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SERUM INTERLEUKINE-6 AND GLUCOSE HOMEOSTASIS IN RESPONSE TO CHRONIC AEROBIC TRAINING IN ASTHMA PATIENTS

Sokhanguei Yahya, Shahsavari Shahbaz, Ahmadi Mohsen
Department of Physical Education and Sport Sciences, Karaj Branch, Islamic Azad University, Alborz, Iran
***Corresponding author:** Sokhanguei Yahya

ABSTRACT
It has been demonstrated that low grade systemic inflammation plays a key role in respiratory diseases such as asthma and chronic obstructive pulmonary disease *(*COPD). To investigate the effect of aerobic training on serum Interleukin-6 (IL-6) in asthma patients, twenty two sedentary males with mild to moderate asthma matched for age 35-50 years and body mass index (BMI) 25-35 kg/m2 were randomized into exercise or control groups. Blood samples were collected, via the cannulated antecubital vein, between 8:00–9:00 a.m. after an overnight fasting for two groups before and after the exercise program (10 weeks, 3 day per week, 55-75 % of HRmax). Blood samples were analyzed for glucose and serum IL-6. A one-way analysis of variance was used to evaluate the differences in variables within groups. Fasting glucose and all anthropometrical markers decreased significantly by aerobic training ($p < 0.05$). Compared to pre-training, serum IL-6 increased significantly ($p = 0.000$) after aerobic program in exercise group but was not changed in control subjects. Based on our data and some previous evidence, improved fasting glucose by aerobic training can be attributed to increase in serum IL-6. Although, further studies should be elucidate about glucose in response to changes in this cytokine.

KEYWORDS: Aerobic exercise, Glucose, Smoking Adipocytokine

INTRODUCTION

Asthma is a chronic disease with features such as narrowing of the respiratory tract and wheezing symptoms (Settin *et al*., 2008). Hyperresponsiveness of respiratory pathways which is caused by narrowing of the respiratory tract in response to allergic triggers or some medications and environmental factors is one of the complications of this disease (Weiss *et al*., 2003). In addition, scientific studies have supported systemic inflammation to be one of the symptoms of asthma and it has been mentioned that inflammatory processes in asthma are affected through a complex network of cytokines and growth factors in inflammatory cells and other cells such as epithelial cells, fibroblasts, and smooth muscle cells associated with inflammation of the mucosa of the respiratory pathways (Bousquet, 2000).

Increased secretion of inflammatory cytokines and decreased levels of inflammatory cytokines in patients with asthma have been already reported by some researchers (Settin *et al*., 2008). For example, it has been found that Interleukin-6 (IL-6), as a cofactor or stimulus of IgE secretion, affects asthma (Deetz *et al*., 1997). Some studies have reported the higher levels of IL-6 in patients with asthma than healthy individuals (Lacy *et al*., 1998). The exact origin of IL-6 secretion is still not fully known, although this cytokine probably derives from the reserve of adipose tissue or peripheral blood mononuclear cells (Charles *et al*., 2008). Additionally, it has been found that secretion of IL-6 from alveolar macrophages increases in patients with asthma (Castro-Rodríguez *et al*., 2007). On the other hand, its increased serum levels and expression in bronchial epithelial cells has been observed (Yudkin *et al*., 1999). It is noteworthy to say that insulin resistance and blood glucose level are higher in patients with asthma than healthy individuals (Ma *et al*., 2010). Scientific literature supports the existence of a significant relationship between serum levels of IL-6 and insulin resistance and blood glucose in patients with asthma (Arshi *et al*., 2010). Based on these pieces of evidence, it seems that there is a relationship between systemic levels of IL-6 and blood glucose in patients with asthma.

The existing evidence corroborates the improvement of inflammatory profile and blood glucose levels in response to external interventions such as diet or exercise in other healthy and patient populations. For instance, studies on other populations of the healthy or the sick indicate the increased serum levels of IL-6 and other cytokines and also blood glucose following the short-term and long-term training programs (Donges *et al*., 2013; Ordonez *et al*., 2013 Talebi-Garakani *et al*., 2013 Jorge *et al*., 2011), while some other studies have reported no change in these variables in response to aerobic trainings (Cavagnolli *et al*., 2014; Lebon *et al*., 2013; Phillips *et al*., 2012). However, few studies have focused on the effect of long-term exercise on IL-6 levels in asthma sufferers. Hence, given the conflicting findings about the response of these variables to aerobic exercises in other healthy and patient populations and fewness of studies in this regard, the present study aims to determine the effects of 10 weeks on IL-6 and blood glucose levels in patients with asthma.

MATERIALS AND METHODS

A totally twenty two sedentary males with mild to moderate asthma (35 – 50 year of old, BMI: 25–35 kg/m2) were recruited through an accessible sampling in present study. Patients assigned to exercise (n=12) and control (n=12) randomly. Asthma diagnosed and its severity determined by spirometry. Patients was non-trained and non-smoker. Those subjects with other chronic diseases were excluded. All study participants completed the consent process and provided written informed consent prior to randomization.

