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Original Article

Regular Exercise Training as a Principal Non-Pharmacological Method Affects Serum Leptin and Cardiovascular Risk Factors in Men with Metabolic Syndrome

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Abstract

Background and Aim: Regular exercise training is the principal non-pharmacological method for the prevention and treatment of metabolic syndrome or other obesity-related diseases. We investigated the effects of aerobic training on leptin and cardiovascular risk factors in middle-aged men with metabolic syndrome.
Methods: Twenty-six sedentary middle-aged males with metabolic syndrome aged 40 ± 5 years were randomly assigned to two groups as exercise (aerobic training, n =13) and control (no training, n =13). The exercise programs were performed 3 days a week for 10 weeks at 55-75% of HRmax. Fasting blood samples were taken before and after the training period for measuring serum leptin and triglyceride (TG), total cholesterol (TC), LDL, and HDL as cardiovascular risk factors.
Results: No significant differences were observed between groups concerning anthropometric and clinical markers at baseline ($p>0.05$). Aerobic intervention resulted in significant decrease in anthropometric markers (abdominal circumference, body mass index, body fat percentage; $p < 0.05$), serum leptin ($p = 0.026$), TG ($p = 0.001$) and HDL ($p = 0.032$) in exercise group, but significant changes were not found in TC ($p = 0.522$) and LDL ($p = 0.546$). There were no changes in all measured variables in the control group.
Conclusion: Based on our finding, it seems that regular aerobic exercise is associated with improved serum leptin and cardiovascular function in patients with metabolic syndrome.

Keywords: Aerobic Exercise, Metabolic Syndrome, Leptin, Cardiovascular Risk Factors.

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Introduction

Metabolic syndrome is a common clinical disorder characterized by a variety of cardiovascular risk factors such as abdominal obesity, elevated blood glucose, hypertension, and lipid abnormality (1). Metabolic syndrome was first proposed by Reaven in 1988 in the Diabetes journal (2). The issue was raised when this researcher identified insulin resistance as a common contributor to the prevalence of certain diseases or metabolic disorders such as hyperinsulinemia, increased cardiovascular risk factors, diabetes, and hypertension. Therefore, the accumulation of afore-mentioned disorders in a person is termed as metabolic syndrome. Obesity has later been suggested as a precursor to the prevalence of most chronic metabolic disorders. The researchers termed the presence of obesity with dyslipidemia, hypertension, insulin resistance, and elevated blood glucose along with elevated triglyceride levels and a decrease in HDL as metabolic syndrome (3). Therefore, the presence of metabolic syndrome in a person mostly indicates obesity-related metabolic diseases. In a study, coronary heart disease was reported to be 2-3 times more common in people

with metabolic syndrome (4). The risk of diabetes was 10 times higher in obese individuals with metabolic syndrome (5). This ratio has also been reported in the prevalence of cardiovascular diseases (6).

Apart from the previously mentioned effective factors on metabolic syndrome prevalence, high levels of adipocytes lead to increased insulin resistance, which is a predictor of metabolic syndrome, through higher secretion of inflammatory mediators and CRP (7). The alteration in leptin levels has also been implicated in the prevalence of metabolic syndrome markers (8). Its direct association with body fat mass has been reported several times; in fact, weight loss or reduction of body fat percentage due to environmental interventions leads to lower systemic leptin levels (9). The potential effects of leptin, its receptors, and its gene expression have also been previously reported on lipid profile indices such as TG, HDL-C, LDL-C, blood glucose, and body mass index (10). Since impairment of lipid profile markers as well as body mass index are characteristics of the metabolic syndrome, likely, changes in leptin levels or expression of its receptors in adipose or muscle tissues play an important role in the pathogenesis of metabolic syndrome (8). Some studies have reported a significant increase in serum leptin in obese individuals or those with metabolic syndrome compared to healthy ones (11). Increased abdominal fat, which is usually a contributing factor to the prevalence of metabolic syndrome, is associated with insulin resistance and leptin increase (12).

