health Interview and Examination Survey (GHS) on 7,124 persons, 18–79 years of age. Results revealed that higher levels of physical activity were associated with higher health-related quality of life among persons with mental disorders as well as physically inactive subjects reported poorer quality of life[41]. However, *Bowen and colleagues* proved that 12-month exercise intervention (225 min/week) improved physical functioning and general health scores among sedentary postmenopausal women (vs. controls)[42]. Improved HRQOL was also noted in another 12-month exercise trial (60 min/day, 3 times/week) among middle-aged adults[43]. While, *Imayama and colleagues* conducted a study one middle-aged women (n=100) and men (n=102) were randomly assigned to either exercise (360 min/week of moderate-to-vigorous aerobic exercise) or control and HRQOL (SF-36) were assessed at baseline and 12 months and proved that this level of exercise may increase HRQOL among overweight men[44]. Similarly, a survey of European adults found that being physically active (N24 MET-h/week) is associated with better mental health compared with being less active (≥ 24 MET-h/week) [45,46]. Moreover, *Hoffmann and colleagues* conducted a study of exercise sessions in a group of 3–5 participants for 1 hour, 3 times per week for 16 weeks. The purpose of the first 4 weeks of exercise is to accustom the participants to exercising (adaptation exercise). During the next 12 weeks, the exercise is designed to achieve an intensity of 70–80% of heart rate reserve. Results proved that moderate intensity aerobic could improve cognition, quality of life, physical health and functional ability in patients with AD[47].

Although the exact mechanism for the effect of exercises on mental health is still unknown, several physiological and psychological mechanisms have been proposed, including increased feelings of self-efficacy, self-perceptions of control, reduced emotional strain and physiological responses to stress, and beneficial effects on neurotransmitters[48]. Also, physical activity may have a trophic effect on the brain, particularly the hippocampus. For instance, exercise increases brain-derived neurotrophic factor (BDNF)[49]. Exercise appears to stimulate neurogenesis[50], enhance neuronal survival[51], increase resistance to brain insults[52,53] and increase synaptic plasticity[54]. Exercise promotes brain vascularization[55,56], mobilizes gene expression profiles predicted to benefit brain plasticity[57]. Social contact may be an important mechanism, and subjects who take regular exercise may, as a result, get positive feedback from other people and an increased sense of self-worth[58].

CONCLUSION

Treadmill walking exercise training is an effective treatment policy to improve quality of life, systemic inflammation and psychological wellbeing in HCV patients.

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