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Pro-inflammatory cytokine Interleukin-1 beta is associated with cardiovascular fitness in sedentary diabetic patients

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Abstract

To determine the relationship of interleukin-1 beta (IL-1β) to cardiovascular fitness and lipid profile in type II diabetic. Fasting blood samples were collected in 38 sedentary adult men with type II diabetic (age 38 ± 5 years, body mass index: 31 ± 3 Kg). After overnight fast in order to measuring IL-1b and lipid profile as total cholesterol (TC), triglyceride (TG), low and high density lipoprotein (LDL, HDL). Maxima oxygen consumption was measured by a stepwise incremental bicycle test. Pearson correlations were used to establish the relationship between variables. Serum IL-1β concentration was negatively related to VO2max and positively related with TC, TG, LDL and resting heart rate ($p < 0.05$). Fasting serum IL-1b was not correlated with HDL ($p = 0.214$). In conclusion, our data demonstrate a relationship between cardiovascular fitness and systemic inflammation in diabetic patients. These finding suggests a sedentary lifestyle and low cardiovascular fitness is associated with increased IL-1β and systemic inflammation.

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Introduction

Nowadays obesity and increase in fat tissue, especially abdominal obesity are the major problems of public health in the worldwide that will causes chronic cardiovascular abnormalities especially type 2 diabetic in middle-aged people and adults (Galic *et al.,* 2010). Type 2 diabetes is the most common endocrine and metabolic diseases in throughout worldwide which involves 30 to 40 percent of obese people (Lazar, 2005). Diabetic is a disease related to obesity and a risk factor for cardiovascular disease which is also associated with arthrosclerosis and (Gu *et al.,* 1998). Some studies have introduced expansion factors of cardiovascular diseases caused by type 2 diabetes as dyslipidaemia, increase of triglyceride (TG) and low-density lipoprotein (LDL) and decrease of high dense lipoprotein (HDL) (Uusitupa *et al.,* 1993; Barrett-Connor *et al.,* 1982).

Adipose tissue is a main source of energy storages and has special significance in energy homeostasis. On the other hand, adipose tissue is not only an inexhaustible source of fat reserve but also an endocrine organ that secrete some biologically active cytokines named adipokines such as leptin, resistin, Visfatin and also adiponectin and interleukins which plays an important role in inflammation, cardiovascular fitness, energy homeostasis and fat - carbohydrate metabolism (Kershaw *et al.,* 2004; Sell *et al.,* 2006). Among them, interleukin 1-beta (IL-1β) is a proinflammatory cytokine that plays important roles in inflammation. However, the role of this cytokine under physiological conditions remains to be clearly delineated. A recent study showed that IL-1β plays an important role in lipid metabolism by regulating insulin levels and lipase activity under physiological conditions (Matsuki *et al.,* 2003). A number of studies have described a positive association between IL-1β gene polymorphism and obesity, suggesting functional effects on fat mass, fat metabolism and body mass (Manica-Cattani *et al.,* 2010). It is reported that serum or plasma of IL-1β is higher in type II diabetic patients than none-diabetic subjects (Osborn *et al.,* 2008; Maedler *et al.,* 2009; Dasu *et al.,* 2007). On the other hand, it is also important to note that cardiovascular or cardiorespiratory fitness in diabetic patients if lower than healthy people.

Physical activity or exercise training has been established to improve the inflammatory profile by inhibition of cytokine-chemokines production, regulation of monocyte activation and adhesion, inhibition of inflammatory cell-growth signals and growth factor production, reduction of soluble apoptosis signaling molecules (Adamopoulos *et al.,* 2002). Some studies have been studied the relation between cardiovascular fitness with inflammation profile. For example, a recent study a statistical signigcant association between elevated serum cytokine levels (especially TNF-alpha) and exercise intolerance (Gielen *et al.,* 2003). But, the relationship between serum IL-1β with cardiovascular fitness has received limited attention. Therefore, in this study we investigated serum IL-1β in relation to maximal oxygen consumption (VO2ma) as a determinant of cardiovascular fitness in type II diabetic patients. We also determined the relationship of this inflammation cytokine with fat profile in these patients.