Anthropometric measurements

At the beginning and after lasted exercise session, anthropometrical markers were measured. Anthropometric parameters such as weight, height, waist circumference after 5 minutes of rest were assessed. 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 at the end of a normal expiration, using a non-stretchable tape measure. Depending on the height and weight, body mass index was calculated using the software of BMI percentile for subjects. Abdominal circumference and hip circumference were measured in the most condensed part using a non-elastic cloth meter.

Blood analysis and training protocol

All blood samples were taken following an overnight 12-hour fast before and after exercise intervention. After sampling in ETDA- or serum-tubes, blood was immediately chilled on ice, centrifuged and aliquots stored at -70 °C until biochemical analyses were performed. Blood samples were analyzed for glucose by the oxidase method and serum IL-6 by ELIZA (Enzyme-linked Immunosorbent Assay for quantitative detection of human IL-6; Human IL-6 Platinum ELISA BMS213/2 / BMS213/2TEN, Austria)

Patients asked to participate in a set of exercises 3 days a week, for 12 weeks by a trained exercise physiologist. In each exercise session, they performed warm-up exercises for 5-10 min, followed by a 30 – 45 min walking–running exercise, with a target heart rate reserve of 55 – 75%, and relaxation exercises for 5 – 10 min at the end. The heart rate, used to calculate the intensity of exercise, was determined by counting heart beats by polar telemetry. Control subjects were instructed to maintain their habitual activities.

Data analysis

Experimental data are presented as means ± SD and were analyzed with the SPSS software version 15.0. The Kolmogorov-Smirnov test was applied to determine the variables with normal distribution. An Independent sample T-test was used to compare all variables between exercise and control subjects at baseline. Pre- and post training glucose, IL-6 and other variables were compared between conditions using a paired-samples t-test. The results were considered statistically significant for $p<0.05$.

RESULTS

Anthropometric and clinical characteristics of the study participants at before and after exercise intervention are showed in Table 1. Baseline characteristics such as age, body weight, body fat percentage and clinical markers did not differ between two groups. Aerobic intervention improved anthropometric parameters of exercise when compared with their baseline levels in exercise group but not in control subjects. As, aerobic program resulted in a significant decrease in body weight ($p<0.001$), abdominal circumference ($p<0.01$), BMI ($p<0.001$) and body fat percentage ($p<0.001$). Compared to pre-training, fasting glucose concentration decreased significantly ($p<0.01$, Fig 1) after exercise program but this clinical variables was not changed in control subjects.

Main objective of this study was to evaluate the effect of exercise intervention on serum IL-6 in studied patients. In this area, a significant increase was observed. On the other hand, aerobic intervention resulted significant increase in this cytokine compared to baseline in exercise group ($p = 0.031$, Fig 2).

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Table 1: Anthropometrical and clinical markers of two groups before and after intervention (Mean + SD.				
Variables	**Exercise group**		**Control group**	
	Pre-training	post-training	**Pre-training**	**post-training**
Age (year)	39.6 (6.2)	39.6 (6.2)	41.5 (2.8)	**41.5 (2.8)**
Height (cm)	174 (2.5)	174 (2.5)	175 (2.5)	**175 (2.5)**
Weight (kg)	93.8 (12.2)	89.6 (13.2)	95.6 (9.1)	**94.9 (7.2)**
Waist circumference (cm)	103.9 (10.1)	101.4 (10.7)	104.1 (9.5)	**102 (7.5)**
Hip circumference (cm)	103.3 (6.2)	101.3 (8.3)	101.1 (9.5)	**99.3 (6.8)**
Abdominal to hip ratio	1.00 (0.05)	1.00 (0.04)	1.03 (0.01)	**1.03 (0.02)**
BMI (kg/m2)	31.06 (3.55)	29.67 (3.89)	31.23 (2.41)	**31.03 (1.91)**
Body fat (%)	28.4 (5.43)	25.9 (5.15)	30.5 (2.22)	**30.3 (2.21)**
IL-6 (pg/ml)	4.71 (3.68)	7.53 (3.39)	4.91 (2.17)	**5.24 (2.28)**
Fasting glucose (mg/dl)	**110 (21)**	**94 (12)**	**108 (12)**	**106 (9)**

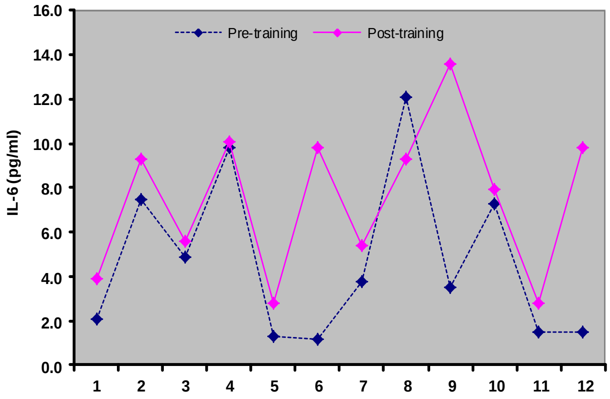

Figure 1: The change pattern of serum IL-6 at before and after training intervention in 12 subjects of exercise group.

