



## **Aerobic exercise program is associated with decreased serum leptin in asthma patients**

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### **Abstract**

Recently, it has been hypothesized that obesity and increased Body mass index (BMI) is associated with asthma prevalence and cytokines secreted by adipose tissue affects the relationship between them. The objective of this study was to evaluate serum leptin in response to aerobic exercise program in adult asthma patients. For this purpose, thirty two adult obese men with asthma disease divided to experimental and control group by randomly. Measurements of anthropometry, spirometry test and fasting blood sampling in order to serum adiponectin measuring were performed before and after aerobic exercise program in experimental (60 min, 3 days/week for 12 weeks) and control groups (without exercise). Statistical analysis was performed with the SPSS software version 15.0 using by independent and paired samples T-test. Significance was accepted at  $P < 0.05$ . Serum leptin were significantly decreased in response to aerobic exercise program when compared with baseline levels in experimental group ( $P = 0.033$ ). Anthropometrical indexes were decreased by exercise training, while FEV<sub>1</sub> and FVC levels were significantly increased by aerobic exercise program in these patients ( $P < 0.05$ ). All variables in control group remained didn't change. Based on this data, it was concluded that exercise training for long time accompanied to loss body weight decreases serum leptin that associated with asthma improvement.

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## Introduction

It has repeatedly reported that Obesity has been associated with an increased prevalence of asthma (Boulet, 2008). The physiological changes associated with obesity can contribute to respiratory symptoms and these should be differentiated from those caused by asthma (Boulet, 2008). Overweight or obese persons reported asthma more often than did thinner persons after adjustment for smoking, education, and physical activity (Nystad *et al.*, 2004). The finding of a recent study states that Boys with high body masses may be at an increased risk for developing asthma (Mannino *et al.*, 2006). While increases in body mass index (BMI) have been associated with the incidence and prevalence of asthma (Tantisira *et al.*, 2004), the mechanisms behind this association are unclear. Obesity can possibly influence the development of asthma through genetic, developmental, hormonal, neurogenic or mechanical influences (Boulet, 2008). Breathing at low lung volumes and changes in the pattern of breathing in obese subjects may alter airway smooth muscle plasticity and airway function (Boulet, 2008). Accumulating evidence indicates that asthma is a disease characterized by inflammation, and there is increasing evidence in the literature that the obesity is an inflammatory state (Hotamisligil *et al.*, 1995; Visser *et al.*, 2001). It has been suggested that the effects of increased BMI on asthma may be mediated by upregulation of inflammatory mechanisms in the airway epithelium (Visser *et al.*, 2001).

The release by adipocytes of various cytokines and mediators such as Interleukin-6, TNF-alpha, eotaxin, and leptin, and the reduction of anti-inflammatory adipokines in obese subjects may possibly contribute to the development or increased clinical expression of asthma in promoting airway inflammation (Boulet, 2008). Although accumulating evidence indicates a positive association between asthma and obesity in adults and children, very little is known about the role of leptin in asthmatic children (Guler *et al.*, 2004). Leptin as inflammatory cytokine is a proteohormone

produced by adipocytes and is thought to act primarily through specific receptors at the hypothalamus (Campfield *et al.*, 1995). Recent evidence has shown the presence of an interaction between leptin and the inflammatory system; however, there is no adequate knowledge about the role of leptin in atopic states such as asthma (Gurkan *et al.*, 2004). It was observed that Leptin receptors exist in human lung tissue, and leptin may have stimulatory effects on the proliferation of cells of a human cell line through its specific leptin receptor (Tsuchiya *et al.*, 1999). In asthma patients, leptin may provide a link between inflammation and T-cell function (Guler *et al.*, 2004). The clinical and research evidence to date support the hypothesis that physical activity and long term exercise training is associated with decreased serum leptin in obese and its related diseases (de Salles *et al.*, 2010; Sheu *et al.*, 2008). But the role of exercise training on systemic leptin in asthma patients has received limited attention. We hypothesized that aerobic exercise program would lead to an improvement in serum leptin in adult obese with chronic asthma patients. Therefore, the present study aimed to investigate serum leptin in response to chronic exercise training in adult obese men with asthma