Material and methods

This semi-experimental study was conducted as part of ancillary study and was approved by Research Council and Ethics Committee of Islamic Azad University, Iran. The main purpose of this study was to compare serum IL-1β, between sedentary adult obese men with and without type 2 diabetic and also to examine its relationship with cardiovascular fitness and lipid profiles in diabetic patients. For this purpose, 38 sedentary adult obese men with diabetes symptoms (type II diabetic) and without diabetes (n = 34) matched for age (38 ± 5 years of old) and BMI (30 ≤ BMI ≤ 36) participated in this study by accidentally samples. After the nature of the study was explained

in detail, informed consent was obtained from all participants.

Table 1. Mean and standard deviation of Baseline level of anthropometric and metabolic characteristics of studied subjects.

Variables	Diabetic group	None-diabetic group
Age (year)	38 ± 5	36 ± 6
Weight (kg)	99 ± 10	98 ± 8
Height (cm)	175 ± 7	174 ± 8
Body Fat (%)	32.35 ± 3.11	32.37 ± 2.36
Body mass index (kg/m^2)	31.75 ± 3.12	23.18 ± 2.44
Triglyceride (mg / dl)	183 ± 33 *	165 ± 26
Total Cholesterol (mg / dl)	203 ± 36 *	181 ± 39
Low density lipoprotein (mg / dl)	133 ± 24 *	111 ± 33
high density lipoprotein (mg / dl)	45 ± 6	44 ± 5
VO2max (mL. kg-1. min-1)	26.11 ± 3.24	25.44 ± 6
Heart rate (bpm)	83 ± 8 *	77 ± 11
IL-1β (ng/ml)	2.92 ± 0.36 *	2.1 ± 0.44

Subjects with a history or clinical evidence of impaired fasting glucose or diabetes, recent myocardial infarction, congestive heart failure, active liver or kidney disease, the other chronic diseases or who were on medications known to alter insulin sensitivity were excluded of none-diabetic groups. Inclusion criteria for diabetic group were existing type 2 diabetic for at least two years. In addition, cerebrovascular disease, kidney and liver disease, growth hormone deficiency and anemia and the other metabolic diseases were of exclusion criteria of the diabetic groups. All subjects were non-smokers and had not participated in regular exercise/diet programs for the preceding 6 months. In diabetic groups, those that were unable to avoid taking hypoglycemic drugs or insulin sensitivity-altering drugs for 12 hours before blood sampling were also barred from participating in the study.

Anthropometric measurements (body height and weight, waist and hip circumference) were performed with the subjects wearing light underwear and without shoes. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m2). Cardiorespiratory fitness was assessed as VO2max (mL kg-1 min-1) was measured using a bicycle ergometer according to Astrand submaximal protocol (Mullis *et al.,* 1999).Resting heart rate (HR) was measured after a 15-min rest in a sitting position and in a quiet environment. The blood samples were collected after 12 hours overnight fast. Serum IL-1β was determined by ELISA method (Enzyme-linked Immunosorbent Assay for quantitative detection of

human IL-1β), using a Biovendor- Laboratorial kit made by Biovendor Company, Czech. The Intra- assay coefficient of variation and senFsitivity of the method were 5.1% and 0.3 pg/mL, respectively. Triglyceride, total cholesterol, HDL-cholesterol was measured directly with enzymatic methods (Randox direct kits) using Kobas Mira auto-analyzer made in Germany.

Statistical analysis

Statistical analyses of data were performed using the SPSS software version 15.0. For the descriptive statistics after having checked the normality of the variables using the Kolmogorov-Smirnov test. An Independent sample T-test was used to compare the serum levels of all variables between diabetic and none-diabetic subjects. The bivariate associations between IL-1β concentration with VO2max, heart rate and lipi profile biomarkers in diabetic patients. The differences between the groups were considered to be significant at a p-value of ≤ 0.05.

Results

Table 1 show the descriptive anthropometric and biochemical features of the study groups. Data were expressed as individual values or the mean ± SD. There was no marked difference between diabetic and none-diabetic groups (p ≥ 0.05). Serum IL-1β levels were significantly higher in diabetic patients in comparison to none healthy subjects (p = 0.019). In addition, fasting lipid profile (LDL, TG, TC) were significantly higher in the type 2 diabetics than in the none-diabetic groups (p < 0.05). HDL concentration and VO2max were almost the same in two groups (p ≥ 0.05).

