RESEARCH PAPER

Increased interleukin-6 is associated with low cardiorespiratory fitness in healthy people

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Abstract

To determine the relationship of maximal oxygen consumption as a cardiorespiratory marker with systemic inflammation. We measured fasting serum interleukin-6 (IL-6) and Tumor necrosis factor-α (TNF-α) and cardiorespiratory fitness (VO2max) in forty one healthy sedentary adult men (aged; 38 ± 4 year, BMI: 32 ± 6.14 kg/m2). The bivariate association between VO2max with IL-6 and TNF-α was examined with the Spearman rank correlation analysis. Serum IL-6 levels significantly negatively correlated VO2max (p = 0.009). A borderline signigcant negative association was observed between VO2max and TNF-α (p = 0.054). Based on this data, it was concluded that cardiorespiratory fitness may be predictor of systemic inflammation.

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Introduction

It has been demonstrated that systemic inflammation is a predictor of cardiovascular disease (Libby *et al.,* 2004). Chronic disease has been strongly correlated with inflammation resulting from the body's release of inflammatory cytokines as a result of injury or infection (Puglisi *et al.,* 2008). The specific mechanisms responsible for these observations are a matter of some debate. Systemic inflammation and increased some cytokines has been known as an important factor in the progression of the syndrome of chronic heart failure (Anker *et al.,* 2004). The inflammatory cytokines secreted by adipose tissue and the other cell types are released into circulation where they regulate different tissues through their local, central, or peripheral actions (Anker *et al.,* 2004). It has been suggested that obesity is associated with elevated levels of tumor necrosis factor-(TNF-) alpha and interleukin-(IL-) 6 have been identified as prognostic heart failure markers (Rauchhaus *et al.,* 2000; Deswal *et al.,* 2001). Plasma concentrations of TNF-α as an inflammation cytokine have been positively correlated with elevated plasma triglycerides and heart failure (Kern *et al.,* 1995). It was found that this cytokine is produced 7.5 times more by the adipose tissue in obese subjects compared with lean counterparts (Kern *et al.,* 1995). Obese persons have increased levels of intramuscular cytokines (Saghizadeh *et al.,* 1996). Increased TNF-α and IL-6 are associated with lower muscle mass or strength and mobility disability (Ferrucci *et al.,* 1999; Ferrucci *et al.,* 2002; Visser *et al.,* 2002), and high IL-6 concentration contribute synergistically to impaired mobility (Cappola *et al.,* 2003).

Regular physical activity, independently of BMI, is associated with lower risk of all cause mortality (Hu *et al.,* 2005). Moreover, physical inactivity has been identified as a stronger predictor than risk factors such as hypertension, hyperlipidemia, diabetes, and obesity for all-cause mortality (Myers *et al.,* 2004).

Cardiorespiratory fitness as ability of a person to perform aerobic exercise is an important factor associated by lower rates of several clinically important outcomes such metabolic syndrome, myocardial infraction and other cardiovascular disease (Kurl *et al.,* 2003). VO2 max is an indicator physical fitness and incorporates aspects of respiratory capacity, cardiovascular health and muscle fitness. It is generally accepted thatVO2max is an accurate predictor of cardiorespir atory fitness (Kullo *et al.,* 2007; Shephard *et al.,* 1968).

Specific interventions promoting weight loss, exercise, or intake of antioxidants have been used by several investigators in an effort to decrease inflammatory cytokines (Puglisi *et al.,* 2008). Reduced physical activity and sedentary lifestyle patterns are among contributing factors in obesity and increased fat tissue, which are in turn associated with increased levels of inflammatory cytokines of body fat tissues. It is also the hypothesized that increased physical activity and active lifestyle bring about increased levels of cardio-respiratory fitness in athletes, obese, or obesity related diseases. There is also the question whether the level of cardio-respiratory fitness associated with levels of inflammatory cytokines are connected with the incidence of cardiovascular disease and mortality. Hence, the main aim of this study is to determine the relationship between VO2max and the inflammatory cytokines such as IL-6 and Tnf-α.