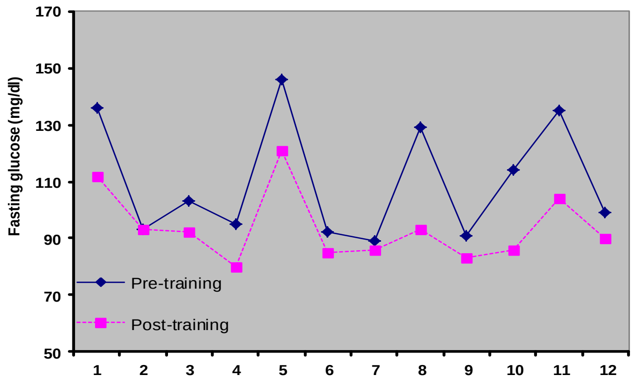

Figure 2: The change pattern of fasting glucose at before and after training intervention in 12 subjects of exercise group.

DISCUSSION

Previous studies suggest the higher levels of IL-6 in patients with asthma, especially those who have a family history of this disease (Settin *et al*., 2008). However, the mechanisms responsible for the role of this peptide mediator in the pathogenesis of this disease are still not fully understood. In the present study, 10 weeks of aerobic exercise was followed by significant increase in IL-6 and insignificant decrease in blood glucose. In fact, it can be concluded from the findings of this study that IL-6 levels increase in patients suffering from asthma in response to relatively long-term aerobic exercises. Recent findings support the role of not only local inflammation but also systemic inflammation in asthma. Systemic inflammation plays a major role in allergic and respiratory diseases and has been introduced as a linking factor between respiratory injuries and cardiovascular diseases. In other words, some studies have reported the declined respiratory function because of systemic inflammation caused by a number of plasma proteins (Kony *et al*., 2004; Mendall *et al*., 2000). Existing evidence about the importance of IL-6 are somewhat varied from different aspects, as scientific resources have reported its both inflammatory and anti-inflammatory properties.

When it comes to the inflammatory properties of IL-6 in patients with asthma, it has been found that its levels increase during asthma attacks. Researchers argue that IL-6 activates the T-cells and natural killer cells, which are of symptoms of asthma. In addition, IL-6 stimulates the synthesis of IgE through increasing the activity of IL-4 and inhibits the growth of fibroblasts and bronchial epithelial cells. Because of above-mentioned functions of IL-6, its importance in the pathophysiology of asthma has been repeatedly raised by researchers (Yokoyama *et al*., 1997). This cytokine is known as a cofactor or stimulus of IgE secretion from ß-cells by increasing the effect of IL-4, indicating the role of this inflammatory mediator in the responses of T-cells and presence of asthma (Deetz *et al*., 1997). Increase in IL-6 leads to increased resistance or narrowing of the respiratory tract. Increased generation of mucus induced by IL-6 of lung epithelium in inflammation respiratory pathways in inflammatory diseases such as asthma can physically block the respiratory pathways which are associated with increased resistance to respiratory pathways and eventually leads to impairment in lungs functions (Rogers, 2004; Agrawal *et al*., 2007). Inhibiting the function of IL-6 in mice with asthma has been reported to be followed by reduced accumulation of eosinophils in the lungs (Doganci *et al*., 2005).

However, some studies have shown that IL-6 levels are increased only in response to inflammatory conditions and it does not seem to have a central role in the inflammatory process (Neveu *et al*., 2009). Increase in IL-6 coincided with a significant reduction in blood glucose in response to exercise in asthma sufferers is somewhat controversial. Although there are few findings in terms of anti-inflammatory properties of IL-6 and the way it affects the blood glucose in patients with asthma, some studies have reported the beneficial effects of IL-6 on carbohydrate and fat metabolism. It has been found that IL-6 increases the insulin-dependent glucose transport (Stouthard *et al*., 1996). Hence, it can be concluded that increased IL-6 levels in response to aerobic exercises in the studied patients with asthma seems to be somehow involved in reduction of blood glucose levels. It is also probable that increased IL-6 levels following training program affects the blood glucose level through some mediating factors. For example, it was found in a study that IL-6 increases glucose uptake in both skeletal muscle and adipose tissue through increasing the activity of AMP-activated protein kinase (AMPK) (Kelly *et al*., 2004). AMPK has a central role in the regulation of metabolism of skeletal muscle and any increase in its activity stimulates fat oxidation (Kahn *et al*., 2005). This also increases glucose uptake through insulin signaling pathways (Fisher *et al*., 2002; Jakobsen *et al*., 2001). Additionally, it has been known that IL-6 increases the transfer of Glute-4 to the plasma membrane (Carey *et al*., 2006). Based on the available evidence, reduced fasting glucose in patients with asthma after exercise in the present study can be somewhat attributed to increased levels of IL-6. However, making a general and more comprehensive conclusion in this regard requires further experimental studies.

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