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Effect of Aerobic Exercise Training on Leptin and Liver Enzymes in Non-diabetic Overweight Hepatitis C Men

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Abstract

Introduction: Leptin is one of the new adipokines that reflects the pathological status of liver tissue in the chronic hepatitis C virus (HCV). This study aimed to investigate the leptin and liver enzymes responses to aerobic exercise (AE) in overweight nondiabetics with HCV.

Material and methods: Forty nondiabetic non-cirrhotic HCV men aged 40–60 years old with a body mass index (BMI) varied from 25–29.9 kg/m2 were divided randomly to study and control groups. The study group (n = 20) received a 3-session continuous moderate-intensity AE per week for 12 weeks while the control group (n = 20) were advised to maintain their normal level of physical activity. Pre and post measurements of weight, BMI, waist circumference, fasting blood glucose (FBG), alanine transaminase (ALT), aspartate transaminase (AST), and leptin were measured for all forty patients.

Results: Statistical ANOVA analysis revealed a post-treatment significant statistical decrease of all variables within the study group ($p < 0.05$) while the control group showed a non-significant difference of all measurements. Post-treatment between-group analysis showed a significant statistical difference in FBG, ALT, AST, and leptin in favor of the study group.

Conclusions: To restore the normal hepatic cellular functions and to prevent HCV-induced hepatic fibrosis, AE is a strong therapeutic modality that lowers leptin levels via weight maintenance and/or loss, increased glucose uptake, and declined liver enzymes.

Keywords: overweight, aerobic exercise, Leptin, Liver enzymes, Hepatitis C

Introduction

Hepatitis C virus (HCV) is one of the main human pathogens that causes chronic liver diseases as hepatic cirrhosis and hepatocellular carcinoma in addition to the increased rate of mortality. Besides the highly-estimated prevalence rate in middle-aged men, 32%, Egypt represents the uppermost prevalence of HCV around the world [1]. HCV-induced hepatic fibrosis rates are lower in women than men due to the probable increase of HCV clearance rate augmented by the anti-fibrogenic effect of estrogen [2].

HCV is the main risk factor for the development of diabetes mellitus (DM) due to the massive destruction

of pancreatic β-cells induced by HCV [3]. Insulin resistance (IR) is a pro-fibrogenic stimulus to liver tissues in HCV patients because many reports stated the presence of impaired glucose metabolism in both muscular and hepatic tissues of nondiabetic HCV patients [4].

Being a serious endocrine organ, adipose tissue is the main source of adipokines and biologically-effective polypeptides like leptin. Leptin plays a strong metabolic action in the control of food intake, sympathetic tone, energy expenditure in conditions of excess energy, neuroendocrine function, appetite, carbohydrates and lipids metabolism, the action of insulin receptors, and secretion of insulin and hormones utilized in lipid metabolism [5].

HCV is now expressed as metabolic liver disease and there are numerous non-invasive plasma biomarkers – including leptin – have been suggested to reflect the HCV-induced progressive fibrotic changes of hepatic tissues. Various studies recorded the involvement of different adipocytokines in the HCV-associated fibrogenesis of hepatic tissues due to the direct fibrotic stimulatory signals to hepatic stellate cells and the indirect stimulation to inflammatory cells as Kupffer cells and macrophages [6]. Elevated serum leptin levels are positively correlated with the body mass index (BMI), fat mass, hepatic steatosis, the severity of hepatic fibrosis stages, and physical fatigue in HCV patients [7].

Despite the known role of regular training in the inhibition/prevention of hepatic disease progression by modulating leptin and insulin signaling/levels [8], the available studies in the area of HCV and leptin are very scarce [9]. This study aimed to investigate the effect of 12-week aerobic training on serum leptin and liver enzymes in nondiabetic overweight men with HCV.

Materials and methods

Ethics

Besides receiving a signed consent form from every participant and planning this trial according to the recommended declarations of Helsinki, this study was approved (under the number of P.T.REC/012/002650) by the Local Ethical Institutional Committee for Human Scientific Research, Physical Therapy Faculty, Cairo University.

Inclusion criteria

Forty men aged 40-60 years old with HCV at least from 6 months were recruited from The National Hepatology and Tropical Medicine Institute with a BMI ≥ 25 to less than 30 kg/m^2, fasting blood glucose (FBG) levels less than 100 mg/dl, and a waist circumference (WC) less than 102 cm during the period from February-November 2020.

Exclusion criteria

A physician screened the patients to exclude those with cirrhotic or hepatocellular carcinoma, renal or respiratory problems, cardiovascular and neurologic diseases, and hypertension. The individuals who participated in any form of physical training or diet counseling in the last 3 months were also excluded.

