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Serum Interleukin-1 beta and maximal oxygen consumption in asthma patients

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Abstract

According to the population studies, it has been indicated that asthma is associated with systemic inflammation, although the molecular mechanisms for this are less understood. The aim of this study was to test whether serum interleukin-1 beat (IL-1ß) is associated with aerobic capacity (VO2max) in adult men with asthma. For this purpose, venous blood samples were collected after an overnight fast in order to measuring serum IL-1ß in thirty one non-trained adult men with mild to moderate asthma. Cardiorespiratory fitness was assessed as VO2max (mL kg-1 min-1) was measured using a bicycle ergometer in a stepwise fashion according to YMCA instrument. The bivariate associations between changes in serum IL-1ß and VO2max were examined with the Pearson rank correlation analysis in studied subjects. Data of statistical analysis showed no significant correlation between these two variables in studied patients ($p = 0.50$, $r = 0.13$). Based on these data, it is concluded that serum IL-1ß is not directly associated with aerobic capacity or cardiovascular fitness in asthma patients. It is likely that these two variables affect each other indirectly or by effects on other hormonal or physiological mediators.

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Introduction

Impaired respiratory performance has a strong relationship with cardiovascular risk factors, atherosclerosis, cardiovascular disease and mortality. However, the pathophysiological mechanisms responsible for this relationship are still unknown (Zureik *et al.*, 2001). Inflammatory processes in asthma are affected by a complex network of cytokines and growth factors that not only secreted by inflammatory cells but also by other tissues such as epithelial cells, fibroblasts and smooth muscle cells, so that inflamed mucosa of the respiratory tracts is consistent with acute or chronic systemic inflammation in asthmatic patients (Bousquet *et al.*, 2000). Literature supports the role of inflammatory processes in the pathogenesis of asthma and its severity (Mohammad, 2013). It has been hypothesized that in addition to the systemic inflammation, inflammation of the respiratory tract is consistent with over-response and narrowing of respiratory tract in asthmatic patients (Kony *et al.*, 2004; Mendall *et al.*, 2000). Hence, including asthma in the inflammatory diseases seems reasonable.

In fact, one of the most important characteristics of asthma is inflammation of the respiratory pathways. It is known that some mediators of the inflammatory processes are involved in the prevalence and severity of the disease (Karjalainen *et al.*, 2002). As these sources indicate increase in systemic levels of inflammatory cytokines and decrease in systemic levels of anti-inflammatory cytokines in these patients (Wang *et al.*, 1994; Sousa *et al.*, 1996). Among them, IL-1ß is an inflammatory cytokine that has a wide potential role in the pathogenesis of asthma (Busse *et al.*, 2001). IL-1ß gene is encoded on chromosome 2, where has been reported to be related to the incidence of asthma in most studies. Interleukins family has been identified to be one of the most important factors involved in the pathogenesis of the disease (Hakonarson *et al.*, 2001). Despite those findings regarding the influence of inflammatory processes in the disease, factors such as obstruction and narrowing of resistance of the respiratory tract are potentially effective on the reduction of respiratory performance in patients. Also, sedentary lifestyle and lack of exercise also facilitate increased severity of the disease. In this context, some literature has noted reduction in cardio-respiratory performance in these patients compared to healthy subjects (Alioglu *et al.*, 2007). These studies have noted that increased cardiorespiratory fitness by short or long-term training programs improves the respiratory performance as well as capacity of the respiratory volumes (Fanelli *et al.*, 2007; Van Veldhoven *et al.*, 2001). Literature indicates a decrease in cardiorespiratory fitness and increased inflammatory cytokine such as IL-1ß in asthmatic patients compared to healthy subjects. But the question is whether each of these factors independently affects the incidence or severity of the disease or interacts with each other. This study aimed to determine the relationship between VO2max, as a physiological indicator of cardiovascular fitness, and IL-1ß, as a member of the cytokine network, in asthmatic patients is done.

Patients and methods

Subjects

Participants were thirty one non-trained adult men with asthma (mild to moderate of intensity) matched for age 39 ± 7 years and body weight 92 ± 12 kg. Asthma diagnosis and its severity were determined by FEV1/FVC. After the nature of the study was explained in detail, informed consent was obtained from all participants.

