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Research Article

AEROBIC CAPACITY IS DIRECTLY RELATED WITH SYSTEMIC INFLAMMATORY IN MALES WITH CHRONIC ASTHMA

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ABSTRACT
Previous observations have shown that asthma is associated with systemic inflammation and low cardiorespiratory fitness, but the physiopathological mechanisms underlying these associations are largely unknown. This study's purpose was to determine whether cardiorespiratory fitness (measured as oxygen consumption per unit of time (VO2max)) is associated with serum TNF-α as inflammatory cytokine in asthma patients. For this purpose fasting serum TNF-α and VO2max were measured in twenty one adult men with chronic asthma. Pearson's correlation coefficient was run for testing of correlation analysis between mentioned variables. A negative significant correlation was found between serum TNF-α and cardiorespiratory fitness ($p = 0.022$, $r = 0.50$). VO2max was also negatively correlated with body weight, BMI, body fat percentage and resting heart rate ($p < 0.05$). Among anthropometrical markers, abdominal circumference was positively correlated with serum TNF-α in studied patients ($p = 0.041$, $r = 0.45$). This study indicates that low cardiorespiratory fitness is associated with increased systemic inflammation in asthma patients.

Keywords: *Asthma, Aerobic Capacity, Systemic Inflammation*

INTRODUCTION
Previous studies indicated a significant relationship between systemic inflammation and obesity and other diseases associated with metabolic disorders (Vinagre *et al.*, 2014; Dahlén *et al.*, 2014). According to these studies, especially those conducted on patients with type 2 diabetes or cardiovascular disease, the increased levels of inflammatory cytokine are associated with increased cardiovascular risk factors (Jung *et al.*, 2014; Aydin *et al.*, 2013). On the other hand, some studies have reported a close positive relationship between inflammatory markers and lipid levels. In addition, a significant negative relationship was found between inflammatory markers and cardiorespiratory fitness levels (Varra *et al.*, 2012).
But there is not still a general consensus on the relationship between cardiorespiratory fitness and all inflammatory cytokines. It seems that each of them follows a distinct pattern. Most studies examined the relationship between specific cytokines such as C - reactive protein (CRP) and cardiorespiratory fitness level (Byrd-Williams *et al.*, 2008; Naidoo *et al.*, 2012). There are few studies on the relationship between cardiorespiratory fitness and other cytokine in healthy and diseased populations. There are also few studies on the relationship between serum levels of Tumor necrosis Factor alpha (TNF-α) and cardiorespiratory fitness levels in asthmatic patients. TNF-α is mainly synthesized and secreted by adipose tissue macrophages. A significant correlation was found between systemic levels of TNF-α and cardiovascular risk factors such as blood triglyceride levels (Jovinge *et al.*, 1998).
Asthma is the disease of respiratory tract with an allergic origin. Physiologically, it is associated with the narrowing of the airways of the respiratory tract. From a clinical perspective, it is associated with sudden attacks of shortness of breath, coughing and wheezing (Figureueroa-Munoz *et al.*, 2001). On the other hand, it is well known that asthmatic patients suffer from the resistance of respiratory pathways, shortness of breath and reduced cardiorespiratory fitness levels (Bonsignore *et al.*, 2004). The reduced VO2max level has been repeatedly reported as a decisive indicator of cardiorespiratory fitness (Varray *et al.*, 1993). On the other hand, a close relationship has been found between systemic inflammation and asthma (Bergmann *et al.*, 2009). TNF-α is possibly involved in the lack of a systematic inflammatory response of

the respiratory pathways in asthmatic patients. The increased levels of this inflammatory proteins or its over-expression in the respiratory pathways have been reported in asthmatic patients (Ying *et al.*, 1991; Bradding *et al.*, 1994).