Serum IL-1β was negatively related with VO2max (p = 0.000, r = 0.66, Fig 1) and positively related with resting heart rate (p = 0.000, r = 0.63, Fig 2) in studied patients. These data indicate serum IL-1β is negatively associated with cardiovascular fitness in studied patients. A significant positive association were observed between serum IL-1β with TG (p = 0.000, r = 0.72), TC (p = 0.000, r = 0.59), LDL (p = 0.041, r = 0.43) and visceral fat (p = 0.004, r = 0.47) in diabetic patients, while we did not significant correlation between IL-1β and HDL (p = 0.214, r = 0.14).

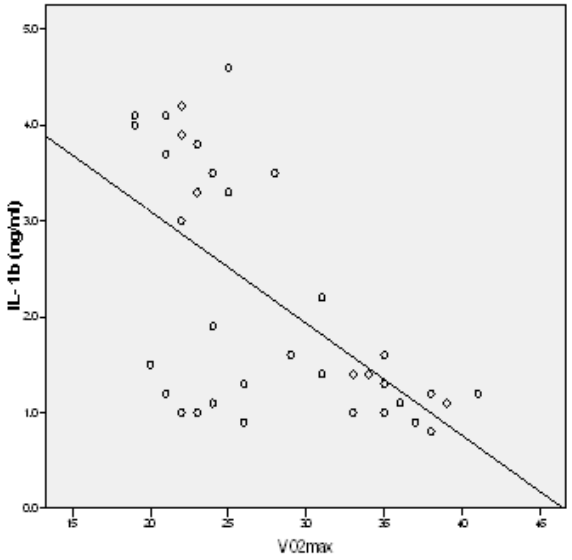

Fig 1. The correlation pattern between serum Il-1b and VO2max in studied patients. This illustration indicates a significant negatively association between serum IL-1b and VO2max in studied patients.

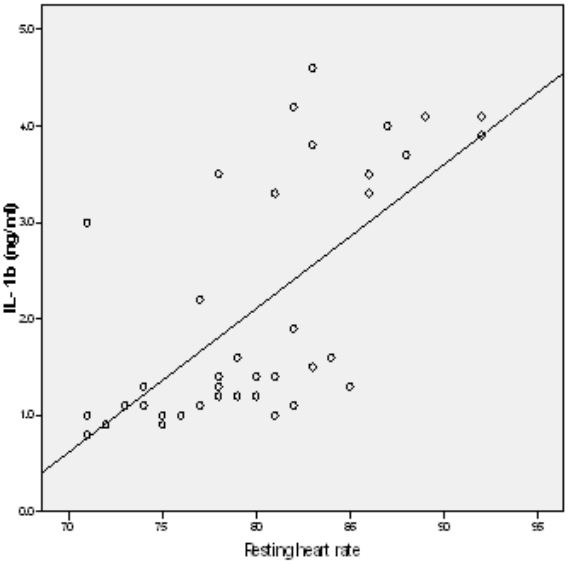

Fig 2. The correlation pattern between serum Il-1b and resting heart rate in studied patients. This illustration indicates a significant negatively association between serum IL-1b and resting heart rate in studied patients.

Discussion

Statistical analysis of present study showed that the baseline levels of total cholesterol, triglyceride, low density lipoprotein and resting heart rate in diabetic patients are higher significantly than none-diabetic subjects. Serum IL-1β was also higher in diabetic patients whew compared to none-diabetic subjects. But, VO2max and high density lipoprotein were similar in two groups. The major finding of our study was a significant negative correlation between serum IL-1β and VO2max in studied patients.