Inclusion criteria

All subjects were inactive, non-smoker and non-alcoholics. Participants were included if they had not been involved in regular physical activity in the previous 6 months. Inclusion criteria to study were as existing mild to moderate asthma for at least 3 years. We also excluded those with history of neuromuscular disease, cardiopulmonary disease, type II diabetes, recent heart failure and active liver or kidney disease.

Anthropometricalmeasurements

Anthropometric measurements of height, weight,

percent body fat, and circumference measurements were taken in the physiology laboratory. All anthropometric measurements were made by the same trained general physician. Weight and height were measured in the morning, in fasting condition, standing, wearing light clothing and no shoes. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m2). Body composition monitor (BF508-Omron made in Finland) with a precision error of less than 100 g was used to measure weight and body fat percentage of the subjects.

Blood analysis and exercise test

Blood was collected between 8:00 and 9:00 a.m. after a 12-h water-only fast with participants in the seated position. All participants refrained from any severe physical activity 48 h before measurements. Blood was drawn from the antecubital vein, separated by centrifugation, frozen, and stored −80 °C until biochemical analysis was performed. Serum used to measuring IL-1ß by ELISA method (Enzyme-linked Immunosorbent Assay for quantitative detection of human IL-1β, Austria). Cardiorespiratory fitness was assessed as VO2max (mL kg-1 min-1) indirectly was measured using a bicycle ergometer (Tunturi, made in Finland) in a stepwise fashion (Mullis *et al.*, 1999). The subjects were advised to avoid any physical activity or exercise 48 hours before the exercise test. Exercise test lasted 15 min in five separate stages without rest between stages.

Statistical methods

Statistical analysis was performed with the SPSS software version 15.0. Normal distribution of data was analyzed by the Kolmogorov-Smirnov normality test. The bivariate associations between changes in serum IL-1ß and VO2max were examined with the Pearson rank correlation analysis in studied subjects. A p-value < 0.05 was considered to be statistically significant.

Results

In this study, we determined relationship between serum IL-1ß and Vo2max as cardiorespiratory fitness in asthma patients. The relations of IL-1ß with some anthropometrical markers were also determined. The physical, physiological and biochemical characteristics of the patients are shown in Table 1. All values are represented as mean ± SD.

Table 1. The physical, physiological and biochemical characteristics of the patients.

	N	Minimum	Maximum	Mean	Std. Deviation
Age (year)	31	26	58	39.19	6.784
Height (cm)	31	170	177	174.10	1.938
Weight (kg)	31	78	114	91.77	10.148
Body mass index (kg/m2)	31	25.83	37.65	30.2626	3.16434
Abdomina circumference (cm)	31	84	130	100.97	10.114
Body fat (%)	31	24.3	37.5	29.903	2.9322
FEV1 / FVC	31	62	72	68.77	2.617
Interleukine-1 beta (pg/ml)	31	1.1	9.7	3.155	2.5972
Valid N (listwise)	31				

Data analysis showed that there is not a significant correlation in serum IL-1ß with VO2max in studied patients (p = 0.50, r = 0.13, Fig 1). Regardless a lack significant correlation between this inflammatory cytokine with VO2max, we observed that there are a positive significant correlation between this cytokine with anthropometrical markers such as body weight (p = 0.008, r = 0.47), abdominal circumference (p = 0.003, r = 0.51), BMI (p = 0.004, r = 0.50, Fig 2) and body fat percentage (p = 0.004, r = 0.51, Fig 3).

Discussion

No study has directly investigated the relationship between inflammation profile and cardiorespiratory fitness in asthmatic patients. What is certain and most previous studies have indicated is that asthmatic patients suffer from increase in inflammatory cytokines and a decrease in cardiorespiratory fitness

compared to healthy subjects. Understanding the importance of the interaction between these factors is potentially important. Despite the evidence in this regard, the findings of this study shows no relationship between cardiorespiratory fitness with the inflammatory profile with emphasis on IL-1ß in the patients. In other words, the significant relationship was observed between serum levels of IL-1ß with VO2max as an indicator of cardiorespiratory fitness in asthmatic patients.