Randomization

An individual – not involved in application of this clinical trial – prepared a randomized computer-developed group list then the patients were divided randomly to study or control groups (Fig. 1).

Intervention

The study group (n = 20) received a 3-month aerobic training, 3 sessions weekly, on an electronic treadmill with no inclination. Every session was started with a 5–minute warming-up then a 30-minute moderate-intensity aerobic training at 60–75% of maximal heart rate (220-age) then the session was ended with 5 minutes of cooling down [10]. The control group (n = 20) were advised to maintain their normal daily physical activity.

Primary outcomes

Five milliliters of blood were obtained from the antecubital vein to assess the serum aspartate transaminase (AST) and alanine transaminase (ALT) (liver enzymes were measured by Hitachi 971 device, Mannheim). Serum leptin was measured by Leptin ELISA Kits, Diagnostic Biochem, Canada.

Secondary outcomes

With an empty bladder and stomach, weight was measured for every participant. The BMI was obtained from dividing the weight (kg) on squared height (meter). WC was measured with an inelastic tape between the iliac crest and lower ribs. FBG levels were measured using (On Call ® Plus Acon, REF G113 – 214, made in China). All measurements (primary and secondary were applied before and after the 3-month study period for both allocated groups)

Statistical analysis

Obtained from a 10-subject pilot study, a size effect equal to 0.83 for the main outcome variable, leptin, was detected by calculating the sample size through the German power analysis program (G*Power version 3.1.9.2, Franz Faul, Uni Kiel) with T-test. The suggested minimum sample size for this trial was 38 hepatitis C patients with the type I and type II error rates was programmed at 5% and 80% power respectively.

The Shapiro-Wilk's test showed a normal distribution of the data so the unpaired test was used to examine