Reduced cardiorespiratory fitness levels and increased levels of TNF-α and its over-expression in the respiratory pathways in asthmatic patients as well as limited studies on the relationship between them in asthmatic patients provide the grounds to perform a study on the relationship between VO2max and TNF-α in asthmatic patients.

MATERIALS AND METHODS

Methods

Subject Characteristics

Participants included twenty nine non-trained adult men (aged 32 ± 6.9 years, body weight 94 ± 5 kg, height 173 ± 2.6cm) with chronic asthma (FEV1/FV, 69 ± 3%). All patients were non-smokers.

Each participant received written and verbal explanations about the nature of the study before signing an informed consent form. Asthma diagnosis at least for 3 years was main inclusion criteria. All subjects were non-smokers and had not participated in regular exercise/diet programs for the preceding 6 months. Subjects included individuals with no cardiovascular diseases, gastrointestinal diseases, kidney and liver disorders or diabetes. This study was conducted with the approval of the Ethics Committee of Islamic Azad University.

Anthropometry

Weight and height of the participants were measured by the same person when the participant had thin clothes on and was wearing no shoes. Anthropometric measurements were performed in all study participants before breakfast. Weight was measured by an electronic balance and height by a stadiometer. Body Mass index (BMI) was calculated using the formula body weight/height2 in terms of kg/m². Abdominal circumference was measured in the most condensed part using a non-elastic cloth meter.

Respiratory Function

Respiratory function was assessed by spirometry. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) and FEV1/FVC ratio were measured twice using a portable spirometer (Minispire, Italya).

Laboratory Analyses and Exercise Test

For measuring serum TNF-α, we used fasting blood samples. All subjects were asked to attend laboratory after 10 – 12 h overnight fast between 8 a.m to 9 a.m. and venous blood samples (5 ml) were collected. Subjects were asked to avoid doing any heavy physical activity for 48 hours before blood sampling. Serum TNF-α was assessed by ELIZA methods. The intra- assay and inter-assay coefficient of variation of the method were 6 and 7.4 respectively.

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 (Mullis *et al.*, 1999). Resting and sub max heart rate were also monitored.

Statistical Methods

The data were reported as mean ± SD, and analysed using the SPSS W statistical package, version 16.0. We verified normal distribution of variables with a Kolmogorov–Smirnov test, and the parametric variables with skewed distribution were expressed as mean ± SD. Pearson's correlation coefficient was performed to examine the relationship between serum TNF-α and physiological components. A P-value of < 0.05 was considered to be statistically significant.

RESULTS AND DISCUSSION

Results

In present study, the association of cardiorespiratory fitness and systemic inflammation with emphasis on serum TNF-α was assessed in adult asthma patients.

Table 1 shows the descriptive anthropometric and biochemical and physiological features of the studied patients. Normally distributed data were presented as means ± Standard deviation /standard error of mean (SEM).

Based on Pearson's correlation coefficient, a negative significant correlation was found between serum TNF-α and cardiorespiratory fitness ($p = 0.022$, $r = 0.50$, Figure 1).

VO2max was also negatively correlated with body fat percentage ($p = 0.013$, $r = 0.53$, Figure 2), body weight ($p = 0.017$, $r = 0.51$) and body mass index ($p = 0.001$, $r = 0.65$) not with abdominal circumference ($p = 0.037$, $r = 0.46$). VO2max as Cardiorespiratory fitness showed good negative correlation with resting heart rate ($p = 0.000$, $r = 0.000$).

Between all anthropometrical markers, only abdominal circumference was positively correlated with serum TNF-α in studied patients ($p = 0.041$, $r = 0.45$, Figure 3).