Thus, given the association between insulin resistance and metabolic syndrome (13), the association between leptin and metabolic syndrome is more justified. Several studies have indicated a positive association between blood leptin levels and metabolic syndrome and its components such as obesity, type 2 diabetes, and hypertension (14). In a recent study on Iranian elderly, significant correlations were found between metabolic syndrome variables (like waist circumference and triglyceride) and serum leptin in both elderly men and women (15). Therefore, it is thought that a decrease in serum leptin along with the improvement of cardiovascular risk factors in response to therapeutic interventions is of considerable importance in improving or reducing the severity of the disease. Although studies on patients with metabolic syndrome are limited compared to studies on other obese populations, some studies have suggested the effectiveness of aerobic training on the levels of inflammatory mediators and cardiovascular risk factors in these patients and other healthy or sick obese populations. Here, we aimed to investigate the effects of aerobic training on leptin and cardiovascular risk factors in middle-aged men with metabolic syndrome.

Methods

Participants

Twenty-six sedentary age-matched obese males (35-45 years, BMI 30–36 kg/m^2) were selected first through purposive sampling in this quasi-experimental study with pre- and post-training design and then divided into exercise (aerobic training, 10 weeks, 3 times/weekly, n= 13) or control (no training, n= 13) groups based on random allocation using a table of random numbers. The main objective of the study was to assess serum leptin and cardiovascular risk factors (TG, TC, LDL, HDL) responses to aerobic training and to compare with control participants.

After the introduction and awareness of the participants of the objectives of the study and once they had signed written consent forms, and the Ethics Committee of Islamic Azad University approved this study.

All participants were non-athletes and no smoker. Participants were included if they had not been involved in regular physical activity in the previous 6 months. Persons with a known diagnosis of previous coronary cardiac disease, chronic airway disease, and impaired hepatic dysfunction, diabetic, and having symptoms that may be indicative of ischemia in electrocardiography were excluded. The height and weight of participants were measured by standard procedures (in underwear, but barefoot) with a Seca 220 scale (22089 Hamburg, Germany).

Overweight was measured by body mass index (BMI Body mass index was measured for each individual by the division of body weight (kg) by height (m2).

Body fat percentage was determined using a body composition monitor (OMRON, Finland). Abdominal circumferences were measured in the most condensed part using a non-elastic cloth meter.

Training protocol

The exercise training program lasted 10 weeks months (3 days/week) exercise intensity ranged from 55-75% of maximal heart rate (HRmax). Each session started with 10 min warm-up, 15-40 min of aerobic exercise, and 5–10 min of cool-down activity. Aerobic exercises in each session included running with no slop. In the first two weeks, participants exercised at low intensity, and the intensity of exercise was gradually increased to 75% of HRmax in the next weeks. In each session, the exercise intensity was controlled using the Polar heart rate tester (made in the US). During the training period, control participants were instructed to maintain their habitual activities. Table 1 provides the distribution of exercise intensity in running time when the training program was conducted.

Table 1: Distribution of exercise intensity in time of running during the training program

Weeks	Exercise intensity (%HRmax)	Time of running
First and second	Intensity < %55	3 × 5 minute
Third and fourth	%55 ≤ intensity ≤ %60	2 × 10 minute
Fifth and Sixth	%60 ≤ intensity ≤ %65	2 × 15 minute
Seventh and eighth	%65 ≤ intensity ≤ %70	2 × 20 minute
Ninth and tenth	%70 ≤ intensity ≤ %75	2 × 20 minute

Measurement of biochemical profile

Fasting blood samples (10-12-hour overnight fasting) were collected at pre and post (48 h after lasted exercise session) intervention concerning measure clinical markers of groups. The participants did not perform any exercise for 48 hours before the blood collection. The blood was centrifuged immediately and serums were stored at -80° until the assays were performed. Serum leptin was determined by the ELISA method. The Intra-assay coefficient of variation and sensitivity of the method was 4.2% and 0.2 ng/mL, respectively for leptin. TG, TC, HDL, and LDL-cholesterol were measured by enzymatic methods (Randox direct kits) using Kobas Mira auto-analyzer made in Germany.

Statistical Methods

All statistical analyses were performed through the use of a statistical software package (SPSS, Version 15.0, SPSS Inc., IL, USA). The normality of distribution was assessed by Kolmogorov-Smirnov. An independent sample T-test was used to compare all variables between the two groups at baseline. To determine the effect of aerobic training on various parameters (leptin, TG, TC, LDL, HDL), the delta values between pre and post-training of each variable were compared by independent T-test between 2 groups.

