

# Aerobic exercise training modulates biochemical parameters in type 2 diabetic patients with chronic hepatitis C

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## ABSTRACT

**Background:** Recent studies suggested that Hepatitis C Virus (HCV) patients may suffer from insulin resistance (IR), lipid profile abnormalities and poor virological response to the antiviral treatment. The beneficial effects of aerobic exercise have been a matter of controversy in the field of HCV management.

**Objective:** This study aimed to measure the impact of aerobic exercise training on insulin resistance, lipid profile abnormalities and virological response in type 2 diabetic patients with chronic hepatitis C.

**Materials and Methods:** Eighty non-hypertensive, non-cirrhotic chronic HCV infection Saudi patients with high Triglycerides (TG), Total cholesterol (TC) and Low Density Lipoprotein Cholesterol (LDL-c) & non-insulin dependent diabetic with insulin resistance. Patients were divided in to two equal groups. The first group received aerobic exercise training, three sessions per week for three months in addition to their antiviral treatment. The second group (B) received only their antiviral treatment.

**Results:** The mean values of Homeostasis Model Assessment-Insulin Resistance- index (HOMA-IR), TC, LDL-c, TG, virologic response and Body Mass Index (BMI) were significantly decreased in group (A), where the mean value of High Density Lipoprotein Cholesterol (HDL-c) was significantly increased, while there were no significant changes in group (B) Also; there was a significant difference between both groups at the end of the study.

**Conclusion:** Treadmill walking exercise training is an effective treatment policy to improve insulin resistance, lipid profile abnormalities and virological response in type 2 diabetic patients with chronic hepatitis C.

**Keywords:** aerobic exercise training, blood lipids, chronic hepatitis C, insulin resistance, type 2 diabetes mellitus

## INTRODUCTION

Globally, hepatitis C virus (HCV) chronically affects about 170 million subjects and the long-term medical complications of HCV include liver cirrhosis, end stage liver disease and hepatocellular carcinoma (1). The standard medical treatment for chronic hepatitis C virus (CHC) include ribavirin (RBV) interferon- alpha (IFN)- $\alpha$  and combined pegylated interferon- $\alpha$  and ribavirin (PR) (2).

HCV is considered as an independent risk factor for insulin resistance and diabetes [3-6], serum level of lipoproteins of varying triglyceride and cholesterol composition determines the level of plasma HCV RNA (7), also sustained virological response (SVR) to antiviral treatment is dependent on the blood lipids concentration (8-11).

In non-diabetic subjects, hypertriglyceridemia, increased serum level of Low Density Lipoprotein Cholesterol (LDL-c), decreased serum level of High Density Lipoprotein Cholesterol (HDL-c) and insulin resistance are closely related in non-diabetic subjects (12). Also, degree of obesity, hyperglycemia and blood lipid profile abnormalities are associated with insulin in older subjects (13) and in obese adolescents (14).

The present study aimed to measure the influence of aerobic exercise on insulin resistance, lipid profile abnormalities and virological response in HCV.

## MATERIALS AND METHODS

### Subjects

Eighty non-hypertensive, non-cirrhotic Saudi patients (46 males and 34 females) of Gastroenterology and Hepatology

Department, King Abdulaziz University Teaching Hospital with chronic HCV infection with high cholesterol, triglycerides and LDL levels and non-insulin dependent diabetics associated with insulin resistance (mean age  $42.59 \pm 3.56$  year) were randomly enrolled in the present study. All these patients were anti HCV positive detected by 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 have anti HCV antibodies by ELISA were selected to undergo Real-Time polymerase chain reaction (RT-PCR) treated with combined pegylatedinterferon- $\alpha$  (PEG-IFN $\alpha$ )-ribavirin therapy. All participants signed a consent form before sharing in the study.

