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The Effect of Aerobic Training on Serum Adiponectin and Leptin Levels and Inflammatory Markers of Coronary Heart Disease in Obese Men

Mohsen Akbarpour

Department of Physical Education, University of Qom, Qom, Iran

Abstract: The aim of this study was to investigate the effect of 12-week aerobic training on the serum Adiponectin and Leptin levels and inflammatory markers of coronary heart diseases in obese men. Sixteen non-athlete obese men were randomly classified in two experimental groups. The experimental group performed the aerobic training protocol three sessions per week for 12 weeks while the control group did not do the training program during the research performance. Five ml of venous blood was taken from the participants at the beginning of the period, in week six and at the end of week 12 in order to measure Leptin, Adiponectin, C-reactive protein, interlukin-6 and tumor necrosis factor-α. Findings showed that aerobic training led to the decrease of CRP[4] (p=0.002), IL-6 (p= 0.001) and Leptin (p= 0.003) and increase of Adiponectin (p= 0.002) in the experimental group compared with the control one. Furthermore, the level of TNF-α decreased in the experimental group after the 12-week aerobic training, which was not statically significant. According to the results of this study, it was determined that regular aerobic exercises decrease the potential risk of coronary heart diseases because of improving the levels of plasma IL-6, Adiponectin, Leptin and CRP. Also, they can be used as effective no pharmacologic treatment to prevent the diseases.

Key words: Aerobic training · Leptin · Adiponectin · Inflammatory markers · Coronary heart diseases · Obese men

INTRODUCTION

From the biological point of view, fat tissue is an active tissue and secretes proteins like TNF-α[1], IL-6 [2]¡IL-[3], Leptin and Adiponectin [1]. Clinical studies have shown that the Adiponectin gene expression and its serum concentration are lower among type 2 diabetes, coronary heart and blood pressure patients compared with healthy people and its concentration decreases in obese people, obese pigs and obese mice [2, 3]. On the other hand, Leptin increases by obesity in contrast to Adiponectin. Adiponectin plays an important role in overcoming insulin resistance caused by taking the diet. Studies on rodents have shown that Adiponectin decreases the level of blood glucose and prevents from fat accumulation in skeletal muscles [4-6]. In comparison with other secreted molecules from the fat cells, this protein has protective metabolism and anti-inflammatory properties and its level in human blood is in inverse ratio to the level of insulin resistance [7]. As far as Leptin is concerned, some scholars have considered it as a warning mechanism for adjusting the body's fat content [4, 8]. This hormone along with insulin affects coronary performance and the sympathetic nervous system [2, 9]. The increase of Leptin, which has been introduced as an independent factor for coronary heart diseases in many studies, comes with the poor performance of the vessel wall [9-11]. In addition to the relationship of obesity with Leptin and Adiponectin, inflammatory markers also cause changes in the body combination and endocrine glands[1, 12], in a way that some studies have reported the relationship between obesity and increase of TNF-α, IL-6 and CRP[4] inflammatory markers and the increased risk of Coronary Heart Disease [4, 13-17]. Therefore, any activity which can adjust the abnormal level of these materials in blood may lead to the prevention from coronary heart diseases.

[1]Tumor Necrosis Factor-α [2]Interlukine-6
[3]Interlukine-8 [4]C- reactive protein

Corresponding Author: M. Akbarpour, Department of Physical Education, University of Qom, Qom, Iran.
Tel: +989131839198.

Physical activities can be considered effective factors in improving obesity. However, there is contradictory information on the effect of physical activities on the level of Leptin, Adiponectin and inflammatory markers (CRP, IL-6 and TNF-α). In this regard, a number of researchers have shown that the concentration of plasma Leptin and Adiponectin is not influenced by physical activities to much extent in healthy people with natural [4, 11, 18-22]. Kobayashi *et al*. (2006) observed that 50 days of walking led to the improvement of the Adiponectin level in healthy men with normal weight [23] while Ellomi *et al*. (2009) observed that two months of an aerobic training program with middle intensity increased Adiponectin and decreased Leptin in obese adolescent boys [24].

Also, it has been determined that regular physical activities and training decrease inflammatory markers and decrease the risk of coronary heart diseases [16]. The results of the studies conducted in this field have shown that doing regular exercises significantly decreases TNF-α, IL-6, IL-1β and CRP [13-15, 25-27] and there is a relationship between higher levels of physical activities and physical fitness and lower levels of these inflammatory markers [28]. At the same time, some scholars like Fairey (2005) and Arsenaulet (2009) reported the lack of change of inflammatory markers during the long term aerobic training [29, 30].