Accumulating evidence indicates that the diseases related to metabolic syndrome are characterized by abnormal cytokine production, including elevated circulating IL-1β, increased acute-phase proteins, e.g., CRP (Sauter *et al.,* 2008) and activation of inflammatory signaling pathways (Juge-Aubry *et al.,* 2003). Recent evidence has shown that IL-1β plays a role in various diseases, including autoimmune diseases such as inflammatory bowel diseases and type 1 diabetes, rheumatoid arthritis, as well as in diseases associated with metabolic syndrome such as atherosclerosis, chronic heart failure and type 2 diabetes (Maedler *et al.,* 2009). Macrophage is known as the primary source of IL-1, but epidermal, epithelial, lymphoid and vascular tissues also synthesize IL-1. IL-1β production and secretion have also been reported from pancreatic islets (Maedler *et al.,* 2009). VO2max as a good determinant of cardiovascular fitness refers to the maximum amount of oxygen that an individual can utilize during intense or maximal exercise. This measurement is generally considered the best indicator of cardiovascular fitness and aerobic endurance. VO2 max is an indicator of your overall physical fitness and incorporates aspects of your respiratory capacity, cardiovascular health and muscle fitness. The ability of respiratory system to take in large volumes of air and the ability of your heart and blood vessels to transport oxygen from lungs to your muscles both contribute to VO2 max. Although VO2max in the obese and none obese diabetic subjects were almost the same in our study, some previous study suggests that its level in diabetic patients in lower than healthy individuals (Nadeau *et al.,* 2009).

Review of research evidence shows that an active lifestyle id associated with lower systemic inflammation in healthy or patients populations (Fallon *et al.,* 2001; Abramson *et al.,* 2002; Petersen *et al.,* 2006). In other words, regular exercise offers protection against all cause mortality and there is evidence from randomized intervention studies that physical training is effective as a treatment in patients with chronic heart diseases, type 2 diabetes and symptoms related to the metabolic syndrome. Chronic diseases such as cardiovascular disease, type 2 diabetes and cancer are associated with chronic low-grade systemic inflammation (Petersen *et al.,* 2006). It was reported that regular exercise induces anti-inflammatory effects with elevated levels of anti-inflammatory cytokines and suppression of inflammation cytokines (Petersen *et al.,* 2006). On the other hand, sedentary life style physical inactivity has been identified as a stronger predictor than risk factors such as hypertension, hyperlipidaemia, diabetes, and obesity for all-cause mortality (Myers *et al.,* 2004).

It has been hypothesized that sedentary life style physical inactivity is associated with low grade systemic inflammation. Chronic low-grade systemic inflammation has been established as a term for conditions in which a 2 to 3 fold increase in the systemic concentrations of TNF-a, IL-1, IL-6, IL-1ra, sTNF-R and CRP is reflected (Petersen *et al.,* 2006). Although the main source of these cytokines is unknown, it is the likely origin of them is mainly the adipose tissue.

The protective effects of physical activity and active life style against diseases such as cardiovascular disease, type 2 diabetes, colon cancer and breast cancer has been extensively reviewed (Lamonte *et al.,*

2005; Thune *et al.,* 2001). In this are, a recent study suggest that exercise could help reduce inflammation in white adipose tissue through mobilization of immune cells producing pro- and anti-inflammatory cytokines (Gomez-Merino *et al.,* 2007). Physical exercise in type 2 diabetic patients with the metabolic syndrome is associated with a significant reduction of inflammatory cytokines biomarkers, independent of weight loss (Balducci *et al.,* 2009).

The present study showed that the increase in serum levels of IL-1β as an inflammatory cytokine is associated with lower levels of VO2max. In fact, if we interpret these findings in a different way, we can say that inactivity or lack of physical activity which is linked with reduced cardiorespiratory or cardiovascular fitness is associated with increased levels of inflammatory cytokines, particularly IL-1β. Scientific sources have confirmed that lack of physical inactivity or a sedentary lifestyle is associated with increased resting heart rate in healthy subjects or patients. Indeed, measuring the resting heart rate is also another crucial indicator of endurance or cardiovascular fitness alongside VO2max. Positive and significant correlation between serum levels of IL-1β and resting heart rate is another key finding of this study indicating the inverse relationship between cardiovascular fitness and increased systemic inflammation. These findings suggest that increased resting heart rate is associated with increased IL-1β. In the end, based on the said findings it seems that measuring VO2max and heart rate as parameters of measuring cardiorespiratory fitness represents a good precursor for determination of the levels of IL-1β in diabetic patients. Though the main molecular mechanisms responsible for it are not yet fully understood which calls for further studies in this field.

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