The original sample consisted of 166 participants who underwent the eligibility assessment. In the enrollment phase, 41 of them were excluded as they didn't meet inclusion criteria and 13 refused to participate, then the randomization was done. This substudy thus included 112 subjects (57 patients in the intervention group and 55 patients in the control group). During the follow up, in the intervention group 10 patients discontinued intervention (5 patients disliked the diet regimen, 2 patients had work related schedule problems and 3 patient discontinued due to unknown reason) and in the control group 9 patients discontinued intervention (5 patients had work related schedule problems and 4 patient discontinued due to unknown reason).In addition, 7 patients in the intervention group and 6 patients in the control group were excluded from the analysis due to insufficient blood sample. This study was approved by the Ethical Committee for Scientific Research, Faculty of Applied Medical Sciences, King Abdulaziz University.

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## Equipment

- Treadmill (Enraf Nonium, Model display panel Standard, NR 1475.801, Holland) was used to perform treadmill walking exercise.
- Commercial kits (Randox, Tokyo, Japan) with K2EDTA were used to measure serum insulin, total cholesterol, triacylglycerol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol.
- Weight and height scale (JENIX DS 102, Dongsang, South Korea) was used to measure weight and height to calculate the Body Mass Index (BMI).

## Measurements

- **Real-Time polymerase chain reaction (RT-PCR)** : Ten milliliter venous blood samples were collected from each participant. The blood samples were withdrawn and kept in heparinized vacuum syringes and stored at -70°C. Serum samples of all participants were tested for RT-PCR to detect serum HCV RNA levels using the COBAS TaqMan HCV test, v2.0 (Roche Diagnostics, Indianapolis, NJ, USA).
- **Blood lipid profile and Insulin resistance measurements:** Overnight fasting venous blood samples were withdrawn and dropped in clean tubes had few mg of K2EDTA, centrifugation and separated plasma was stored at -20° for plasma lipid profile analysis Total cholesterol (TC), Triglycerides (TG), High density lipoprotein (HDL) and Low density lipoprotein (LDL). Also, Homeostasis Model Assessment-Insulin Resistance- index (HOMA-IR) was used for determination of insulin sensitivity using the equation: [fasting glycemia (mmol/L)· fasting insulin (mIU/L)]/22.5 [15].
- **Evaluation of anthropometric parameters:** Body weight was measured with a calibrated balance scale (HC4211, Cas Korea, South Korea) and the body height was measured using (JENIX DS 102, Dongsang, South Korea), while BMI was determined by equation: BMI = Body weight / (Height)<sup>2</sup>.

All measurements of Total cholesterol, TG, LDL, HDL, BMI, HOMA-IR and virological response were taken before the starting of the study (pre-test) and repeated at the end of the study (post-test) after three months.

## Procedures

Following the previous evaluation, where the subjects doing the laboratory test were unaware of the group of the subjects; hence, we can extrapolate no bias in subject's selection as all participants were enrolled into two study groups:

- **The training group (Group A):** Forty patients (24 males and 16 females) treated with combined pegylatedinterferon- $\alpha$  (PEG-IFN $\alpha$ )-ribavirin therapy were submitted to the aerobic exercise training to complete a 12-week aerobic exercise-training program on a treadmill aerobic exercise (Enraf Nonium, Model display panel Standard, NR 1475.801, Holland). Each session of physical exercise was divided in: 5 minutes of warm up, with stretching exercises and circling of members and body; 30 minutes of aerobic exercise divided into row ergometer (15 minutes) and bicycle ergometer (15 minutes) and 5 minutes of cold down at the end, with stretching, flexibility and relaxation exercises, consisting of five sessions/week for 12 weeks. The training program was performed at 70%-80% of the individual age-predicted HR<sub>max</sub>.
- **The control group (Group B):** Forty patients (22 males and 18 females) treated with combined pegylatedinterferon- $\alpha$  (PEG-IFN $\alpha$ )-ribavirin therapy were asked to maintain their ordinary life style and received no exercise training.