However, because of contradictory results on the effect of aerobic activities on the serum Adiponectin and Leptin levels and inflammatory markers and the existence of differences in the preparation level, gender, age and training program of participants and also lack of studies which have investigated the effect of long term aerobic training on the serum Adiponectin and Leptin levels and inflammatory markers in obese men and lack of convincing evidence based on the effect of long term exercises on the performance of Adiponectin and Leptin levels and inflammatory markers, the present study attempted to examine the effect of 12-week selected aerobic training on the serum Adiponectin and Leptin levels and inflammatory markers (CRP, IL-6 and TNF-α) in obese men.

MATERIALS AND METHODS

Participants: After the call for research at Mobarakeh Islamic Azad University, the obese, male, non-athlete students who volunteered to participate in this study received and filled out a questionnaire which included personal characteristics, health, smoking and physical training history. Then, their height and weight were measured and their body mass index (BMI) was calculated by placing the numbers related to weight and height in the equation (weight in kg was divided by the squared height in m). From among 167 volunteers who were qualified for this research, 40 people were chosen using random sampling with replacement. The participants were non-athlete and their age ranged from 20 to 25 years old. Their BMI was between 30 and 33 kg/m^2. Also, they had no smoking and allergy history and took no medicine since at least 2 weeks before the research and during the research period and followed their own normal diet. They first filled out and signed the consent form. Then, they were allocated to 2 groups of experimental and control with 30 people in each and using simple random sampling. The participants' general characteristics are given in Table 1.

Physiological Measurements: To measure weight and height, a digital scale and a tape were used, respectively. BMI was also calculated by placing the numbers related to height and weight in the equation (squared height in m / weight in km) and body fat percentage was computed by measuring subcutaneous fat in three areas of chest, abdomen and thigh and placing it in Jackson and Pollock Equation (Williams, 2002) [31].

Table 1: Participants' general characteristics (mean± standard deviation)

Group ----------				
Variable	Experimental training group (N=30)	Control group (N=30)	F	P
Age (year)	23.2±2.5	22.7±2.7	6.325	0.684
Weight (kg)	86.94±5.8	88.76±7.51	7.623	0.892
Height (cm)	170.13±4.45	172.03±6.47	6.146	0.712
VO_{2max}(ml.kg/min)	36.14±2.43	35.96±1.78	1.697	0.541
BMI	30.05±2.26	30.60±2.45	2.06	0.522
Body fat %	23.89±2.73	24.58±2.61	3.52	0.683

To estimate aerobic power of subjects, we conducted a Walking and runing 2400 meter test. Aerobic power of subjects was calculated using the following equation [31]:

$$VO2max\ (mL \bullet kg\text{-}1 \bullet min\text{-}1) = 88.02 - 0.1656 \times (weight_{(kg)}) + 2.76 \times (time_{(min)}) + 3.716 \times 1$$

The Training Program: First, the maximum heart rate was measured for each person using the following formula: 208-(0.7 * age)[32].

In this research, the experimental group performed a 12-week aerobic training program (per week 3 sessions). The aerobic training program included a 10-min warm-up by fast walking, slow running and stretching. Then, continuous running was done with the intensity between 75 and 85 percent of the maximum heart rate of the participants. The running period was 15 min in the first session and, every two sessions, 1.5 min was added to the running period in a stepwise way so that the running period reached 30 min. After that, this period was kept until the last session of the training program (the end of the 12th week). Exercise intensity was controlled using a belt heart rate sensor (polar beat) and, at the end of each session, a cool-down was performed by slow running and stretching for 10 min.

Blood Sampling: To investigate biochemical variables, in the first stage, the participants of each group were required not to do any sport activities until two days before the test and to maintain their normal diet. Then, 5 ml blood was sampled from the participants after 12 h of fasting which was taken from their left-hand antecubital vein while sitting and resting. The blood sampling was conducted for the experimental and control groups at 8 a.m. After this stage, the experimental group performed the aerobic training program for 12 weeks(per week 3 sessions). Also, after 6 and 12 weeks of aerobic training and after 48 h of the last training session and 12 h of fasting, the second and third stages of blood sampling from the participants of the control and experimental groups were done similar to the first stage.

The subjects in the control group did not do any training program and proceeded with their normal daily routine. All protocols were approved by the Graduate Council of faculty of Physical Education and Sports Science, Islamic Azad University Mobarakeh branch.

Biochemical Measurements: To measure inflammatory markers (serum TNF-α, CRP and IL-6), Elisa method was applied using the kits from the French Diaclone Company in the order of sensitivity degrees less than 7, 2 and 8 pg/mL.