## Material and methods

### Subjects

Subjects were thirty two adult obese men (age  $38 \pm 5$  yrs, body mass index  $31.08 \pm 14$  Kg) with mild to moderate asthma that participated in this study by accessible sampling and divided to experimental and control groups by randomly. This is was a semi-experimental study. The main objective of study was to determine serum leptin in response to an aerobic exercise training program (3 days/week for 12 weeks) in asthma patients. Each participant received written and verbal explanations about the nature of the study before signing an informed consent form. Asthma severity was determined from spirometric index (FEV<sub>1</sub>), degree of airway hyperresponsiveness, and amount of medication prescribed.

### **Inclusion or exclusion criteria**

History of asthma and medication were recorded by a specialist physician. Minimum age of getting affected by asthma is 5 years old. Subjects with a history or clinical evidence of impaired fasting glucose or diabetes, orthopedic abnormalities, recent myocardial infarction, congestive heart failure, active liver or kidney disease, growth hormone deficiency or excess, neuroendocrine tumor, anemia were excluded. All subjects were non-smokers and had not participated in regular exercise/diet programs for the preceding 6 months. In addition, exclusion criteria included inability to exercise and supplementations that alter carbohydrate-fat metabolism.

### *Measurements*

All measurements were performed before and after exercise program in experimental and control groups. At first, Forced expiratory volume in 1 s (FEV<sub>1</sub>) and forced vital capacity (FVC) and Maximal voluntary ventilation (MVV) were measured by Spirometry tests (Minispire model, Made in Italy) in order to asthma diagnosis as well as to determine the asthma severity. Patients were asked to avoid having tea or coffee as well as other airways dilator food for at least 4 hours prior to spirometry test. The measurements for weight, height, abdominal and hip circumference were first performed. The weight and height of the participants were measured by the same person when the participant had thin clothes on and was wearing no shoes by using the standard hospital scales. Abdominal circumference and hip circumference were measured in the most condensed part using a non-elastic cloth meter. Body mass index (BMI) was calculated using weight divided by squared height. Visceral fat and body fat percentage was determined using body composition monitor (OMRON, Finland). After anthropometric measurements, Fasting blood samples were taken after an overnight fast between the hours of 8 to 9 am in order to measuring serum leptin. Serums were immediately separated and stored at -80° until the assays were performed. Serum leptin was determined

by ELISA method, using a Biovendor- Laboratorial kit made by Biovendor Company, Czech. The Intra- assay coefficient of variation and sensitivity of the method were 7.6 % and 0.2 ng/mL, respectively. Subjects were instructed to refrain from intense physical activity for 48 h before testing.

After all measurements, the experimental group participated in an aerobic exercise program (60 min, 3 days/week for 12 weeks, %60-80 HR<sub>max</sub>). Each session started by 15 min of flexibility exercises, 30-40 min of aerobic exercise and 5-10 min of cool down activity. Aerobic exercises in each session included walking on a treadmill and stationary cycling. Initially, subjects exercised at low intensity and the intensity of exercise was gradually increased to 80% of peak heart rate in next sessions. The intensity of the activity of any person was controlled using the Polar heart rate tester (made in the US). Finally, all measurements of blood sampling, spirometry and anthropometrical indexes were repeated in 48 hours after lasting session of exercise.

### *Statistical analyses*

Data were analyzed by computer using SPSS software version 15.0. Baseline characteristics were compared by using independent t-tests in the case of normal distribution of data sets, and using the Kolmogorov-Smirnov's test when at least in one of the data sets the normal distribution was excluded. Student's t-tests for paired samples were performed to determine whether there were significant within-group changes in the outcomes. A p-value < 0.05 was considered to be statistically significant. All values are represented as mean ± SD.

### **Results**

Table 1 show the Baseline and post training serum leptin levels, anthropometrical indexes and spirometry parameters of the study groups. Data were expressed as individual values or the mean ± SD. The data of independent sample T-test showed no differences in all

variables between two groups in baseline condition (Table 1).

