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ORIGINAL ARTICLE

Association of Systemic Inflammation and Cardiorespiratory Fitness in Males with Chronic Asthma

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ABSTRACT
Based on accumulating experimental and epidemiologic data, it is expected that asthma affects both cardiorespiratory fitness and inflammation. The objective of this study was to assess relationship between serum interleukin-6 (IL-6) with VO2max as cardiorespiratory fitness in males with chronic asthma. For this purpose, fasting serum of IL-6 was measured in twenty four adult men with chronic asthma aged 35 – 45 years and VO2max were measured by a stepwise incremental bicycle test. For statistical analysis, the relationship between variables was analyzed by computing Pearson's correlation coefficient. Statistical significance was accepted at p-value<0.05 or lower. There was no correlation between serum IL-6 and VO2max in studied patients (p = 0.45, r = 0.16). It can conclude, systemic inflammation is not associated with cardiorespiratory fitness in chronic asthma.
Keywords: *Cardiorespiratory fitness, Inflammation, Asthma*

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INTRODUCTION

Few studies have noted the similar levels of ventilatory fitness and cardiorespiratory fitness between asthmatic patients and healthy individuals [1]. However, most studies support reduced exercise capacity and VO2max as a measure of cardiorespiratory fitness in these patients compared to healthy individuals [2]. These studies have reported lower levels of both aerobic fitness and anaerobic fitness in these patients compared to healthy individuals [3]. Also, some studies have showed that asthmatic patients have relatively lower cardiorespiratory fitness due to reduced cardiac output and stroke volume [4].

However, the damage to 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 [5]. Despite the low levels of cardiorespiratory fitness in these patients, some studies have also shown the presence of systemic inflammation in these patients [6, 7]. These studies have supported a close relationship between systemic inflammation and inflammation of the respiratory tracts in these patients [8]. 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 [9]. For example, increased levels of Interleukin-6 (IL-6), as an inflammatory cytokine, have frequently been reported in allergic conditions [10]. Some studies also show higher levels of the inflammatory cytokine in asthmatic patients compared to healthy individuals [11].

These patients have increased levels of inflammatory cytokines such as IL-6 and decreased VO2max as a measure of cardiorespiratory fitness compared to normal individuals. However, the question is whether these variables are independent of each other in these patients, or directly or indirectly interact each other. In this context, although some studies have reported an association between serum or plasma

levels of inflammatory cytokine with cardiorespiratory fitness in other healthy or patient populations [12, 13], but few studies have looked at the relationship between them in asthma patients. Therefore, in this study, the relationship between IL-6, as a marker of inflammation in asthma patients, with VO2max, as an indicator of cardiorespiratory fitness, were determined.

METHOD AND SUBJECTS

Human patients and inclusion criteria:

Twenty four non-trained adult men (35 - 45 years) with chronic asthma participated in the study by accessible sampling. The diagnosis of asthma was made by spirometry test. Each participant received written and verbal explanations about the nature of the study before signing an informed consent form. All subjects were non-smokers and had not participated in regular exercise/diet programs for the preceding 6 months. The exclusion criteria were as follows: Patients with known history of other chronic diseases such and diabetes, kidney, liver cancer and cardiovascular disease.

Anthropometrics, spirometry and Blood analysis

Blood samples were obtained for biochemical assays, and anthropometric measurements were taken, including measurement of height and weight and spirometric factors (including FEV1, FVC and FEV1/FVC), using standardized techniques.

All anthropometric measurements were made by the same trained general physician. Body weight and height were measured on the same day to the nearest 0.1 kg and the nearest 0.1 cm, respectively. Body mass index was calculated from the weight and height measures. Abdominal circumference and hip circumference were measured in the most condensed part using a non-elastic cloth meter. Percentage of body fat and visceral fat was estimated by bioelectrical impedance method (Omron Body Fat Analyzer, Finland). We used three parameters to assess cardiorespiratory functions: forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and forced expiratory volume in 1 s / forced vital capacity (FEV1/FVC%). Subjects were asked to refrain from tea, coffee, chocolates and caffeinated soft-drinks on 4 hours before Spirometry. Subjects were instructed to take maximum inspiration and blow into the pre-vent pneumotach as rapidly, forcefully and completely as possible for a minimum of 6 seconds, followed by full and rapid inspiration to complete the flow volume loop. The best of the three trials was considered for data analysis [14].