Material and methods

The study population consisted of 41 healthy sedentary adult men that participated in this study by voluntarily. The age range was 36-43 years, with a mean age of 38 years (BMI: 32 ± 6.14 kg/m2). These 41 men did not differ signigcant from the remaining participants regarding baseline measurements of body weight, body mass index (BMI), waist circumference. Approval for the original study had been given in 2010 and 2011 by

the Ethics Committees of Islamic Azad University, Iran. After the nature of the study was explained in detail, informed consent was obtained from all participants.

None of the participants had ongoing cardiovascular disease, infections, renal diseases, hepatic disorders, use of alcohol, and use of nonselective β blockers and presence of malignancy.

Participants were non-athletes, non-smokers and non-alcoholics. Daily food records were kept for 48 h preceding each test session, and subjects were instructed to refrain from caffeine consumption and intense physical activity for 24 h before testing. No difference was observed in the subjects' diets 48 h before each measurement.

Table 1. The descriptive anthropometric and biochemical features of studied subjects.

Variable	Mean	Standard deviation	Range
Age (years)	38	4	36 – 43
Weight (kg)	101	11	90 - 106
Height (cm)	177	10	166 - 186
Body mass index (kg/m²)	32.26	6.14	26 - 34
Systolic blood pressure (mmHg)	128	11	119 - 139
Diastolic blood pressure (mmHg)	89	7	80 - 93
Cholesterol (mg / dl)	181	26	171 - 214
Triglyceride (mg / dl)	165	32	148 - 186
Low density lipoprotein (mg / dl)	119	31	110 - 149
high density lipoprotein (mg / dl)	43	5	39 - 49
IL-6 (pg/ml)	15.58	4.12	12.3 - 18.8
TNF-α (pg/ml)	69	14	51 - 78
VO2max (mL. kg-1. min-1)	25.41	3.12	23 - 29

The examination procedures were the same at all three occasions. The examinations took place in the morning after an overnight fast at Alternative. Weight was measured by an electronic balance and height by a stadiometer. Height and body mass were measured using a wall- mounted stadiometer and a digital scale, respectively. Body mass index was calculated as body mass (in kilograms) divided by height squared (in square meters). The arterial systolic and diastolic blood pressures (BP) were calculated after they rested for 10 minutes with a mercury manometer with appropriate sleeves from the right and left arm, in sitting position on the condition that they had not eaten anything, had not taken any caffeine, had not smoked or exercised thirty minutes before the measurement, and then the averages were calculated. 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 (Mullis *et al.,* 1999).

Basal, fasting blood samples were taken after an overnight fast to determine IL-6 and TNF-α. Serum IL-6 was determined by ELISA method (Enzyme-linked Immunosorbent Assay for quantitative detection of human IL-6). The Intra- assay coefficient of variation and sensitivity of the method were 3.4% and 0.92 pg/mL, respectively. Serum TNF-α was determined by ELISA method (Enzyme-linked Immunosorbent Assay for quantitative detection of human TNF-α total). The Intra- assay coefficient of variation and sensitivity of the method were 7.7% and 5.0 pg/mL, respectively.

Statistical analyses

Data were analyzed using the program SPSS software version 15. The Kolmogorov-Smirnov test was applied to determine the variables with normal distribution. Pair-wise correlations between VO2max with IL-6 and CRP were assessed by Pearson's partial correlation coefficients before and after adjustment for age.

Results

Anthropometric and metabolic characteristics of the study participants are shown in Table 1. All values are represented as mean ± SD. The finding of Kolmogorov- Smirnov's test showed Normal distribution of data.

The data of Pearson's partial correlation showed that VO2max as cardiorespiratory fitness is negatively related with serum IL-6 (p = 0.009, r = 0.65). This data demonstrated that increased cardiorespiratory fitness is associated with decreased systemic inflammation. In other word, an increase in VO2max may be affects serum Il-6 concentration. Although, the relation between VO2max and TNF-α was liner and inverse, but this relation was not significant from statistical perspective (p = 0.054, r = 0.36). Small number of participants was a main limitation of this study. It is likely that low number of participants to be a factor in lack significant relation between VO2max and TNF-α in this study. Because, the finding of Pearson analysis showed a borderline signigcant negative association between VO2max and TNF-α values. In addition, VO2max levels correlated negatively with body weight, systolic and diastolic blood pressure, abdominal to hip ratio (WHO) and BMI in studied subjects (p < 0.05).