A paired t test was used to determine the mean differences between pre and post-intervention values on all variables. A P-value of less than 0.05 was regarded as indicative of a significant difference.

Results

Baseline and post-training anthropometric indexes of the two groups are shown in Table 2. The results are shown as mean±SD. Based on data of independent t-test, No significant difference in all anthropometric indexes was found between the exercise and control at baseline ($p > 0.05$). Aerobic training induced a significant decrease in anthropometric indexes in the exercise group ($p < 0.05$) but there were no changes in these variables in the Control group ($p > 0.05$) (Table 2). At baseline, no significant differences were observed between groups in circulating leptin and cardiovascular risk factors (Table 3). A significant

difference was observed in leptin mean difference (the difference between pre and test) between 2 groups (p = 0.020). On the other hand, findings from intra-group changes by paired t-test indicate that the aerobic training leads to a significant decrease in serum leptin levels in the exercise group (p = 0.026) but no change was found in control participants (p = 0.510) (Figure 1). Table 3 shows the significant levels of intra-group changes in serum leptin of 2 groups.

Table 2. Pre and post-training of anthropometric indexes of 2 groups

Variables	Exercise group			Control group		
	Pre-training	**Post-training**	**Sig**	**Pre-training**	**Post-training**	**Sig**
Weight (kg)	101.2 ± 13.7	97.2 ± 13.7	*< 0.0001*	101.5 ± 12.3	101.54 ± 12.6	*0.999*
Height (cm)	175.5 ± 5.22	175.5 ± 5.22	---	175.6 ± 4.15	175.6 ± 4.15	----
AC (cm)	111 ± 11.3	107.2 ± 10.7	*< 0.0001*	110 ± 10.4	109.5 ± 11.04	*0.337*
BMI (kg/m^2)	32.8 ± 3.59	31.5 ± 3.55	*< 0.0001*	32.90 ± 3.58	32.91 ± 3.75	*0.954*
Body fat (%)	32.5 ± 4.03	28.9 ± 2.67	*0.001*	32.8 ± 3.28	32.5 ± 3.55	*0.230*

AC, abdominal circumference; **BMI:** body mass index

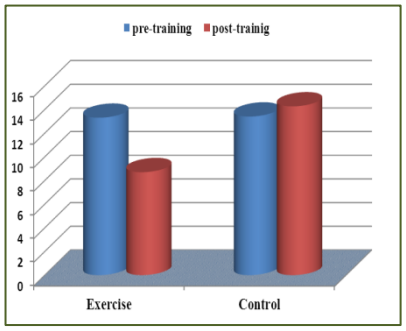

Figure 1. Pre and post training of serum leptin in studied groups. Aerobic training resulted in a significant decrease in osteocalcin in exercise participants. But this variable remained no change in control participants.

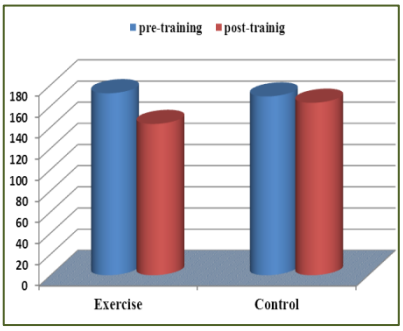

Figure 2. Pre and post training of triglyceride in studied groups. Aerobic training resulted in a significant decrease in triglyceride in exercise participants. But this variable remained no change in control participants.

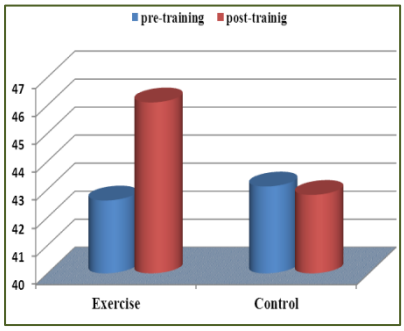

Figure 3. Pre and post training of HDL-cholesterol in studied groups. Aerobic training resulted in a significant increase in HDL-cholesterol in exercise participants. But this variable remained no change in control participants.