The statistical analysis showed significant decrease in serum leptin after aerobic exercise program when compared with baseline level in exercise group ( $p = 0.033$ , Fig 1). In addition, FVC, FEV<sub>1</sub> and MVV levels

were also significantly increased in response to exercise program when compared with baseline levels ( $P < 0.05$ ). In experimental group, exercise training resulted in significant decrease in anthropometrical indexes such as BMI, body weight and body fat percentage ( $P < 0.05$ ).

**Table 1.** Mean and standard deviation of anthropometrical and biochemical variables of experimental and control groups in baseline and after intervention.

variables	Control group		Experimental group	
	Baseline	post-exercise	Baseline	post-exercise
Weight (kg)	94 ± 8	94 ± 9	94 ± 8	89 ± 7
Height (cm)	175 ± 5.6	175 ± 5.6	176 ± 6.1	176 ± 6.1
Age (year)	39 ± 6	39 ± 6	38 ± 5	38 ± 5
Abdominal circumference (cm)	105.1 ± 8	104.9 ± 7	105.3 ± 8.50	100.3 ± 7.3
Hip (cm)	104.5 ± 5.7	104.6 ± 6.8	105.1 ± 5	101.7 ± 5.6
AHO (Ratio)	1.005 ± 0.11	1.002 ± 0.12	1.002 ± 0.09	0.99 ± 0.13
BMI (kg/m <sup>2</sup> )	30.71 ± 2.33	30.71 ± 2.33	30.32 ± 2.52	28.23 ± 3.36
Body fat (%)	28.21 ± 3.31	28.85 ± 2.23	29.02 ± 3.41	25.12 ± 6.03
FEV <sub>1</sub> (%)	75.6 ± 7.1	75.3 ± 6.5	76 ± 6.8	84 ± 5.9
FVC (%)	89.3 ± 5.4	90 ± 6.3	90 ± 5.3	97 ± 8.1
MVV	119 ± 11	120 ± 9	118 ± 9	132 ± 12.3
Serum leptin (ng/ml)	7.86 ± 2.11	8.01 ± 2.14	7.93 ± 2.56	6.01 ± 2.11

FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; MVV, Maximal voluntary ventilation

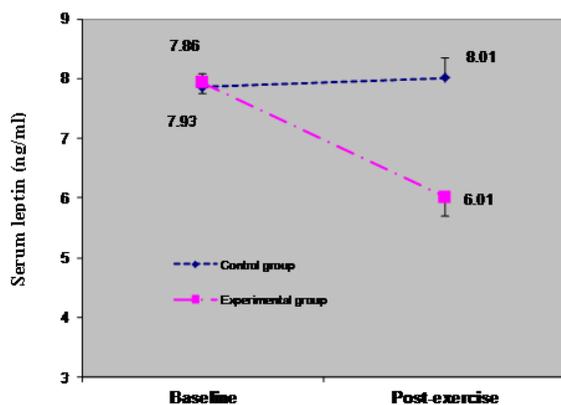
BMI, body mass index; AHO, Abdominal to hip circumference ratio

## Discussion

Our study finding showed decreased serum leptin following aerobic exercise program when compared with baseline levels. These findings support the positive role of exercise training on systemic inflammation in asthma patients. Decreased serum leptin in present study was associated with decreased BMI, body fat percentage and body weight in studied patients. It is reported that Weight loss improves asthma control and reduces medication needs (Boulet, 2008). To support these data, studies have found that obesity precedes and predicts the onset of asthma (time effect), that increased obesity leads to more severe asthma (dose-response effect), that weight reduction (by diet or gastric bypass) improves

asthmatic symptoms, and that obesity co-occurs with intermediate asthma phenotypes (obese young girls undergoing early menarche) (Castro-Rodríguez, 2007). Asthma is a chronic inflammatory disease and in the last years obesity has also been catalogued as a systemic inflammatory disease considering that adipose tissue is an endocrine organ that produces cytokines that can promote severity of asthma; therefore generating interest in the investigators to perform studies that can relate both conditions (Hilda Segura *et al.*, 2007). A large body of evidence suggests an increased risk of incident asthma with an increase in body mass index (Nystad *et al.*, 2004; Celedon *et al.*, 2001). Recent epidemiologic studies have demonstrated that several biological mechanisms play

