Journal of Biodiversity and Environmental Sciences (JBES)
ISSN: 2220-6663 (Print) 2222-3045 (Online)
Vol. 4, No. 2, p. 358-363, 2014
http://www.innspub.net

RESEARCH PAPER OPEN ACCESS

Impact of chronic exercise training on pro-inflammatory cytokine interleukine-6 in adult men with asthma

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Article published on February 21, 2014

Key words: Interleukin-6, Aerobic training, Chronic asthma.

Abstract

Evidence supports an important contribution of low-grade systemic inflammation in asthma or *chronic obstructive pulmonary disease*. The objective of present study was to determine whether aerobic training program affect serum IL-6 in males with asthma. For this purpose, fasting blood samples were collected before and at the end of aerobic training (3 months/3 days weekly) in order to measuring serum interleukin-6 in twenty two adult men with chronic asthma that randomly divided into exercise or control groups. Anthropometrical markers were also measured before and after exercise program in two groups. Independent student T test was used for between group's comparison at baseline and paired T test used for determine significant changes in variables by exercise intervention. Exercise program decreases body weight, body mass index and body fat percentage compared to baseline. There were no significant differences for serum IL-6 [pre, 5.33(3.6); post, 5.65(2.71) pg/ml (p = 0.76)]. These data suggest that long term aerobic training is not associated with an anti-inflammatory property in asthma patients. Further studies are necessary to elucidate the significance of this exercise program on other inflammatory cytokines.

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Introduction

Impaired respiratory function has a strong association with cardiovascular risk factors, atherosclerosis, hardening of the arteries, cardiovascular diseases and mortality. Although the pathophysiologic mechanisms responsible for this association remain undefined (Zureik *et al*., 2001), among respiratory diseases, asthma is of significant importance and its prevalence, especially in the past two decades, is increasing largely in industrialized and developing countries so identifying and creating effective strategies to prevent, improve or reduce its severity is of significant importance.

Inflammatory processes in asthma are affected by a complex network of cytokines and growth factors secreted not only by inflammatory cells but also by other tissues, such as epithelial cells, fibroblasts and smooth muscle cells, as inflamed mucosa of respiratory pathways are associated with systemic acute or chronic inflammation in patients with asthma (Bousquet *et al*., 2000). Inflammatory cytokines secreted from adipose tissue or other tissues of the body are among the clinical factors affecting the respiratory pathways inflammation in such patients. Understanding of asthma as an inflammatory disease has led to numerous studies on the symptoms of the incidence of inflammation, such as certain cytokines like IL-6 in respiratory pathways inflammation. Increased levels of IL-6 as an inflammatory cytokine in allergic conditions have repeatedly been reported (Deetz *et al*., 1997). The levels of inflammatory cytokines in asthma patients significantly increase compared to healthy subjects (Broide *et al*., 1992). Significant increases in these patients, especially during asthma attacks have frequently been reported (Yokoyama *et al*., 199*2).

Symptoms of inflammation of the respiratory pathways due to the use of antigens are similar to the time when levels of IL-6 increase (Yokoyama *et al*., 1997). Some studies also report that the levels of IL-6 increases only in response to inflammatory conditions rather than having a central role in the inflammatory process (Neveu *et al*., 2009). Among effective strategies to improve or reduce the severity of the disease, and the role of exercise training program on inflammatory cytokines, particularly IL-6 is been less frequently studied. However, despite the lack of adequate studies on the role of exercise on serum or plasma levels of this inflammatory cytokine in these patients, its significant changes or decrease in response to different training programs in some of chronic inflammatory diseases like type 2 diabetes and obesity have repeatedly been reported (Jung *et al*., 2008; Monzillo *et al*., 2003), although the findings are not entirely consistent. Given limited studies on the role of exercise on systemic levels of this cytokine in asthmatic patients, this study aims to determine the effect of aerobic training on serum levels of IL-6 in these patients.

Method and subjects

Subjects

Twenty two sedentary, nonsmoking (BMI: 28-33 kg/m2) men, aged 37-48 years with mild to moderate asthma were recruited for participate in this study. Subjects were randomly selected into exercise or control groups. Exercise program lasted three months aerobic exercise program. After the nature of the study was explained in detail, informed consent was obtained from all participants. Subjects were asked to complete questionnaires on anthropometric characteristics, general health, smoking, alcohol consumption and present medications. Height of the barefoot subjects was measured to the nearest 0.1 cm. Body weight was measured with the subject wearing light clothes. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m2). Body fat percentage was determined using body composition monitor (OMRON, Finland).