The measurement of plasma Adiponectin concentration was done using the Elisa method and Adipogen Adiponectin kit made in South Korea (Adipogen.co-south Korea) with the sensitivity of 0.1 ìg/ml. The outside of test coefficient of variation was less than 3.9% in this kit and its inside of test coefficient of variation was less than 8.6%. The concentration of plasma Leptin was measured by the Elisa method and using Leptin kit (Mediagnost, Reuttlinger, Germany) with the sensitivity of 0.1 ng/ml and its inside of test coefficient of variation was less than 5%.

Also, the receiving diet during the research was controlled using the 24-h food recall questionnaire standardized by the Nutrition Group, Tehran University of Medical Sciences (in week 0, week 6 and week 12).

Statistical Analysis: Statistical analysis of data was calculated for each group using means and standard deviation. Then Kolmogorov-Smirnov test was used to ensure normal distribution of data. The student's t test was used to evaluate between-group analysis of variance with repeated measure. ANOVA[3] for within-group evaluation according to the corrective procedure Green house-Giser (GG) were used. The T-test with Bonferony amendment was used to analyze significant differences observed by determining the difference location to reduce error paired samples. The significant level was P=0/05 for all the calculations and all the statistical tests were conducted using SPSS software ((version 13, Michigan, USA).

RESULTS

The results obtained from the current research showed that 6 and 12 weeks of aerobic training increase VO_{2max} (p=0.0001), decrease body fat percentage (p=0.001) and decrease body mass index (p=0.001) compared with the control group. Moreover, after 6 weeks of training, levels of serum Leptin (0.19), CRP (p=0.27) and IL-6 (p= 0.36) decreased in the control group and level of plasma Adiponectin (P=0.31) increased which was not statistically significant. However, after 12 weeks of training, the levels of serum Leptin (P=0.012), CRP (p=0.002) and IL-6 (P= 0.001) significantly decreased in the control group; the level of plasma Adiponectin (p= 0.002) significantly increased compared with the pre test stage

Table 2: Changes of mean and standard deviation of inflammatory markers in training and control groups in different stages of the test

Variable	Groups	Pre test (week 0)	Mid test (week 6)	Post test (week 12)
Vo_{2max}(ml.kg/min)	Experimental group	35.83±2.3	37.93±1.15 † ‡	39.9±1.8 † ‡
	Control	36.84±1.7	35.84±2.1	36.03±1.8
Body Fat %	Experimental group	23.74±2.85	21.18±1.49 † ‡	19.78±1.5 † ‡
	Control group	24.36±2.04	23.83±1.8	23.99±2.2
CRP(pg/ml)	Experimental group	1.70±0.43	1.43±0.4	1.06±0.46 † ‡
	Control	1.68±0.51	1.72±0.45	1.65±0.42
TNF-α (pg/ml)	Experimental group	13.32±3.28	12.94±3.11	10.16±3.25
	Control group	13.07±2.82	13.57±2.67	12.80±2.95
IL-6 (pg/ml)	Experimental group	7.42±3.21	5.26±3.45	1.93±0.69 † ‡
	Control group	8.01±3.86	8.62±4.07	8.23±3.34
Adiponectin (µg/ml)	Experimental group	16.75±1.48	17.44±1.78	18.43±1.65 † ‡
	Control group	16.52±1.33	16.47±1.49	16.53±1.51
Leptin (ng/ml)	Experimental group	2.34±0.27	2.30±0.25	2.25±0.22 † ‡
	Control group	2.32±0.20	2.34±0.24	2.31±0.21

† denotes significance in the pre test (p<0/05)

‡ denotes significance between the experimental and control groups (p<0/05)

(before doing the exercises) while the level of serum Leptin, Adiponectin, CRP and IL-6 in the experimental group did not demonstrate a significant difference between mid test (week 6) and post test (week 12) {CRP (p= 0.091) and IL-6 (P= 0.065), Leptin (P= 0.062) and Adiponectin (P= 0.071)} (Table 2). Furthermore, no within group differences were observed in the stages of the control group (P>0.05).

The results of the independent t test showed a significant difference in the levels of serum Leptin, Adiponectin, CRP and IL-6 of the experimental group compared with those in the control group after 12 weeks of aerobic training in a way that, in the experimental group, the levels of serum Leptin, CRP and IL-6 were 36.76%, 76.55% and 2.6% less than those of the control group and the level of Adiponectin was 11.49% more than that in the control group {CRP (P= 0.002) and IL-6 (P= 0.001), Leptin (P= 0.003) and Adiponectin (P= 0.001)}. In the pre test stage (week 0) and mid test stage (week 6), no significant difference was observed in the levels of research variables between control and experimental groups (P>0.05).