**Table 1: Mean value of demographic data for participants in both groups**

	Group (A)	Group (B)	P-value
Age (year)	42.51± 7.84	43.62± 7.19	0.513
BMI (kg/m <sup>2</sup> )	32.42 ± 2.65	32.96 ± 3.14	0.742
Hb (gm/dl)	11.96± 1.52	12.25± 1.43	0.681
Albumin (gm/dl)	3.71± 0.89	3.55± 0.87	0.753
Total Bilirubin (mg/dl)	1.35± 0.67	1.41± 0.59	0.614

**Table 2: Mean value and significance of cholesterol, LDL, HDL, TG, HOMA-IR and virological response of group (A)**

	Mean ± SD		P-value
	Before	After	
Cholesterol (mg/dL)	251.54 ± 23.16	226.12 ± 20.42	0.008*
LDL (mg/dL)	172.18± 11.53	153.41± 10.18	0.006*
HDL (mg/dl)	33.76 ± 2.29	39.42 ± 2.15	0.008*
TG (mg/dl)	89.14± 6.75	72.63± 5.98	0.013*
HOMA-IR	5.91± 1.78	4.11± 1.32	0.012*
HCV-RNA (KIU/mL)	1000723.12± 225.64	121752.81 ± 216.22	0.005*

LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglyceride; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance- index; HCV: Hepatitis C Virus; (\*): indicates a significant difference, P < 0.05

**Table 3: Mean value and significance of Total cholesterol, LDL, HOMA-IR and virological response of group (B) before and after treatment**

	Mean ± SD		P-value
	Before	After	
Cholesterol (mg/dL)	248.92± 22.76	251.35 ± 21.58	0.648
LDL (mg/dL)	171.53± 10.22	172.81± 10.15	0.572
HDL (mg/dl)	34.26± 2.18	33.12 ± 2.13	0.631
TG (mg/dl)	90.34± 5.69	92.15± 4.72	0.528
HOMA-IR	5.62± 1.91	5.93± 1.74	0.476
HCV-RNA (KIU/mL)	1000671.55± 217.13	240521.73 ± 212.91	0.013*

LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglyceride; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance- index; HCV: Hepatitis C Virus; (\*): indicates a significant difference, P < 0.05

**Table 4: Mean value and significance of Total cholesterol, LDL, HOMA-IR and virological response of group (A) and group (B) after treatment**

	Mean ± SD		P-value
	Group (A)	Group (B)	
Cholesterol (mg/dL)	226.12 ± 20.42	251.35 ± 21.58	0.028*
LDL (mg/dL)	153.41± 10.18	172.81± 10.15	0.014*
HDL (mg/dl)	39.42 ± 2.15	33.12 ± 2.13	0.023*
TG (mg/dl)	72.63± 5.98	92.15± 4.72	0.034*
HOMA-IR	4.11± 1.32	5.93± 1.54	0.011*
HCV-RNA (KIU/mL)	121752.81 ± 216.22	240521.73 ± 212.91	0.002*

LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglyceride; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance- index; HCV: Hepatitis C Virus; (\*): indicates a significant difference, P < 0.05

## 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. Statistical analyses were performed using SPSS version 17.0 for Windows (Statistical Package for the Social Sciences, SPSS Inc. Chicago, IL, USA). For descriptive purposes, mean values of untransformed and unadjusted variables are presented (mean ± SD). Statistical significance was accepted at the 95% confidence level (P < 0.05).

## RESULTS

Both study groups were considered homogeneous regarding the demographic variables (Table 1). The mean values of HOMA-IR, TG, TC, LDL-c, Virological Response and BMI decreased significantly after aerobic exercise training in the study group (A), where the mean value of HDL-c increased significantly, while there were no significant changes in group (B) except their Virological Response (Table 2 and 3). Also; there was a significant difference between both groups at the end of the study (Table 4).