Inclusion and exclusion criteria

Inclusion criteria for study group were determined as existing asthma for at least three years. All subjects were non-smokers. All participants had not participated in regular exercise/diet programs for the preceding 6 months. We also excluded people who had any self reported physician diagnosed chronic

disease (arthritis, stroke, hypertension, cancer, heart attack and chronic cough). Furthermore patients with overt diabetic were also excluded from the study. Those that were unable to avoid taking drugs for 12 hours before blood sampling were also barred from participating in the study.

Blood sampling and exercise program

Aerobic exercise program for exercise group included 3 sessions per week and lasted 3 months. Exercise intensity was 60-80% of maximal heart rate. Each session involved 5-10 min warm up, 40-60 min aerobic exercise consists of Running on a flat surface with no slope or kick pedal on a stationary bicycle in mentioned intensity and cool up at the end. Fasting blood samples were collected before and 48 hour after lasted session of exercise program. Serums were immediately separated and stored at -80° until the assays were performed. Serum IL-6 was determined by ELISA method ((Enzyme-linked Immunosorbent Assay for quantitative detection of human IL-6))

Statistical Analysis

Data were analyzed by computer using the Statistical Package for Social Sciences (SPSS) for Windows, version 11.5. We verified normal distribution of variables with a Kolmogorov–Smirnov test, and the parametric variables with skewed distribution were expressed as mean ± SD. Comparisons between the means of each group were done using the independent t-test. Pre- and post exercise serum IL-6 and anthropometrical markers were compared between conditions using a paired-samples t-test. The differences between the groups were considered to be significant at a p-value of ≤ 0.05.

Results

Baseline and post training IL-6 levels and anthropometrical indexes before and after intervention of two groups are shown in Table 1. The data were reported as mean and standard deviation. At baseline there were no differences in the age, body weight, body mass index and body fat (%) between the two groups ($p \geq 0.05$). serum IL-6 were also similar in two groups at baseline ($p \geq 0.05$). We also observed significant decreases in body weight ($p = 0.000$), Body mass index ($p = 0.000$) and body fat p-percentage ($p = 0.002$) (Fig 1). Serum IL-6 levels did not change by exercise program when compared with baseline ($p = 0.76$, Fig 2).

Table 1. Pre and Post training of anthropometrical markers and IL-6 in exercise and control group (M ± SD).

Variables	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m²)	BF (%)	Interleukin -6 (pg/ml)
Exercise group *(pre)*	40.3 (3.48)	94.5 *(11.8)*	173.7 *(2.81)*	31.3 *(3.51)*	28.48 *(5.35)*	5.33 *(3.6)*
Exercise group *(post)*	40.3 (3.48)	89.9 *(13.1)*	173.7 *(2.81)*	29.8 *(3.98)*	26.53 *(5.99)*	5.65 *(2.71)*
Control group *(pre)*	41.6 (3.8)	95.2 *(4.8)*	174.3 *(3.21)*	31.34 *(3.21)*	29.11 *(3.84)*	5.49 *(2.31)*
Control group (post)	41.6 (3.8)	94.9 *(5.6)*	174.3 *(3.21)*	31.24 *(3.81)*	28.90 *(2.44)*	6.11 *(1.62)*

BMI, body mass index; BF, Body fat percentage;

Discussion

Understanding of asthma as a chronic inflammatory disease has led to several studies to determine the degree and symptoms of incidence of inflammation, such as certain cytokines and their related proteins in these patients. The findings of this study showed that three months of aerobic exercise did not alter levels of IL-6 in asthmatic patients. In other words, a three-month program of aerobic exercise three times a week led to no significant change in serum IL-6 in men with mild to moderate asthma. However, the training program significantly decreased anthropometric parameters such as weight, body mass index and body fat percentage. Although previous studies have somehow described exercise as a peripheral intervention effective in improving inflammation, it is expected that three months of exercise should also be associated with a decrease in IL-6 in asthmatic

patients. However, our findings are somewhat controversial. The findings of this study are observed while most studies report higher levels of IL-6 in asthmatic patients than in healthy subjects. However, it is recognized that increased levels of IL-6 or some other inflammatory cytokines such as CRP and TNF-α are associated with impaired lung function (Wu *et al.*, 2005). IL-6 plays an important role in the pathophysiology of asthma and its level drastically increases in these patients especially during asthmatic attacks (Yokoyama *et al.*, 1995). In addition to adipose tissue, alveolar macrophages, bronchial epithelial cells and mast cells are also involved in secretion of iL6 in asthmatic patients (Gosset *et al.*, 1991; Marini *et al.*, 1992).