key role in the relationship between obesity and asthma. Common genetics (Beuther *et al.*, 2006), obesity related increase in serum levels of proinflammatory adipokines (Scherer, 2006) or decrease in anti-inflammatory adiponectin (Yamauchi *et al.*, 2001) and many of the obesity related biochemical changes/co-morbidities may contribute. Decreased serum leptin by exercise program in our study was accompanied increased FEV<sub>1</sub>, FVC and MVV in studied subjects. These data demonstrated that decreased leptin as inflammation cytokine decreases airway resistance and improves respiratory functional in asthma patients. Study by Guler et collegous showed higher serum leptin in boy with asthma when compared to none- asthma subjects (Guler *et al.*, 2004). These authors suggested that leptin is a predictive factor for having asthma (Guler *et al.*, 2004). A number of studies have demonstrated that serum leptin is increased during allergic reactions in the airways and may play a role in the relationship between obesity and asthma (Shore *et al.*, 2005; Gurkan *et al.*, 2004). Animal experiments have evaluated the effects of leptin and obesity on airway inflammation in response to both allergic and nonallergic exposures and suggest that airway inflammatory response is enhanced by both endogenous and exogenous leptin (Beuther *et al.*, 2006).



**Figure 1:** The changes pattern of serum leptin concentration in control and exercise groups of studied subjects. Aerobic exercise program significant decreases serum leptin in exercise group, while this variable remained without change in control group

Hyperplasia and hypertrophy of airway smooth muscle (ASM) are characteristic features of airway remodeling in asthma and play important role in airway resistance in these patients (Shin *et al.*, 2008). Although the physiopathological mechanisms how obesity influences smooth muscle function are less understood. Leptin induces pulmonary inflammation after ozone exposure in mice (Shore *et al.*, 2003), and augments AHR in ovalbumin-sensitized mice (Shore *et al.*, 2005). This inflammation cytokine induces cytokine production and cell proliferation in hematopoietic cells (Huang *et al.*, 2000) and human umbilical vein endothelial cells (Park *et al.*, 2001). However, it has yet to be established whether leptin influences ASM cell proliferation and cytokine production by ASM cells. Leptin mRNA was detected in the lungs of mice (Shore *et al.*, 2005). Additionally, leptin receptors were observed in ASM (Shin *et al.*, 2008). Recent evidence has shown that Leptin may modulate angiogenesis and airway remodeling by promoting the release of VEGF from ASM cells, and thus being a potential therapeutic target in obese asthmatic patients (Shin *et al.*, 2008). On the other hand, another study confirmed Leptin receptors in human lung tissue, and they reported that leptin may have stimulatory effects on the proliferation of cells of a human cell line through its specific leptin receptor. Leptin may provide a link between inflammation and T-cell function in asthma (Guler *et al.*, 2004). In this area, some recent study has reported that leptin is positively related with serum immunoglobulin E (IgE) a negatively related with FEV<sub>1</sub> in asthma patients (Guler *et al.*, 2004).

In general, although the effect of prolonged exercise on leptin levels in previous studies had focused more on healthy obese subjects or obesity-related diseases such as diabetes, cardiovascular disease or metabolic syndrome. This study, however, demonstrated that a 3-month aerobic exercise program with 3 sessions per week, significantly reduced serum leptin levels in patients with asthma. According to some previous studies on other healthy and sick obese populations,

once the training program is associated with at least 5 percent reduction of body weight it can modify the inflammatory cytokine levels. Aerobic training program in the present study was associated with 6% reduction of body weight. Hence, this study validates the necessity a minimum of 5% reduction of body weight in response to exercise to reduce serum leptin levels in asthmatic patients. Also in the present study, the reduction in serum leptin levels and body weight was associated with improvement in respiratory function parameters such as FEV1 and MVV in the subject patients which supports the role of leptin in the resistance of respiratory pathways in patients with asthma.

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