As far as TNF-α is concerned, the results of the analysis of variance with repeated measurement did not show any significant differences within the groups in the control and experimental groups. Although its level decreased in the experimental group after 6 and 12 weeks of training, it was not significant. Furthermore, the results of the independent t test did not show a significant between group difference between control and experimental groups in three test stages (P>0.05).

DISCUSSION

In this research, the focus was on the created compatibilities in the amount of Adiponectin and Leptin hormones and coronary heart inflammatory markers (serum TNF-α, CRP and IL-6 and) via doing exercises. Appropriate levels of these factors in the blood can prevent from diseases like metabolic syndrome, type 2 diabetes and coronary heart diseases. To this end, the levels of Leptin, Adiponectin and coronary heart inflammatory markers (serum TNF-α, CRP and IL-6) were measured before and after performing the training protocol.

The results of the present research showed that 6 and 12 weeks of aerobic training with medium intensity in obese men can increase VO_{2max}, decrease body fat percentage and body mass index in the experimental group. Also, the results showed the decrease of CRP and IL-6 inflammatory markers and decrease of plasma Leptin as a consequence of 12 weeks of aerobic training with medium intensity in obese men so that, after 12 weeks of aerobic training, the difference in the level of plasma Leptin, CRP and IL-6 in the experimental group significantly decreased compared with those in the control group. Also, the significant difference of these factors was observed in the experimental group from the pre test to the post test stages; in the first 6 weeks of aerobic training in the experimental group, the change level of plasma Leptin, CRP and IL-6 inflammatory factors was not noticeable, which probably showed the effectiveness of training period, training intensity and

duration on these factors. As the length of training period increased, significant decrease occurred in the level of plasma Leptin, CRP and IL-6 in the experimental group after 12 weeks. These results were in line with the reports of Miyatake (2004), Fatouros (2005), Kohut (2006), Kadoglou (2007), Eriksson (2008), Walther (2008), Nicklas (2008), Campbell (2009), Elloumi (2009) and Christiansen (2010), which were based on the decrease of Plasma Leptin, CRP and IL-6 as a result of doing aerobic training [13-15, 25-27, 33-35]. However, the findings of this research were different from those of Fairey (2005), Ara (2006) and Arsenault (2009) [29, 30, 36]. This contrast can be attributed to the differences of the studied groups in terms of race, training period, intensity, duration and type of training [28].

The present research demonstrated the significant increase of plasma Adiponectin due to 12 weeks of aerobic training in the experimental group compared with the control one. Moreover, a significant difference was observed in the plasma Adiponectin of the experimental group from the pre test to post test stages while this increase was not significant in the first 6 weeks of the training program from the pre test to the mid test. Increase of Adiponectin as a result of 12 weeks of aerobic training was probably a preventive factor for the diseases related to Adiponectin [4, 18]. In this research, the increase of Adiponectin hormone after being adjusted to the aerobic activity was similar to a number of previous studies[4, 18, 24, 34]. In a study, eight young obese women had a significant decrease in the level of Leptin hormone and fat after performing an aerobic training program for seven weeks; moreover, their level of Adiponectin increased [37] and, in another study, after obese and insulin-resistant people performed 19 weeks of aerobic training along with diet, their visceral fat decreased and the level of Adiponectin increased [38]. Other studies found no results for the effect of training on the level of Adiponectin, which may be because of the difference in age, gender and type of training program and intensity and duration of training [39, 40].

As far as TNF-α is concerned, the results obtained from this study showed no significant within group differences in the level of serum TNF-α while, in the experimental group, TNF-α showed 2.86% and 23.76% decrease after 6 and 12 weeks of aerobic training, respectively. These results were in line with the findings of Fairey (2005) and Arsenault (2009) [29, 30].

Therefore, the results obtained from this study showed a significant decrease in the level of CRP (p= 0.002), IL-6 (P= 0.001) and Leptin (P= 0.012) and an increase in the level of Adiponectin (P= 0.002) after 12 weeks of aerobic training while it was not significant as far as TNF-α was concerned.