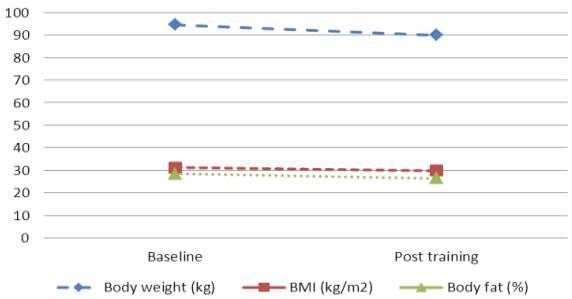

Fig. 1. Body weight, Body mass index and Body fat percentage at before and after exercise program of exercise groups.

Increased secretion of IL-6 has also been observed by alveolar macrophages in asthmatic patients (Castro-Rodríguez, 2007). On the other hand, increased serum levels and expression of IL-6 in bronchial epithelial cells have also been reported in some studies (Yudkin *et al.*, 1999). Mast cells and eosinophils increased in asthmatic patients have also been found to release higher levels of IL-6 in these patients (Bradding *et al.*, 1994; Hamid *et al.*, 1992). This point should also be noted that IL-6 also triggers T Cells as well as natural killer cells representing the characteristics of asthma. Levels of IL-6 in asthmatic children, particularly those with a family history of the disease are significantly higher than their healthy counterparts (Settin *et al.*, 2008). These data have revealed that disruption of IL-6 levels are associated with pathophysiologic changes in respiratory pathways as its increase leads to increased resistance or narrowing of the respiratory tract. Increased mucus production by lung epithelium caused by IL-6 during inflammation of respiratory pathways in inflammatory diseases such as asthma can physically block the respiratory pathways, which are associated with increased resistance of respiratory pathways and ultimately leads to lung dysfunction (Rogers, 2004; Agrawal *et al.*, 2007). Increased accumulation of eosinophils in the lungs in response to increased levels of IL-6 has been observed previously (Wang *et al.*, 2000; Qiu *et al.*, 2004). Furthermore, inhibition of IL-6 function by neutralizing or inhibiting its receptor in asthmatic rats reduces the accumulation of eosinophils in the lungs (Doganci *et al.*, 2005).

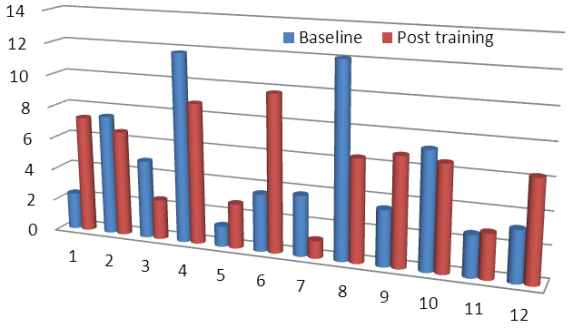

Fig. 2. Serum Il-6 at before and after exercise program of exercise groups.

Despite the foregoing, long-term training programs are expected to be associated with improved inflammatory profile in obese patients or inflammatory diseases. But the findings of this study suggest that a three-month aerobic exercise does not affect the levels of IL-6 in asthmatic patients. Of course, this inflammatory cytokine or other similar inflammatory cytokines remaining unchanged, in response to long-term exercise has also been reported in some other chronic diseases (De Luis *et al.*, 2007; Nassis *et al.*, 2005).

References

Agrawal A, Rengarajan S, Adler KB, Ram A, Ghosh B, Fahim M, Dickey BF. 2007. Inhibition of mucin secretion with MARCKS-related peptide improves airway obstruction in a mouse model of asthma. Journal of Applied Physiology **102,** 399–405.

Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. 2000. Asthma from bronchoconstriction to airways inflammation and remodeling. American Journal of Respiratory and Critical Care Medicine **161,** 1720–1745.

Bradding PJA, Roberts KM, Britten S, Montefort R, Djukanovic R, Muller CH. 1994. Interleukin-4, -5, and -6 and tumor necrosis factor-α in normal and asthmatic airways: evidence for the human mast cell as a source of these cytokines. American Journal of Respiratory Cell and Molecular Biology **10,** 471–480.

Broide DHM, Lotz AJ, Cuomo DA, Coburn EC, Federman I. Wasserman. 1992. Cytokines in symptomatic asthma airways. Journal of Allergy and Clinical Immunology **89,** 958–967.

Castro-Rodríguez JA. 2007. Relationship between obesity and asthma. Archivos de Bronconeumología **43(3),** 171-5.

De Luis DA, Aller R, Izaola O, Gonzalez Sagrado M, Bellioo D, Conde R. 2007. Effects of a low-fat versus a low-carbohydrate diet on adipocytokines in obese adults. Hormone Research **67(6),** 296-300.