Discussion

The main finding of our study was a high negative correlation between serum IL-6 and VO2max as a predictor marker of cardiorespiratory fitness. Low physical activity and cardiorespiratory fitness are associated with higher levels of IL-6 (Pischon *et al.,* 2003).

Elevated levels of serum IL-6 strongly predict mortality and functional decline in older persons (Reuben *et al.,* 2002). Not only does adipose tissue release cytokines, but also skeletal muscles express cytokines that have direct autocrine and paracrine effects (Saghizadeh *et al.,* 1996). TNF-*α* is generally accepted that play a critical role in the pathogenic mechanisms of a number of chronic inflammatory diseases (Cristina *et al.,* 2005). Binding of TNF-*α* to its receptors results in activation of intracellular signaling processes that lead to release of pro-inflammatory mediators and apoptosis, through the recruitment and activation of adaptor proteins (Wajant *et al.,* 2001). It was observed that a basal circulating IL-6 level is sensitive to the extent of regular physical activity (Fischer *et al.,* 2007). In addition, some other studies observed that basal IL-6 levels are lower in humans devoted to a physically active lifestyle (Reuben *et al.,* 2003; Colbert *et al.,* 2004; Panagiotakos *et al.,* 2005). Exercise training has been demonstrated that improve the inflammatory profile by inhibition of cytokine chemokines production, regulation of monocyte activation and adhesion, inhibition of inflammatory cell-growth signals, reduction of soluble apoptosis signaling molecules (Adamopoulos *et al.,* 2002), and attenuation of monocyte endothelial cell adhesive interaction (Adamopoulos *et al.,* 2011).

In present study, despite a negative significant correlation between serum IL-6 and VO2max, there was not significant correlation between TNF-α with VO2max. In fact, despite a liner and negative relation between VO2max and TNF-a, but this relation was not significant from statistical perspective. A limitation of our study may be the small number of participants, although this limitation seems not to be a major factor affecting the results and end points of the study. It seems that lack signigcant correlation between VO2max and TNF-a may be due to small number of participants.

On the other hand, it is also important to note that production and removal of TNF-alpha and IL-6 may be, at least partially, from independent mechanisms and may have opposing effects (Smart *et al.,* 2011). While there is reasonable evidence supporting our present findings that basal IL-6 levels are associated with cardiorespiratory fitness, the possible mechanisms involved are not well known. These findings clearly show that high levels of inflammatory cytokines in circulating blood leads to reduced cardiovascular capacity and ultimately to cardiovascular diseases like diabetes or metabolic syndrome and other chronic diseases associated with obesity. The inverse relationship between active lifestyle and higher levels of cardiovascular fitness and low levels of inflammatory cytokines, especially IL-6 in the subjects shows that exercise and active lifestyle as a none-pharmacological anti-inflammatory factor leads to decreased levels these cytokines.

To support this data, in a recent study, a strong and highly signigcant correlation was observed between improvements in peak VO2 (15%) and reduction in TNF-alpha and IL-6 (Adamopoulos *et al.,* 2002). Also, Plasma TNF-alpha is also documented to decrease after twice daily 6-minute walk tests in heart failure patients (Xu *et al.,* 2002). Of course, it has been known for some time that alterations in levels of the cytokines IL-6 and TNF-alpha are not necessarily uniform (Smart *et al.,* 2011). Additionally, some studies show an association between high physical fitness and low serum level of cytokines as IL-6, independently of fat mass, tobacco consumption or endocrine and metabolic deficiencies. Hence, creating a dynamic lifestyle and implement physical activity in healthy subjects and chronic disease such as cardiovascular and respiratory diseases as a non-pharmaceutical ways to reduce inflammation Systemic recommended.

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