The subjects did not perform any exercise for 48 hours before the blood collection and one week before exercise test. Blood samples were obtained were taken between 8:00 and 9:00 a.m. after 10 to 12 hours overnight fast, then centrifuged for separate serum. Serum used to measuring IL-6 by ELISA. Cardiorespiratory fitness was assessed as VO2max (mL kg-1 min-1) was measured using a bicycle ergometer in a stepwise fashion according to YMCA instrucment. This protocol was performed in 5 continues stage without rest between stages. Each stage lasted 3 minute [15].

Data analysis

For the nonparametric variables; the median, along with the minimum and maximum values, were expressed in the descriptive tables. Whereas variables tested revealed an abnormal distribution, the Pearson correlation coefficient test was chosen for evaluating the correlations between resistin concentration and insulin sensitivity and beta cell function. All statistical tests were performed and considered significant at a $P \leq 0.05$

RESULTS

This study aimed to determine relationship between serum IL-6 as an inflammatory cytokine and VO2max as cardiorespiratory fitness in adult males with asthma.

Anthropometric characteristics of the study participants are described in Table 1. All values are reported as mean and standard deviation. Serum level of IL-6 and Spirometrical characteristics of the study participants are also shown in Table 2. Based on Pearson correlation coefficient test, there was no correlation between serum IL-6 and VO2max in studied patients ($p = 0.45$, $r = 0.16$, Fig 1).

Table 1: The descriptive anthropometric of studied patients

Variable	Mean	Standard deviation	Range
Age (years)	39.71	2.94	35 - 45
Weight (kg)	92	7.11	79 – 111
Height (cm)	174	1.81	171 – 178
Body mass index (kg/m^2)	30.3	2.04	26.7 – 35.4
Body Fat (%)	29.46	1.89	26.3 – 33.9
Abdominal Circumference (cm)	97.9	7.14	86 – 114
Hip circumference (cm)	97.1	5.48	84 - 113

Table 2: Serum level of IL-6 and Spirometrical characteristics of the study patients

Variable	Mean	Standard deviation	Range
FVC (%)	83	6.7	71 – 96
FEV1 (%)	77	5.3	69 – 88
FEV1/FVC (%)	68	3.1	60 – 71
PEF (%)	78	9.7	63 - 93

FVC, forced vital capacity; **FEV1**, forced expiratory volume in 1 s;
FEV1/FVC: forced expiratory volume in 1 s / forced vital capacity; **PEF,** Peak expiratory flow

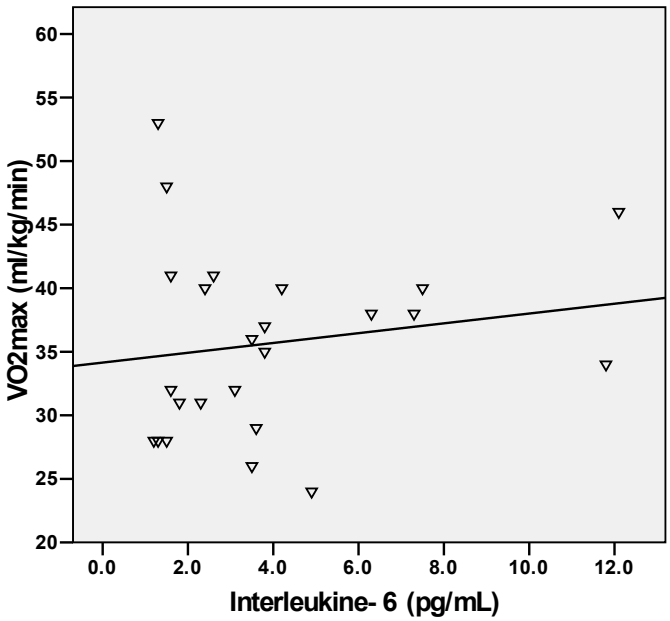

Fig 1: Relationship of serum IL-6 and VO2max in asthma patients: no significant correlation

