



# Improved Glucose and IL-6 by Aerobic Training Despite no Change in Insulin and Insulin Resistance in Obese Women

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## Abstract

**Background:** Regular physical activity is recognized as a non-pharmacological treatment of inflammation and glycemic profile.

**Objectives:** This exercise aimed to determine the effect of aerobic training on serum interleukin-6 (IL-6), glucose and insulin resistance in obese females.

**Patients and Methods:** Thirty-two middle-aged obese women (body mass index [BMI],  $32 \pm 3$  kg/m<sup>2</sup>) aged 35 to 45 years were randomly assigned to exercise (aerobic training, n=16) and control (n=16) groups. Exercise subjects were completed a 12 weeks aerobic training program as 3 sessions per week at 60%-80% of HRmax and control subjects received no training. Pre- and post-training of fasting serum IL-6, insulin, insulin resistance, and glucose concentration were measured and compared between 2 groups. Results were compared using t test at a significance level of  $P < 0.05$ .

**Results:** Exercise group obtained significant decreases in BMI, body fat %, and abdominal obesity as well as the concentrations of serum IL-6 and fasting glucose ( $P < 0.05$ ). No significant difference was observed between pre- and post-training of insulin and insulin resistance in the exercise group ( $P > 0.05$ ). There were no alterations in these variables in the control group ( $P > 0.05$ ).

**Conclusions:** These data suggest that aerobic training may improve glycemic profile in absence of change in insulin resistance of women with abdominal obesity.

**Keywords:** Exercise, Glucose, Inflammation, Insulin resistance, Obesity

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## Background

A sedentary lifestyle has been reported to be among the foremost environmental factors leading to obesity and metabolic syndrome. On the other hand, obesity is associated with diseases such as hyperglycemia, hypertension, and hyperlipidemia as well as the emergence of atherosclerosis and cardiovascular diseases (1,2). In addition to the role of heredity and genetics, numerous hormonal factors are influential in homeostasis and energy balance as well as carbohydrate and fat metabolisms. Research evidence suggests that adipocytes secrete various peptide or protein mediators such as inflammatory cytokines. The systemic levels and the expression of receptors of such mediators are altered in the presence of obesity and overweight (3). Cytokines are inflammatory mediators, which are produced by mononuclear blood cells, adipocytes, hepatocytes, and skeletal muscles (4) and their basic levels have been reported to be different in obese or overweight people in comparison with people with normal weight (5). Clinical studies in adults have

demonstrated that chronic inflammation is effective in the pathogenesis of diseases such as atherosclerosis (6), type 1 and 2 diabetes (7), cancer (8), some neurological diseases (9), and the immune system diseases (10).

Among inflammatory cytokines, interleukin 6 (IL-6) is from cytokines secreted by adipose tissue and some other tissues that have both inflammatory and non-inflammatory role (11). The exact location or source of IL-6 secretion is not yet fully understood, although this cytokine may have been derived from reserves of adipose tissue or peripheral blood mononuclear cells (4). The role it plays has been identified in both innate and adaptive immunity. Scientific resources have noted increased gluconeogenesis and thus, increased blood glucose (hypoglycemia) and ultimately, increased blood insulin (hyperinsulinemia) in response to an injection of IL-6 (12). Similar metabolic responses have been observed in humans after subcutaneous injection of IL-6 (13). Based on this evidence, the researchers believe that IL-6 increases the insulin-dependent glucose transport (14)

and or glycogen synthesis in adipocytes (15), although some other studies have focused on the lack of its impact on glucose or insulin (16).

Hence, the establishment of environmental solutions such as changing dietary behaviors is among the primary goals of health researchers in order to maintain the balance of inflammatory mediators. Since systemic levels of these cytokines are disturbed by a sedentary lifestyle and overweight people are often inactive and have sedentary lifestyles. It seems that doing short or long-term physical activities and the weight loss resulting from such activities is to some extent associated with improvements in the levels of these cytokines and their associated diseases. In this regard, some previous studies have suggested that muscle contractions resulting from long-term aerobic or resistance exercises are associated with the improved inflammatory profile, while diet-induced weight loss does not bear such consequences (4). The findings of another study exhibited that physical activity, even in the absence of weight loss, leads to the significant reduction of resistin and other inflammatory cytokines such as IL-6 (17). However, in another study on obese subjects, despite the significant loss of body weight during 12 weeks of exercises, no significant change in serum levels of IL-6 was observed (18). On the other hand, another scientific resource reported that regular exercises in the form of 5 times per week for 8 weeks caused significantly increased IL-6 in diabetic and non-diabetic mice (19). Reviewing research evidence reveals the lack of consensus on the IL-6 response to different short and long-term exercise training. Inconsistency in the findings can be attributed to differences in age, gender, weight loss, and body fat mass, type, intensity of exercises, and duration of exercise, and some other related factors.