## DISCUSSION

Chronic hepatitis C is a systemic disease, leading to metabolic sequel as a result of the HCV interaction with glucose

and lipid metabolism leads to insulin resistance, type 2 diabetes, hypercholesterolemia and hepatic steatosis (16). Insulin resistance may be directly linked to the HCV (17). As a recent study (18) recommended for more data to confirm a reduced virological response after antiviral regimens. Our study was a trial to measure the influence of aerobic exercise on insulin resistance, lipid profile abnormalities and virological response of HCV treatment. The findings of this study showed that three months of aerobic exercise training led to significant decreased mean values of HOMA-IR, TG, TC, LDL-c, Virological Response and BMI in group (A), while the mean value of HDL-c was significantly increased, while there were no significant changes in detraining group (B) except in Virological Response. Also; there was a significant difference at the end of the study between the two study groups. The comparison of our results with other studies is difficult, because of few published studies evaluating virological response to exercise training in HCV patients.

Eizadi et al. stated that prolonged aerobic exercise improved lipid profile, reduced insulin resistance and increased insulin sensitivity in obese patients (19). Also, Konishi et al. applied a program of walking exercise for 15 patients with HCV and founded that aerobic exercises decreased body fat and improved insulin resistance (20). Similarly, Jiménez and Ramírez-Vélez found that eight weeks of strength training for obese subjects improved insulin sensitivity (21).

The possible mechanism by which insulin sensitivity can be improved by exercises is that active muscle contraction causes membrane depolarization that increased cytoplasmic calcium concentration and causes activation of 5'-adenosine monophosphate-activated protein kinase that causes translocation of glucose transporter protein-4 (GLUT-4) to the plasma membrane (22) or changing the energy state of the cell as a result of high intracellular ratio of adenosine monophosphate to adenosine triphosphate (23). Also, the improved effects on fatty acid metabolism due to changed expression of a number of lipogenic and glycolytic enzymes in the liver caused by 5'- Adenosine monophosphate-activated protein kinase activation (23, 24). Finally, the anti-inflammatory effects of aerobic exercise reduces the level of serum IL-6 which may inhibit insulin resistance (25).

In line with our results, there are many previous studies demonstrated that blood lipid levels modulation as a result of aerobic exercise training. Durstine et al and Kelley meta-analysis, reported that aerobic exercise training for 8 weeks significantly increase HDL-c levels in adults (26, 27). HDL-c is a

lipoprotein that protects against atherosclerosis, partly because of its antiproliferative and antithrombogenic effects (28). Also, Jiménez and Ramírez-Vélez found that obese subjects practiced strength training for eight weeks experienced reduction in LDL-c and increase in HDL-c levels (21).

An interesting finding was that an improvement in the virological response in the experimental group received aerobic exercise training. Modulation of insulin resistance following exercise training may be the possible mechanism by which virological response improved by aerobic exercises, this explanation is supported by Hanouneh et al. stated that presence of metabolic syndrome among HCV patients increase the risk of failure to their standard anti-viral treatment by about 4 times than patient with no metabolic syndrome (29).

The current study has important strengths and limitations. The major strength is the supervised nature of the study. The supervised physical activity training program removes the need to question compliance or to rely on activity questionnaires. Further, all exercise sessions were supervised and adherence to activities was essentially 100%. Moreover, the study was randomized; hence, we can extrapolate adherence to the general population. In the other hand, the major limitations is the small sample size in both groups that may limit the possibility of generalization of the findings in the present study. Finally, within the limit of this study, aerobic exercise training is recommended for modulation of insulin resistance, lipid profile abnormalities and virological response in type 2 diabetic patients with chronic hepatitis C. Further researches are needed to explore the impact of other exercise training techniques on quality of life and other biochemical parameters among type 2 diabetic patients with chronic hepatitis C.

## CONCLUSION

Treadmill walking exercise training is an effective treatment policy to improve insulin resistance, lipid profile abnormalities and virological response in type 2 diabetic patients with chronic hepatitis C.

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