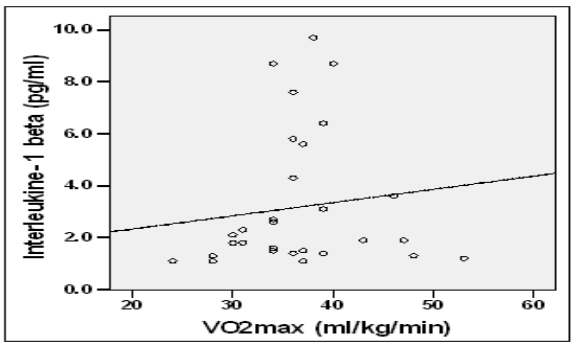

Fig. 1. Relation between Maximal oxygen consumption and serum IL-1ß .

Genetic findings have shown that the influence of inflammatory processes is applied through genetic polymorphisms of cytokine genes. The relationship between a number of genetic polymorphism of IL-1ß with both severity and susceptibility of individuals to certain inflammatory diseases has been identified (Bidwell *et al.*, 1999).

Fig. 2. Relation between serum IL-1ß and body mass index.

IL-1ß is one of the important inflammatory cytokines. It has been found that polymorphisms of its gene have a key role in the pathogenesis of several inflammatory diseases (Hurme *et al.*, 1998). Although the role of this cytokine has not been considered by many researchers, its importance in the prevalence and severity of asthma has been reported (Busse *et al.*, 2001).

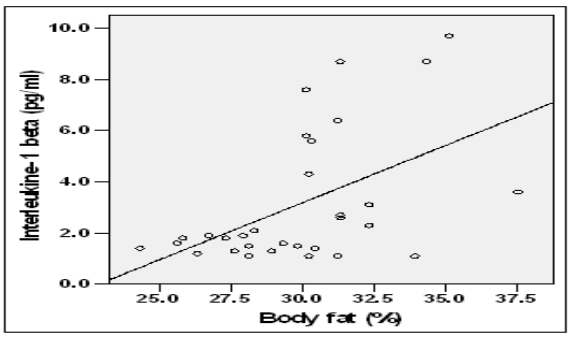

Fig. 3. Relation between serum IL-1ß and body fat percentage

Although no study has been conducted about the relationship between cardiorespiratory fitness and inflammatory processes in asthmatic patients, previous findings in healthy or patient populations are more or less contradictory and incongruent. In a way that some of those studies have supported a direct relationship between VO2max with the inflammatory cytokines or other peptide mediators (Kullo *et al.*, 2007; Jae *et al.*, 2008), while others have denied any relationship between them (Varra *et al.*, 2012; Cicchella *et al.*, 2013). For example, a significant relationship between VO2max as an indicator of cardiorespiratory fitness with certain cytokines such as TNF-α and IL-6 were observed in overweight children, while its relationship with other cytokines such as IL-1ß, IL- 10 and CRP were insignificant in the studied population (Utsal *et al.*, 2013).

It is also possible that the relationship between VO2max and inflammatory processes is independent from inflammatory systemic cytokine levels in these patients and the inflammatory profile in respiratory tracts or in limited breathing space is associated with cardiorespiratory fitness in these patients. To better understand the interaction between them, the interaction between VO2max with inflammatory cytokines in respiratory tracts or pulmonary spaces should be investigated. In this regard, it is known that alveolar macrophages secrete interleukin-1 in response to certain stimuli. The secretion of this cytokine can affect production and secretion of other

inflammatory cytokines such as TNF-α, IL-6, IL-8 and adhesion molecules in smooth muscle cells of the respiratory tracts, epithelial cells, and endothelial cells (Aya *et al.*, 2010). The scientific evidence has reported increased levels of IL-1ß in the alveolar-bronchial fluid in patients which increases with the severity of the disease (Mohammad, 2013). It is known that the expression of IL-1ß in alveolar macrophages increases in asthmatic patients, and the levels of IL-1ß in the alveolar-bronchial fluid in asthmatic patient increases compared to healthy individuals (Broide *et al.*, 1992). The direct role of IL-1ß in the pathogenesis of asthma has been concluded from studies in which administration of IL-1ß in rats led to inflammatory variations, such as increased numbers of neutrophils in alveolar-bronchial fluid and increased response of airways to bradykinin (Tsukagoshi *et al.*, 1994).

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