Deetz DC, Jagielo PJ, Quinn TJ, Thorne PS, Bleuer SA, Schwartz DA. 1997. The kinetics of grain dust–induced inflammation of the lower respiratory tract. American Journal of Respiratory and Critical Care Medicine **155,** 254-259.

Doganci AT, Eigenbrod N, Krug GT, De Sanctis M, Hausding VJ, Erpenbeck B, Haddad HA. 2005. The IL-6R chain controls lung Treg development and function during allergic airway inflammation in vivo. Journal of Clinical Investigation **115,** 313–325.

Gosset PA, Tsicopoulos B, Wallaert C, Vannimenus M, Joseph AB, Tonnel A. 1991. Increased secretion of tumor necrosis factor and interleukin-6 by alveolar macrophages consecutive to the development of the late asthmatic reaction. Journal of Allergy and Clinical Immunology **88,** 561–571.

Hamid QJ, Barkans Q, Meng S, Ying JS, Abrams AB. 1992. Human eosinophils synthesize and secrete interleukin-6, in vitro. Blood **3,** 1496–1501.

Jung SH, Park HS, Kim KS, Choi WH, Ahn CW, Kim BT. 2008. Effect of weight loss on some serum cytokines in human obesity: increase in IL-10 after weight loss. Journal of Nutritional Biochemistry **19(6),** 371-5.

Marini ME, Vittori J, Hollemborg S. 1992. Expression of the potent inflammatory cytokines, granulocyte-macrophage-colony- stimulating factor and interleukin-6 and interleukin-8, in bronchial epithelial cells of patients with asthma. Journal of Allergy and Clinical Immunology **89,** 1001–1009.

Monzillo LU, Hamdy O, Horton ES, Ledbury S, Mullooly C, Jarema C. 2003. Effect of lifestyle modification on adipokine levels in obese subjects with insulin resistance. Obesity Research **11(9),** 1048-54.

Nassis GP, Papantakou K, Skenderi K, Triandafillopoulou M, Kavouras SA, Yannakoulia M. 2005. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. Metabolism **54(11),** 1472-9.

Neveu WA, Allard JB, Dienz O, Wargo MJ, Ciliberto G, Whittaker LA. 2009. IL-6 Is Required for Airway Mucus Production Induced by Inhaled Fungal Allergens. Journal of Immunology **183(3),** 1732-8.

Qiu ZM, Fujimura K, Kurashima S, Nakao N. 2004. Enhanced airway inflammation and decreased subepithelial fibrosis in interleukin 6-deficient mice following chronic exposure to aerosolized antigen. Clinical & Experimental Allergy **34,** 1321–1328.

Rogers DF. 2004. Airway mucus hypersecretion in asthma: an undervalued pathology? Current Opinion in Pharmacology **4,** 241–250.

Settin A, Zedan M, Farag M, Ezz El, Regal M, Osman E. 2008. Gene polymorphisms of IL-6(-174) G/C and IL-1Ra VNTR in asthmatic children. Indian Journal of Pediatrics **75(10),** 1019-23.

Wang JRJ, Homer Q, Chen JA. 2000. Endogenous and exogenous IL-6 inhibit aeroallergen-induced Th2. inflammation. Journal of Immunology **165,** 4051–4061.

Wu SJ, Chen P, Jiang XN, Liu ZJ. 2005. C-reactive protein level and the correlation between lung function and CRP levels in patients with chronic obstructive pulmonary diseases. Zhong nan da xue xue bao. Yi xue ban **30(4),** 444-6.

Yokoyama A, Kohno N, Fujino S, Hamada H, Inoue y, Fujioka S, Ishida S, Hiwada K. 1995. Circulating interleukin-6 levels in patients with bronchial asthma. American Journal of Respiratory and Critical Care Medicine **151,** 1354–1358.

Yokoyama A, Kohno N, Sakai K, Kondo K, Hirasawa Y, Hiwada K. 1997. Circulating Levels of Soluble Interleukin-6 Receptor in Patients with Bronchial Asthma. American Journal of Respiratory and Critical Care Medicine **156(5),** 1688-91.

Yudkin JS, Stehouwer CD, Emeis JJ. 1999. C reactive protein in healthy subjects: associations with obesity, insulin resistance and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thrombosis Vascular Biology **19,** 972-8.

Zureik M, Benetos A, Neukirch C. 2001. Reduced pulmonary function is associated with central arterial stiffness in men. American Journal of Respiratory and Critical Care Medicine **164,** 2181-5.