Table 1: Descriptive characterstics of anthropometrical, physiological and spiromertry markers of studied payients

	N	Minimum	Maximum	Mean	Std. Deviation
Age (year)	21	32	58	39.00	6.870
Height (cm)	21	169	178	172.76	2.587
Weight (kg)	21	78	109	93.90	9.492
Body mass index (kg/m2)	21	27.0	35.6	31.433	2.8361
Abdomina circumference (cm)	21	90	118	103.38	8.709
Body fat (%)	21	26.3	34.6	30.824	2.4797
Resting heart rate (bpm)	21	71	92	80.38	6.376
IgE	21	164	558	352.24	99.835
TNF-a (pg/ml)	21	30.0	98.0	54.333	22.8415
Forced vital capacity	21	73	100	88.19	8.841
Forced expiratory volume in 1 second	21	58	87	76.10	8.578
FEV1/FVC	21	62	72	68.95	2.941
VO2max (ml/kg/min)	21	22	58	37.38	10.947

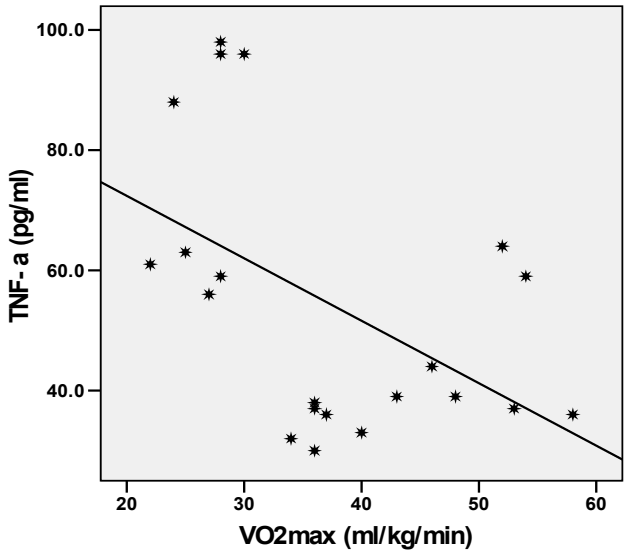

Figure 1: Relationship between serum TNF-α and VO2max. This Figure shows that serum TNF-α negatively correlated with VO2max

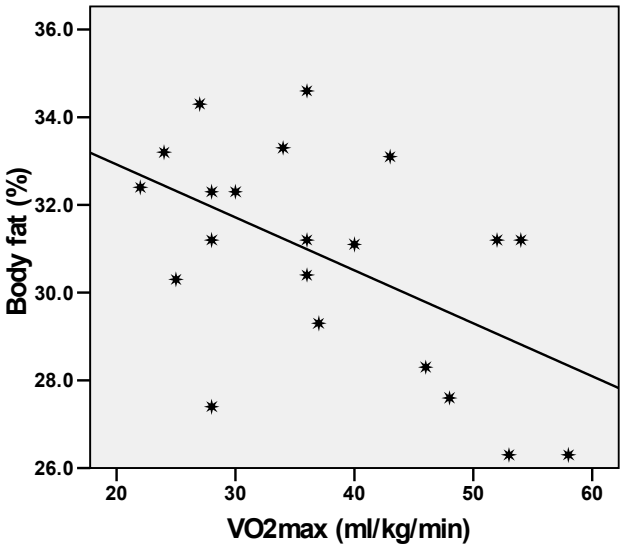

Figure 2: Relationship between VO2max and body fat (%). This figure shows that VO2max negatively correlated with body fat (%).

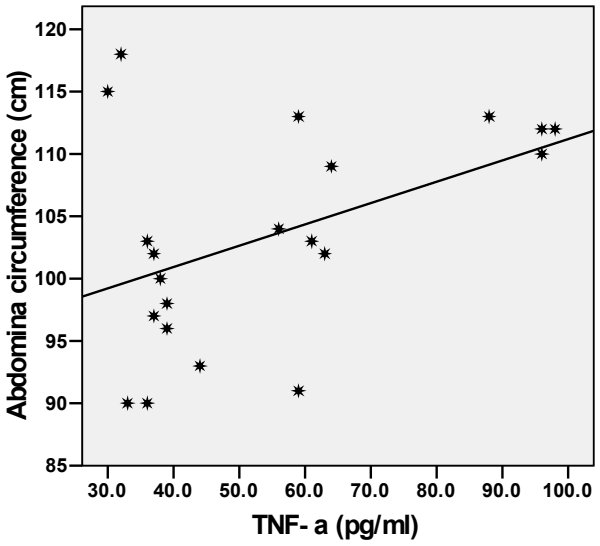

Figure 3: Relationship between serum TNF-α and abdominal circumference. This figure shows that serum TNF-α positively correlated with abdominal circumference.