### Objectives

This study aims to examine the effects of a 12-week aerobic training program on serum levels of IL-6 as well as glucose and insulin resistance in sedentary overweight women.

### Patients and Methods

#### Subjects

Participants of this semi-experimental study included 32 middle-aged obese women (body mass index [BMI],  $32 \pm 3 \text{ kg/m}^2$ ) aged 35 to 45 years. The study protocol was approved by the institutional ethics committee (Ethical code: 31547) of Islamic Azad University, Iran. Each participant received written and verbal explanations about the nature of the study before signing an informed consent form.

#### Exclusion and Inclusion Criteria

Inclusion criteria for the test group were: healthy, middle age, obesity (BMI  $\geq 30$ ). Participants were included if they had not been involved in regular physical activity/diet in the previous 6 months. None of the subjects used drugs or therapies for obesity, and none had a past history of disease or injury that would prevent daily exercise. Potential participants were excluded from the study if they reported smoking, had a history of heart disease, stroke, diabetes, or were taking glucose-lowering medication.

#### Anthropometric Measures

All anthropometric measurements were made by the same-trained general physician and under the supervision of the same pediatrician following standard protocols. Weight was measured to the nearest 100 g using digital scales (Salter, Tonbridge, United Kingdom). Obesity was measured by BMI. The BMI was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured after a normal expiration under the midline of the subject's armpit, at the midpoint between the lower part of the last rib and the top of the hip. Hip girth was measured at the level of the greatest protrusion of the gluteal muscles with underwear. Abdominal to hip circumference ratio was measured by dividing the abdominal circumference into that of the hip. Percentage of body fat was estimated by bioelectrical impedance method (Omron Body Fat Analyzer, Finland).

#### Training Protocol

The intervention lasted a 12-week aerobic training program, 3 sessions per week, consisting of a warm-up then a 45–60-minute treadmill exercise at a work intensity of 60%–80% of max heart rate followed by a cooling-down period. Heart rate in each session was controlled by polar telemetry. The main exercise in each session was running at the mentioned intensity. The heart rate, used to calculate the intensity of exercise, was determined by counting heart beats by polar telemetry. The exercise intensity at first week was 60% of max heart rate that gradually increased at last sessions of exercise program. Control subjects were instructed to maintain their habitual activities. Participants were instructed to maintain their usual diet throughout the duration of the study.

#### Laboratory and Clinical Measurements

A venous blood sample was collected from all the subjects who came after a 12-hour overnight fast between the hours of 8 to 9 AM (pre-training). Subjects were asked to avoid doing any heavy physical activity for 48 hours before blood sampling. After the last training bout, subjects rested for 48 hours, and then fasting blood samples were

taken similar to pretest (post-training). After each blood sampling, serums were immediately separated and stored at  $-80^{\circ}$  until the assays were performed. Serums were used to measure IL-6, insulin and glucose concentration. IL-6 concentration was determined by enzyme-linked immunosorbent assay kit (Biovendor Company, Czech) according to the manufacturer's instruction. Intra- and inter-assay coefficients of variation were 3.4 and 5.2%, respectively. Glucose was determined by the oxidase method (Pars Azmoon kit, Tehran). Insulin was determined by ELISA method (Demeditec, Germany) and the intra-assay and inter-assay coefficient of variation of the method were 2.6% and 2.88 respectively. Insulin resistance was determined according to the HOMA-IR as the product of fasting plasma glucose (mM) and insulin ( $\mu\text{U/mL}$ ) divided by the constant 22.5 (20).

### Data Analysis

All statistical analyses were performed by using a statistical software package (SPSS, version 15.0, SPSS Inc., IL, USA). Normal distribution of data was analyzed by the Kolmogorov-Smirnov normality test. Independent student *t*-test was used for comparison of variables between 2 groups at baseline. Paired *t*-test was used to determine the mean differences between pre- and post-training values of all clinical and anthropometric variables of each group. A *P* value of less than 0.05 was considered as statistically significant.

### Results

Anthropometric characteristics of the study participants are described in Table 1. Data are expressed as mean  $\pm$  standard deviation (SD). No significant differences

were found in body weight, BMI, body fat percentage, abdominal obesity, and other anthropometrical markers between 2 groups at baseline.

Descriptive anthropometric characteristics at pre- and post-training of studied subjects are shown in Table 2. Aerobic training resulted in significant decrease in body weight and other anthropometrical markers in the exercise group ( $P < 0.05$ ), but all these variables remained without change in the control group ( $P > 0.05$ ) (Table 2).

Pre- and post-training serum IL-6 and other independent variables are shown in Table 3. No baseline differences were found between groups for IL-6 ( $P = 0.363$ ), glucose ( $P = 0.512$ ), insulin ( $P = 0.328$ ), and insulin resistance ( $P = 0.519$ ).