Based on the finding of the independent t-test, there was a significant difference between groups concerning the mean difference of TG (p = 0.019) and HDL (p = 0.029) (Table 3). In addition, findings from intra-group changes indicates that the aerobic training leads to a significant decrease in TG (p = 0.001, Figure 2) and increase in HDL (p = 0.032, Figure 3) in exercise group but no change was found in mentioned variables in control participants (TG, p = 0.348; HDL, p = 0.747).

There were no statistically significant differences between the delta of TC (p = 0.746) and LDL (p = 0.283) between 2 groups. Also, based on paired t-test data, no significant differences were found between pre and post-training of these variables of either exercise or control groups (Table 3).

Table 3. Pre- and post-training of clinical markers of 2 groups

Variables	Exercise group			Control group		
	Pre-training	Post-training	Sig	Pre-training	Post-training	Sig
Leptin (ng/mL)	13.3 ± 9.73	8.70 ± 5.75	0.026	13.4 ± 7.14	14.26 ± 5.59	0.510
TC (mg/dL)	195 ± 40.4	188 ± 41.9	0.522	192 ± 34.6	189 ± 47.9	0.761
TG (mg/dL)	172 ± 58.6	143 ± 50.7	0.001	169 ± 47.6	163 ± 49.6	0.348
LDL (mg/dL)	117 ± 31.2	113 ± 23.7	0.546	122 ± 19.2	127 ± 26.8	0.347
HDL (mg/dL)	42.6 ± 3.57	46.1 ± 4.99	0.032	43.1 ± 3.17	42.8 ± 3.02	0.747

TC, total cholesterol; **TG:** triglyceride; **LDL**, low-density lipoprotein cholesterol; **HDL:** high-density lipoprotein cholesterol

Discussion

The main finding of the present study was a significant decrease in serum leptin levels in men with metabolic syndrome in response to aerobic training. In other words, 10 weeks of aerobic training led to a significant decrease in leptin in middle-aged men with metabolic syndrome that previously had an inactive lifestyle. Although the exercise program was associated with a significant increase and decrease in HDL and TG of the study patients, respectively, cholesterol and LDL levels did not change significantly. Albeit studies are limited regarding the response or adaptation of leptin and lipid profile indices to different exercise methods in patients with metabolic syndrome, some discrepancies are observed in populations associated with metabolic syndromes such as patients with type 2 diabetes and cardiovascular diseases. For example, in the study by Tan et al. (2016), 10 weeks of aerobic training in the absence of dietary control resulted in a significant reduction in body mass and body fat percentage along with a decrease in leptin, triglyceride, and blood glucose in overweight middle-aged women (16). On the other hand, in Lopez et al.'s (2016) study, although 12 weeks of aerobic-resistance training, in addition to decreasing body fat mass, resulting in a significant decrease in leptin, CRP, and insulin resistance in overweight girls, the levels of some inflammatory and anti-inflammatory components such as adiponectin, Resistin, interleukin-10, and TNF-α did not change significantly (17).

Researchers believe that the health status and type of exercise program strongly influence the pattern of response or adaptation of inflammatory and metabolic components in healthy and sick populations. For example, in the study by Maltais et al. (2016), despite a decrease in body fat mass in response to 12 weeks of resistance training, no significant change was observed in leptin, insulin, and glucose levels in overweight elderly men (19). In a study by Nuri et al. (2016), although 8 weeks of aerobic training in three sessions of walking at the intensity of 50-60% of maximal heart rate per week correlated with weight loss and cardiovascular resistance in men with rectal cancer, leptin levels, and insulin resistance did not change significantly (18). In a study by Colombo et al. (2013), 12 weeks of moderate-intensity aerobic training did not significantly affect the levels of triglyceride, cholesterol, and LDL, although abdominal circumference and body mass index decreased and HDL increased in patients with metabolic syndrome (22).