Discussion

Although some previous studies showed the lack of relationship between the cardiorespiratory fitness and inflammatory markers in other healthy and diseased populations (Varra *et al.*, 2012), the present study showed as significant relationship between the serum levels of TNF-α in asthmatic patients and cardiorespiratory fitness. In other words, the findings showed a significant inverse relationship between the serum levels of TNF-α as an inflammatory cytokine and VO2max as a measure of cardiorespiratory fitness in asthmatic patients.

Some studies revealed that TNF-α as an inflammatory cytokine affects several processes involved in the pathophysiology of asthma (Hotamisligil *et al.*, 1993; Vgontzas *et al.*, 1997; Zhang *et al.*, 2001). The increase in this inflammatory cytokine is associated with enhanced synthesis of eosinophils in epithelial cells (Godding *et al.*, 1995) which in turn release autoxine affecting eosinophils involved in pulmonary fibroblasts (Sato *et al.*, 2001) and epithelial cells (Lilly *et al.*, 1997; Koyama *et al.*, 1999). It also causes the secretion of IL-6 in eosinophils (Gounni *et al.*, 2000), over-production of IL-8 by alveolar macrophages (Cromwell *et al.*, 1992) and bronchial epithelial cell damage (Kampf *et al.*, 1999), activity of endothelial cells (Bjornsdottir *et al.*, 1999) and bronchial stenosis (Martin *et al.*, 2001).

Aside from asthma, several previous studies revealed that the low or reduced levels of cardiorespiratory fitness are associated with an increased risk of glucose intolerance and incidence of type 2 diabetes in individuals with normal glucose levels. These mechanisms are independent of adipose tissue levels. On the other hand, reduced cardiorespiratory fitness levels are responsible for systemic inflammation processes. However, another study showed a direct correlation between VO2max and TNF-a before and after 6 months of aerobic training which is somewhat controversial (Lindgärde *et al.*, 2011). In contrast, the training program led to a significant increase in both TNF-α and VO2max levels in the study population. The findings of another study showed no significant relationship between circulating levels of TNF-α with its expression in subcutaneous adipose tissue prior training and after three months of aerobic exercises (Arsenault *et al.*, 2009). This is likely that the increase in TNF-α levels after aerobic training is mostly derived from other tissues isolated from adipose tissue (Lindgärde *et al.*, 2011). On the other hand, the researchers found a positive correlation between TNF-α and VO2max in American women before and after 6 months of aerobic exercise independent of the influence of adipose tissue (Lindgärde *et al.*, 2011). In another study, no significant correlation was found between TNF-α and VO2max in overweight young men. However, the relationship between VO2max and IL-6 was negative and significant (Varra *et al.*, 2012). In another study on overweight children, the serum levels of TNF-α had a negative and significant correlation with VO2max (Utsal *et al.*, 2013). The above findings suggest discrepancies in the findings on the relationship between these variables in different populations. Based on this evidence, it may be concluded that the relationship between inflammatory markers and cardiorespiratory fitness does not follow as similar pattern depending on the type of population and cytokine. The findings of these studies are different with those found in this study. Although a causal relationship was not found between TNF-α and VO2max in asthmatic patients, the correlation between them suggest that these two variables affect each other directly or indirectly affecting other mediators involved in systemic inflammation or inflammation of the respiratory pathways.

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