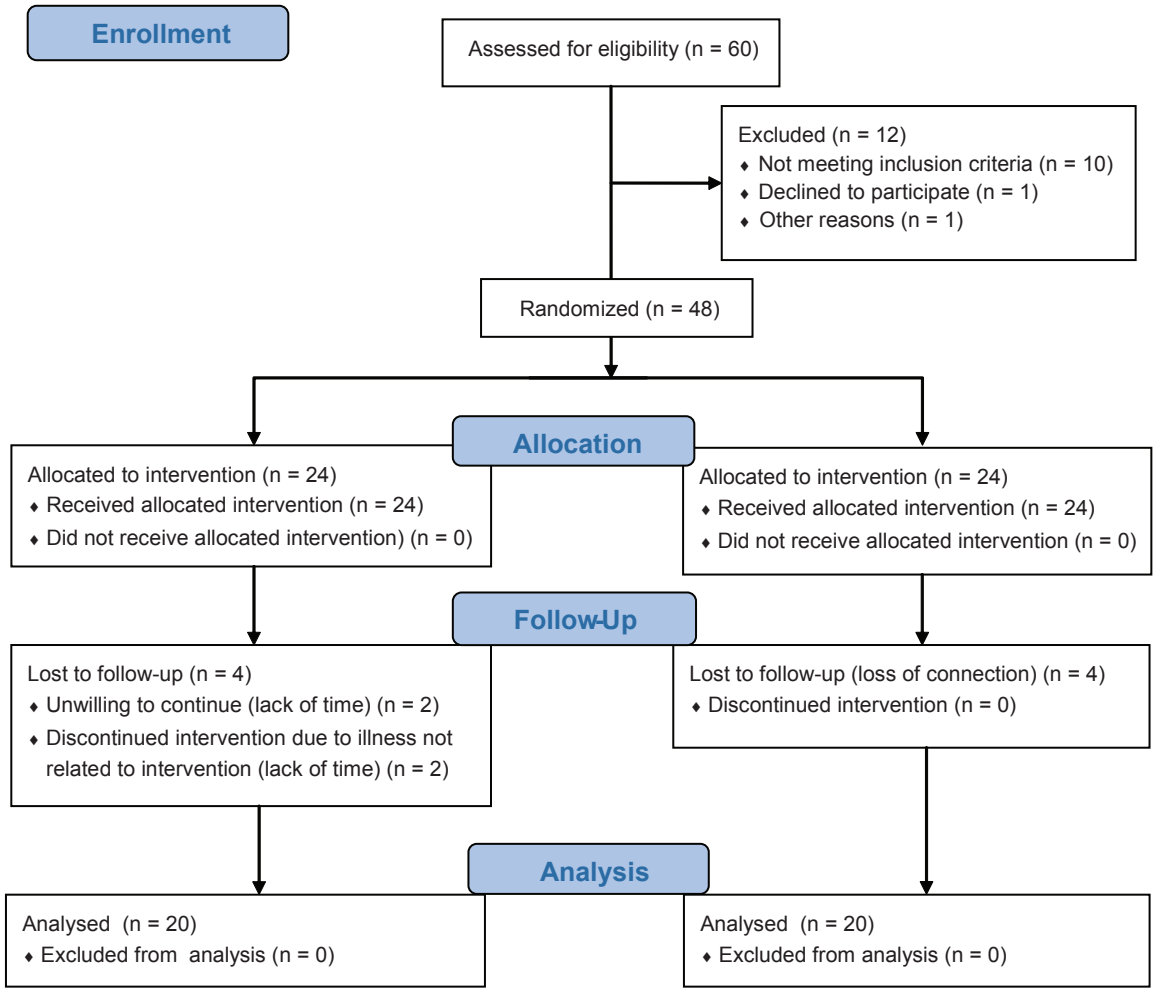

Fig.1. Consort flow diagram for the study

the pretreatment significance of anthropometric data between groups. Also, the within – and among-group statistical significances were tested by the parametric test, ANOVA. The analysis of data – at a significant P-value level less than 0.05 – was done by version 18 of the SPSS program (IBM Corp. Chicago. SPSS Inc.).

Results

Pre-treatment among-group anthropometric (weight, height, BMI, and WC) analysis by unpaired test showed a non-significant statistical difference (Tab. 1). There was a significant statistical decrease in all variables within the study group while the control group showed a non-significant statistical difference in the all measured variables. Among-group comparison of post-treatment values showed a significant statistical difference in FBG, ALT, AST, and leptin values in favor of the study group while the anthropometric variables showed a non-significant difference (Tab. 2).

Discussion

Besides the induced-deterioration of liver disease by high leptin levels, overweight is the main risk factor for the development of IR and type 2 DM among HCV patients [11]. Besides its importance for maintaining the normal mental, physical, psychological health issues [12–15], exercise promotes the health of the liver, relieves the side effects of medications, improves immunity, promotes the sense of well-being, enhances weight maintenance and/or loss, lowers the sensation of chronic fatigue, improves blood oxygen levels, and enhances the full-energized sensation by the excretion of endorphins in HCV patients [16].

Despite the gained minimal anthropometric and FBG changes, a 12-week aerobic exercise resulted in a highly significant statistical decrease of leptin and liver enzymes in overweight non-diabetic HCV men.

Decreased serum leptin levels after chronic physical training may be justified by glycogen evacuation, glycolysis inhibition, increased glucose utilization,

Tab.1. Pre-treatment anthropometric data in both groups

Variable	Study group	Control group	P value
Age (year)	47.85 ± 5.38	49.40 ± 5.30	0.364
Weight (kg)	79.05 ± 4.05	78.60 ± 4.56	0.744
Height (cm)	168.30 ± 3.89	169.05 ± 5.12	0.605
BMI (kg/m^2)	27.86 ± 1.01	27.50 ± 1.31	0.342
WC (cm)	89.45 ± 5.10	88.80 ± 5.30	0.695

Data are expressed as mean ± standard deviation; BMI – body mass index; WC – waist circumference; P value significance < 0.05.

Tab.2. Within – and among-result comparisons of pre & post data in both groups

Variable	Study group (n = 20)	Control group (n = 20)	Among-group P-value
Pre-weight (kg)	79.05 ± 4.05	78.60 ± 4.56	0.744
Post-weight	78.71 ± 4.27	78.77 ± 4.52	0.966
P-value within group	0.041*	0.277	
Pre-BMI (Kg/m^2)	27.86 ± 1.01	27.50 ± 1.31	0.342
Post-BMI	27.65 ± 1.02	27.57 ± 1.41	0.834
P-value within group	0.002*	0.292	
Pre-WC	89.45 ± 5.10	88.80 ± 5.30	0.695
Post-WC	88.40 ± 5.87	89.00 ± 5.43	0.739
P-value within group	< 0.001*	0.458	
Pre-FBG (mg/dl)	89.50 ± 5.47	90.95 ± 5.16	0.394
Post-FBG	87.65 ± 5.52	91.70 ± 6.26	0.037*
P-value within group	0.035*	0.380	
Pre-ALT (u/L)	77.35 ± 26.57	74.25 ± 26.76	0.715
Post-ALT	57.9 ± 24.38	74.55 ± 26.91	0.047*
P-value within group	<0.001*	0.898	
Pre-AST (u/L)	61.50 ± 31.04	63.90 ± 31.29	0.809
Post-AST	45.85 ± 24.24	64.25 ± 31.45	0.045*
P-value within group	<0.001*	0.916	
Pre-leptin (ng/ml)	7.40 ± 1.31	7.35 ± 1.38	0.907
Post-leptin	6.29 ± 1.63	7.46 ± 1.32	0.017*
P-value within group	<0.001*	0.596	

Data are expressed as mean ± standard deviation; mg/dl – milligram per deciliter; u/L – unit per liter; ng/ml – nanogram per milliliter; AST – aspartate transaminase; ALT – alanine transaminase; * significant P-value, P value significance (< 0.05).

modulation of energy balance, and increased sensitivity to hormones involved in both fat and carbohydrate metabolism as insulin, thyroxin, and cortisol [16].