Various studies have shown that Adiponectin and Leptin hormones and inflammatory mechanisms have key roles in pathological processes of several chronic diseases like coronary heart diseases, cancer, type 2 diabetes and chronic obstructive pulmonary disease. It seems that chronic low-grade inflammation is determined by the high level of CRP, IL-6, TNF-α and Leptin [4, 16, 28] and, with regard to the relationship between physical activity and lower levels of inflammation, protective mechanisms of heart can be suggested. A common concept about the pathophysiologic mechanisms of inflammation associated with atherosclerosis is the production of cytokines along with inflammation in response to the oxidized LDL stimulation and macrophages along with atherosclerotic plaque[28]. The cytokines associated with inflammation which are produced during this process include IL-1B, IL-6 and TNF-α. It was determined in laboratory experiments that different combinations of cytokines stimulate the production of CRP and Leukocytosis[41]. Research has shown that regular sport activities decrease oxidized LDL and serum levels of IL-6 and CRP [28, 29]. Therefore, the effect of regular exercise on the levels of IL-6 can be responsible for decreasing CRP in the experimental groups. On the other hand, the relationship between physical activity and lower levels of inflammation can be created through the relationship between endurance training and lower degrees of general and abdominal obesity. It has been determined that obese people produce higher levels of Leptin and mediators of inflammation including TNF-α, IL-8 and IL-6 compared with thin people in the control group while obese people have lower levels of Adiponectin compared with thin people [2, 3, 29]. Endurance training can decrease the production of mediators of inflammation from fat tissues by directly affecting the fat tissues and increasing dipoles (by increasing the activity of hormone-sensitive lipase) and increase the production of anti-inflammatory mediators like IL-10 from the fat tissues [5]. The result of these changes is that aerobic training can decrease the circulating level of inflammatory markers (CRP) by decreasing sources of inflammation. Moreover, fat tissues are considered an endocrine organ because of secreting different materials like TNF-α, IL-6, Leptin and Adiponectin [1]. It is likely that TNF-α stimulates the production of IL-6 which, as a powerful stimulator, leads to the production of liver CRP [5, 15]. Therefore, the high

level of fat tissues in obese people leads to the increase in the level of serum CRP (in a cascade way). In addition, TNF-α is one of the main and most basic mediators of inflammatory processes which refers to the high level in fat tissues (especially, visceral fat) and its levels in circulation indicates the production of this factor in the fat tissues [16]. There are different findings on the effect of exercises on the level of TNF-α; some have reported its decrease [5] and some others have shown its lack of change [29] in response to physical training. In the present research, it was determined that the serum level of TNF-α did not change in response to 12 weeks of aerobic training because the half-life of TNF-α was low in blood [42]. Therefore, according to these findings, TNF-α cannot be considered a stable marker for the inflammation situation. Thus, CRP can be used for indicating the status of systemic inflammation [43]. CRP is an inflammatory indicator which is made by liver cells in response to inflammatory factors and is secreted from the liver [5, 15]. So, the present study is in line with the investigations which show a negative correlation between physical fitness and chronic inflammation and demonstrate that physical training leads to decreasing inflammation status of CRP and IL-6 [30]. Therefore, a relationship can be found between the increase of inflammatory markers as a result of obesity and atherosclerosis [5].

Furthermore, lower levels of inflammation caused by compatibility with physical activities can be attributed to the anti-oxidation effects of physical activities. Although the level of anti-oxidants was not measured in the present research, research evidence has shown that aerobic training noticeably decreases oxidation stress by increasing the anti-oxidant capacity of the body [44]. Regular physical training inhibits the release of inflammatory mediators of IL-1β, IL-6 and TNF-α from fat tissues by decreasing the stimulation of the sympathetic system and increasing anti-inflammatory cytokines; as a result, the concentration of cell adhesive molecules decreases [44, 45].

Also, many scholars believe that the increase of Adiponectin concentration and decrease of plasma Leptin after long term physical activities are because of the decrease in weight and body fat and improvement of body combination as a result of disturbing the balance between the received and consumed energy [23, 46]. Many studies have investigated the relationship between body combination and levels of plasma Leptin and Adiponectin and most of the findings have demonstrated a negative relationship between weight, body mass index, waist size, fat distribution (waist to hip ratio) and fat mass on the one hand and Adiponectin on the other and the positive relationship of these factors with Leptin [2, 4].

Finally, it seems that the amount of training can be an effective factor on the response of plasma inflammatory markers, Leptin and Adiponectin (CRP, IL-6 and TNF-α); in other words, long term physical activities affect the concentration of the response of plasma inflammatory markers, Leptin and Adiponectin (CRP, IL-6 and TNF-α) [19].

Therefore, considering the findings of this research, it was shown that regular and long term aerobic physical training lead to the significant decrease of CRP, IL-6 and Leptin and increase of Adiponectin as new indicators which predict cardiovascular events and, finally, decrease of general inflammation of body.

CONCLUSION

In sum, it can be inferred that regular aerobic training decreases the potential risk of coronary heart diseases by improving the amount of plasma IL-6, Adiponectin, Leptin and CRP and it can be used as an effective nonpharmacologic treatment for preventing these diseases.

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