Obesity plays an important role in the risk of cardiovascular diseases and metabolic syndrome due to creating chronic systemic inflammation and damage to the immune responses to stress (23). Despite numerous studies, evidence points to the mechanisms responsible for the effect of external stimuli such as diet or physical activity on the components effective on energy homeostasis and appetite control in healthy or sick obese individuals. Researchers have noted that depending on the type of exercise, different exercises exert various effects on the appetite-regulating hormones in obese individuals (24). In vitro studies have revealed that leptin has a central role in energy homeostasis (25). Various effects of impairment have been reported in

systemic levels of leptin or its receptors on components of the metabolic syndrome in healthy and sick populations (8-26). A significant increase has been reported in its serum levels in the presence of obesity and metabolic syndrome (11). Adipose tissue is the major site of leptin secretion, so plasma or serum leptin concentrations strongly correlated with body fat mass, and its decrease in response to a decrease in body fat percentage has been frequently reported (9). In this regard, some studies have reported a simultaneous decrease of both leptin and triglyceride as well as blood glucose in response to aerobic training in obese or overweight people (16). In the present study, the decrease in serum leptin in response to aerobic training in men with metabolic syndrome was associated with a decrease in triglycerides and a simultaneous increase of HDL.

Genetic differences between leptin gene and leptin receptors have been found to correlate with changes in its concentration and activity, which strongly influence levels of lipid profile such as LDL, HDL, triglyceride, and blood glucose (10, 29). In vitro studies have indicated that leptin gene polymorphisms are capable of altering systemic levels of lipid profile and prevalence of metabolic syndrome (30, 27). Leptin receptor gene polymorphisms such as Gln 223 Arg have been found to provide the basis for the development of metabolic diseases by regulating leptin levels (31). Researchers believe that HDL-C and LDL-C levels and body fat mass are key components of the metabolic syndrome, and leptin receptor gene polymorphisms, by affecting them, provide the basis for the incidence of metabolic syndrome and other metabolic diseases (8). Researchers have noted that impairment in the levels of the components of metabolic syndrome determinants not only affects systemic leptin levels but also in most cases influences the leptin receptors. Despite elevated serum leptin or plasma levels in obese or metabolic syndrome individuals, increased leptin resistance at cellular levels associated with a decrease in insulin sensitivity and an increase in cardiovascular risk factors (8). On the other hand, regular exercise training, in addition to improving systemic leptin levels, affects leptin sensitivity. For example, in the study by Long et al. (2016), 12 weeks of voluntary running exercise associated with weight loss and increased leptin sensitivity in mice having a high-fat diet (32). These researchers reported that regular exercise training improves metabolic disorders by increasing the activity of the leptin signaling pathways in the hypothalamus (32).

In the present study, the exercise program correlated with a decrease in serum leptin levels and weight loss and body fat percentage. Based on the above evidence, the decrease in serum leptin of the study population can be attributed to a decrease in body fat mass. Other studies have also suggested weight loss and body fat percentage along with decreased leptin levels and improved HDL in response to exercise training (16, 17, 33, 34). However, some studies have reported no change in leptin and some diagnosis symptoms of the metabolic syndrome or components of the inflammatory profile in the presence of weight loss and body fat percentage due to diet or exercise training (17, 18). For example, in the study by Ohe et al. (2013), 6 months of changing lifestyle patterns in the form of exercise and diet did not correlate with changes in leptin and LDL in women with metabolic syndrome (35). Accordingly, some other factors appear to affect serum leptin levels, independent of body weight changes and body fat percentage, where hypothalamic leptin resistance is one of the major causes of increased blood leptin. In vitro studies have shown that leptin may control appetite, increase metabolism, and reduce adipose tissue through stimulating phosphatidylinositol 3 kinases (PI3K) in hypothalamic cells (36). Similar to insulin, researchers have reported an increase in the resistance of hypothalamic cells to the effects of leptin as one of the major factors of elevated blood leptin levels (37). It is noted that some studies have suggested a minimum 10% reduction in body weight as a prerequisite for improving cardiovascular risk factors and inflammatory components in obese individuals (38).

Conclusion

The findings of the present study emphasize the improvement of serum leptin in response to aerobic

training in these patients. Despite unchanged cholesterol and LDL levels, aerobic training is also associated with improved cardiovascular risk factors in these patients. Based on the findings of the present study and other available evidence, improvement of cardiovascular risk factors in response to aerobic training appears to be rooted in a decline in serum leptin. However, understanding the major cellular-molecular mechanisms responsible for these changes in response to exercise requires further studies.

Conflict of Interest

The authors declared no conflict of interest.

Acknowledgment

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Funding/Support

The authors declare that they have no conflict of interest.

Ethics

The Ethics Committee of Islamic Azad University approved this study (Ethics Code: 1397.348).

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