The main objective of present study was to determine IL-6 response to aerobic intervention in studied obese women. Data by paired *t*-test showed a significant decrease in serum IL-6 in exercise group but not in control subjects. Compared to pre-training, fasting glucose concentration was also decreased by aerobic training in exercise subjects but not in control subjects. Despite a significant decrease in serum IL-6 and glucose, no significant alterations were observed in serum insulin and insulin resistance by aerobic intervention in the exercise group. All variables remained without change in the control group (Table 3).

### Discussion

Higher levels of inflammatory cytokines or adipokines for increased levels of adipose tissue point to the fact that excess adipose tissue plays a central role in metabolic syndrome and insulin resistance (7,21). In addition, sedentary lifestyle and lack of exercise training have been identified as risk factors for a wide range of obesity-related

**Table 1.** Mean and Standard Deviation of Anthropometrical Indices of 2 Groups at Baseline

Group	Age (y)	Height (cm)	Weight (kg)	AC (cm)	HC (cm)	BMI ( $\text{kg/m}^2$ )	BF (%)	Visceral Fat
Exercise	38.4 $\pm$ 7.65	162 $\pm$ 4.86	83 $\pm$ 8.45	107 $\pm$ 7.4	104 $\pm$ 11	32.1 $\pm$ 2.76	44.7 $\pm$ 4.55	8.2 $\pm$ 1.07
Control	37.3 $\pm$ 2.39	161 $\pm$ 4.66	83.7 $\pm$ 4.81	108 $\pm$ 8	105 $\pm$ 10	31.73 $\pm$ 1.58	31.73 $\pm$ 1.58	8.3 $\pm$ 1.14
<i>P</i> value	0.423	0.521	0.411	0.635	0.652	0.238	0.513	0.611

Abbreviations: AC, abdominal circumference; HC, hip circumference; BMI, body mass index, BF, body fat percentage.

**Table 2.** Pre- and Post-training of Anthropometric Characteristics of Studied

Variables	Exercise Group			Control Group		
	Pre-training	Post-training	<i>P</i>	Pre-training	Post-training	<i>P</i>
Weight (kg)	83 $\pm$ 8.45	81 $\pm$ 8.46	0.011	83.7 $\pm$ 4.81	83.6 $\pm$ 4.71	0.221
AC (cm)	107 $\pm$ 7.4	103 $\pm$ 8	0.029	108 $\pm$ 8	108 $\pm$ 7	0.323
HC (cm)	104 $\pm$ 11	101 $\pm$ 9	0.031	105 $\pm$ 10	106 $\pm$ 11	0.412
BMI ( $\text{kg/m}^2$ )	32.1 $\pm$ 2.76	31.6 $\pm$ 2.80	0.017	31.73 $\pm$ 1.58	31.71 $\pm$ 1.57	0.325
BF (%)	44.7 $\pm$ 4.55	43 $\pm$ 4.54	0.023	44.1 $\pm$ 2.95	43.3 $\pm$ 2.57	0.632
Visceral fat	8.2 $\pm$ 1.07	7.5 $\pm$ 1.25	0.009	8.3 $\pm$ 1.14	8.3 $\pm$ 1.63	0.531

Data are shown as mean  $\pm$  SD.

Abbreviations: AC, abdominal circumference; HC, hip circumference; BMI, body mass index, BF, body fat percentage.

**Table 3.** Pre and Post-training of Clinical Markers of Studied Groups

Variables	Exercise Group			Control Group		
	Pre-training	Post-training	P	Pre-training	Post-training	P
Interleukin-6 (pg/mL)	6 ± 1.49	5.1 ± 1.28	0.011	5.9 ± 1.40	6 ± 0.86	0.367
Glucose (mg/dL)	94 ± 8.9	80 ± 6.4	0.004	97 ± 8.7	97 ± 7.6	0.346
Insulin (µU/mL)	6.2 ± 4.8	5.7 ± 1.75	0.218	6.1 ± 3.16	6.2 ± 2.25	0.374
Insulin resistance (HOMA-IR)	1.43 ± 1.11	1.16 ± 0.37	0.119	1.46 ± 0.74	1.48 ± 0.54	0.241

Data are shown as mean ± SD.

chronic diseases, especially cardiovascular diseases (22). The training program is introduced as a factor to modify obesity risk and is regarded as an effective treatment method to improve inflammation. In the present study, continuous aerobic training for 12 weeks significantly reduced the serum levels of IL-6 in obese female adults who had a sedentary lifestyle. In the present study, decreased serum IL-6 was accompanied with improved fasting glucose. Activated insulin signaling pathway inhibitors which are induced by IL-6 and other cytokines and secreted by adipose tissue, increase insulin resistance particularly in healthy or sick obese populations. These factors gradually damage the insulin signaling pathways in insulin receptors and insulin receptor substrate levels (23). Similar processes may also occur in the pancreas because they contain low levels of macrophages. Thus, it seems that the decline of IL-6 levels in response to aerobic training of obese women has an effect on the reduced fasting glucose since both fasting glucose and IL-6 levels significantly reduced after 12 weeks of aerobic training in obese women. However, according to the fact that the index of insulin resistance showed no significant changes, it seems likely that changes in the IL-6 levels via independent pathways to insulin resistance have led to a decrease in blood glucose.