DISCUSSION

Despite the sufficient evidence about the beneficial effects of exercise on energy homeostasis and cardiorespiratory fitness, no significant relationship between IL-6 serum levels, as an inflammatory cytokine, with VO2max, as a determinant indicator of cardiorespiratory fitness in asthmatic patients, was observed in this study. The fact that physical activity improves the inflammatory profile in healthy or patients populations has already been reported by many previous studies [16, 17], although some studies has reported increase in inflammatory cytokine following long-term exercises. As in a study, it was observed that the despite the improvement in cardiorespiratory fitness after 6 months of aerobic exercise, levels of the TNF-α, as an inflammatory cytokine, increased significantly [18]. Some studies also reported that short-term or long-term exercise programs do not affect inflammatory or anti-inflammatory cytokines [19]. However, the literature suggests that reduced levels of cardiorespiratory fitness are responsible for the increase in systemic inflammatory processes [18]. Adipose tissue is a major source of IL-6 secretion, and it was found that increased body fat is associated with reduced fitness [20].

Recognition of asthma as an inflammatory disease led numerous studies into the determination of symptoms of inflammation such as some cytokine such as IL-6 in inflammation of respiratory tracts. On the other hand, higher levels of IL-6, as an inflammatory cytokines, have been noted in allergic condition [10]. It is known that the level of this inflammatory cytokines in asthmatic patients is significantly higher compared to healthy individuals [11]. Some studies have also suggested that IL-6 levels are highly increased during asthma attacks [21]. Symptoms of inflammation of the respiratory tracts due to consumption of antigens are similar to when IL-6 levels are increased [22]. However, some literature has suggested that IL-6 levels increase in response to inflammatory conditions, rather than having a central role in inflammatory processes [23].

Mast cells and eosinophils are a source of IL-6 secretion. On the other hand, it has been found that the number of these cells increase with this disease, which in turn leads to secretion of higher levels of IL-6 under these conditions [24, 25]. IL-6 activates T cells and natural killer cells, that are characteristic of

asthma, and also, causes IgE synthesis through increased IL-4 activity. Based on this evidence, its importance in the pathophysiology of asthma has been repeatedly raised by researchers [22]. In another words, IL-6 is a cofactor or effective stimulus for the secretion of IgE from ß-cells by increasing the effect of IL-4, which refers to the role of this inflammatory mediator in responses of T2 cells and the presence of asthma [10]. Data have revealed that the disruptions in IL-6 levels are associated with pathophysiological changes in respiratory tracts, so that their increase leads to higher strength or narrowing of the respiratory tract.

On the other hand, the literature has consistently emphasized on lower levels of cardiorespiratory fitness in asthmatic patients compared to healthy individuals [2]. In other words, narrowing of the respiratory tract or resistance of the respiratory pathways reduces the oxygen transfer of to the lungs in these patients, which leads to reduced oxygen supply to the tissues, especially the respiratory muscles and decreased VO2max. Both IL-6 and VO2max are disrupted in asthmatic patients, and literature has supported reduced VO2max and increased IL-6 in these patients. However, the findings of this study suggest insignificant relationship between them in these patients, which is somewhat controversial. Although the lack of significant relationship between these variables may be assigned to the low number of samples, it is possible that these two variables are not directly but indirectly affecting the other hormonal or psychological mediators' levels. In this context, the findings of a recent study showed a significant relationship between IL-6 and the periphery of waist independent of fitness level on each of them [26]. Consistent with findings in other studies, no relationship between IL-6 and VO2max in American and Peruvian women was observed [18]. Lack of relationship between IL-6 and VO^2max in this study, even after 6 months of aerobic exercise was observed which was associated with a significant increase in VO_2max [18].

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