Increased sensitivity to insulin after prolonged exercise may be explained by repetitive stimulation to many protein carriers – including glucose transporter-4 – that increase the utilization of glucose uptake into the cellular membrane of active skeletal muscles, the responsible tissue for consuming 80% of circulating glucose [17].

The mechanism of reduced serum levels of ALT and AST levels in response to aerobic exercise in HCV patients may be explained by the enhanced immune system, increased production of anti-inflammatory markers, increased fighting to infected hepatic cells,

reduction of viral replication, lower rates of infection spread, increased resistance of hepatic cells to inflammation, and prevention of further cellular hepatic inflammation [18].

Lowered lipid oxidation and steatosis of the whole body, increased metabolism of fatty acids and hepatic lipids, stimulation of hepatic and muscular protein kinases, lowered production of hepatic glucose, and inhibited proliferation of hepatic stellate cells may be the responsible causes of decreased liver enzymes after a 3-month aerobic training in patients with HCV [19].

The current study was supported by Nasif et al. [18] who stated that an eight-week moderate-intensity training was able to restore the normal hepatic cellular function in addition to increased resistance to infection by enhanced immune cytokines and liver enzymes (AST and AST) in HCV patients. The gained modulatory changes of hepatic lipid metabolism after a 6-week aerobic training in nonalcoholic fatty liver patients is the cause of liver enzymes decrease [20]. A twelve-week aerobic exercise improved fatigue symptoms in non-cirrhotic HCV patients may be due to the observed decline of systemic inflammatory markers [10].

In addition to the acquired improvement of quality of life, exercise – as an adjunctive therapeutic modality in a 15-month weight maintenance and/or loss program – resulted in decreased serum insulin and liver enzymes in overweight patients with chronic liver disease [21]. The improved virological response may be the cause of improved IR after aerobic exercise in HCV patients with metabolic syndrome [22].

The regular walking – combined with a diet regimen – declined the occurrence rate of HCV via improved IR, liver enzymes, leptin levels, and body fat [23]. A pilot study recommended the importance of exercise in the enhancement of physical and psychological HCV-related aspects of life [24].

The decreased levels of serum leptin and insulin in sedentary females may be related to decreased levels of lipids after an eight-week exercise [5]. Due to the expressive changes in the genes of adipokines located in adipose tissue, a 8-week aerobic training is considered an effective intervention in decreasing weight and leptin in overweight women [25].

An eight-week supervised aerobic training program resulted in a decrease of both leptin and anthropometric indices in overweight healthy young men [26]. A twelve-week moderate-intensity aerobic exercise resulted in a highly statistically significant improvement of leptin in sedentary obese men [27]. A six-week aerobic training appeared to be a non-prescriptive treatment tool to improve IR by lowering the levels of insulin and adipokine mediators – including leptin – in sedentary men [28].

On the other hand, despite the importance of regular physical activity in the prevention of risk factors – including obesity and high blood glucose levels – for liver diseases, an eight-week aerobic exercise revealed no significant effects on liver enzymes of older women [29].

Despite improved muscular strength and IR via an eight-week resistive training, a non-significant change of leptin – in sedentary overweight men – was noted. Leptin has not improved due to the not enough reduced amount of both body mass and fat to produce significant changes in adipokines levels [30].

Despite the hopeful improvement of insulin levels in 55 older adults with mild cognitive impairment after a 16-week aerobic training, leptin levels showed nonsignificant improvement [31]. Serum leptin did not show a significant change after the 8-week training period may be due to the selected type and intensity of exercise parameters (high-intensity interval training) [16].

Limitations

There were many limitations in this study as small number of patients, nonparticipating females, the short duration of exercise, and loss of follow up should be examined in future studies.. Investigating the response of leptin and liver enzymes to aerobic exercise training plus diet control versus exercise should be addressed in future studies.

Conclusions

Despite the minimal anthropometric changes, aerobic training is considered a good approach for weight control (loss and/or maintenance) in nondiabetic overweight men with HCV. To prevent the development of IR, type 2 DM, and hepatic steatosis (the main risk factors for hepatic fibrosis in patients with HCV), regular exercise is very important to lower serum leptin and liver enzymes via increased insulin sensitivity and glucose utilization in patients with HCV.

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Conflicts of interest

The authors declare no conflict of interest.

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