Some scientific resources have noted that the release of IL-6 increasingly rises in response to acute exercise and the extent of such increase is relevant to the intensity and duration of the exercise test, involved muscle mass, and aerobic capacity. Researchers believe that active skeletal muscles contractions are a major source of circulating IL-6 levels in response to acute exercise as its levels increase up to 60 times during heavy endurance exercises such as marathons (24).

It should be noted that the anti-inflammatory effect of acute exercise on IL-6 is different from chronic/long-term exercise training. In this regard, it was suggested that the increase of IL-6 production in skeletal muscles after intense exercises plays a protective or anti-inflammatory role (25). So that, increased IL-6 in response to intense acute exercise leads to an increased synthesis and release of IL-10 and IL-1ra as 2 anti-inflammatory cytokines as well as inhibiting the release of tumor necrosis factor alpha (TNF- $\alpha$ ) (25). Hence, one of the anti-inflammatory

effects of acute exercise can be attributed to the reduced TNF- $\alpha$  synthesis leading to insulin resistance reduction resulted from TNF- $\alpha$  (25). However, in response to long-term exercise training, baseline and post-training levels of IL-6 decrease by mechanisms such as increased glycogen storage, improved anti-oxidative capacity, and improved insulin sensitivity. Reduced circulating IL-6 levels ultimately lead to decreased circulation C-reactive protein (CRP), supporting anti-inflammatory property of long-term exercise training (25). Furthermore, in contrast to intense acute exercise, chronic/long-term exercise training may reduce basal IL-6 production. Accordingly, a decreased IL-6 concentration at rest appears to characterize normal training adaptation, suggesting anti-inflammatory effects of chronic exercise training (26).

However, it should be pointed out that the IL-6 response to long-term exercises varies depending on the type and intensity of exercise, duration of exercise, and studied populations. Despite the available evidence, there is no consensus on the response of IL-6 or other anti-inflammatory/inflammatory markers to exercises since the main mechanisms responsible for the cytokine response to exercise are still not fully recognized. In addition, non-significant reduction in the inflammatory cytokines was observed in a study containing an exercise intervention for 20 weeks on a large group of young and middle-aged, black and white, sedentary, and healthy men and women (27).

In another study, 6 months regular exercise led to no change in the IL-6, TNF- $\alpha$  and CRP levels of post-menopause obese women (28). Researchers in some studies have differently reported the responses of various cytokines to a specific exercise program. For example, in a recent study, 12 weeks of aerobic or resistance training led to a significant reduction in IL-6 and TNF- $\alpha$  of obese middle-aged men, but their serum CRP levels did not significantly change (29). In other words, 24 weeks of combined aerobic-resistance training with moderate to severe intensity, despite no weight change and diet control, led to significant reduction of inflammatory factors associated with obesity and improved insulin resistance of obese middle-aged men (30).

Confirming the impact of weight loss or body fat percentage on the inflammatory profile, especially in obese

people (31,32), the findings of the present study showed that regular aerobic training for 12 weeks significantly reduced the inflammatory cytokines of obese women. Therefore, the significant reduction of IL-6 serum after 12 weeks aerobic training may be attributed to changes in weight and body fat percentage compared to pre-exercise levels. In this regard, some researchers have supported the direct relationship between the environment and the vertical thickness of the abdomen and the IL-6 levels (33). In the same vein, relatively moderate-intensity aerobic training for 8 weeks significantly reduced IL-6 and some other inflammatory cytokines of a group of young obese people (34). In another study, 10 weeks of aerobic training led to significant reductions of IL-6 and TNF- $\alpha$  in obese females with Down syndrome (35).

### Conclusion

Long-term aerobic training for 12 weeks is associated with a significant reduction in serum IL-6 of obese females. Based on the findings of this study, IL-6 response to aerobic training is independent of changes in insulin resistance. Hence, the possible effect of IL-6 on blood glucose is likely independent of insulin resistance in obese females.

### Authors' Contributions

ME: Study concept and design, drafting of the manuscript. MTG: Study concept and design, drafting of the manuscript. ZM: Administrative, technical, and material support. AA: Administrative, technical, and material support.

### Conflict of Interest Disclosures

The authors declare no potential conflicts of interest relevant to this article.

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