Simultaneous increased Inteleukine-6 and decreased glucose concentration in response to a single bout cycling exercise

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Abstract

Pro-inflammatory cytokine interleukin-6 (IL-6) is known to play important role in glucose homeostasis. To investigate serum IL-6 response to acute exercise and to determine the relationship between Changes in its levels with changes in glucose concentration in response to exercise. Venous blood samples were obtained before and after a single bout incremental cycling test in order to measuring serum IL-6 and glucose concentration in eighteen none-trained adult overweight or obese men (26 ≤ BMI ≤ 33 kg/m2, 38 ± 6 years). Statistic analysis was done with SPSS 15.0 for Windows using by paired samples T-test and Pearson methods. Cycling exercise test resulted in significant increase in serum IL-6 (p = 0.021) and significant decrease in glucose concentration (p = 0.033). In response to exercise test, Changes in serum IL-6 was negatively correlated with change in glucose concentration (p = 0.000, r = -0.74). These finding suggest the anti-inflammatory effect of single bout exercise on glucose homeostasis.

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Introduction
Systemic inflammation has been long known to be a key factor in insulin resistance and glucose homeostasis (Rotter et al., 2003). Prospective studies in adults have shown that chronic low-grade inflammation may contribute to the pathogenesis of diseases such as atherosclerosis, type I- and type-II diabetes and the other metabolic diseases (Hotamisligil, 2006; Libby, 2006). In a recent study, IL-6 did not increase whole-body glucose disposal in either healthy subjects or patients with type 2 diabetes, whereas it reduced insulin concentrations in the patients to values comparable with those of the healthy subjects, suggesting that IL-6 might have favorable effects on insulin action (Petersen et al., 2005). It is reported that IL-6 enhances insulin-stimulated glucose transport (Stouthard et al., 1996) or glycogen synthesis (Weigert et al., 2004) in myotubes and/or adipocytes, but others (Rotter et al., 2003) have found opposite effects; thus, further studies are warranted. In general, though, IL-6 is known as an inflammatory cytokine and most studies point out that the levels of inflammatory cytokines in increases obese patients and obesity related diseases, but some recent findings have indicated that this cytokine, increases insulin-induced glucose transport (Carey et al., 2006). However there have been only a few studies on the fact that an increase in IL-6 leads to a decrease in blood glucose levels. Accumulating evidence suggests the protective effects of regular exercise against diseases such as cardiovascular disease, type 2 diabetes, colon cancer and breast cancer (Lamonte et al., 2005; Thune et al., 2001). No studies have tested the simultaneous responses of serum IL-6 and glucose concentration to a single bout exercise, and this is the main aim of the present study. We hypothesized that increased Inteleukine-6 is associated with decreased glucose concentration in response to a single bout cycling exercise.

Material and methods
Subjects
The Study Protocol was approved by the Ethics Committee of Azad University, Iran. Eighteen adult (38 ± 6 years mean ± standard deviation of mean (SD)) none-trained overweight or obese (26 ≤ BMI ≤ 33 kg/m²) men participated in the study. Participants were included if they had not been involved in regular physical activity in the previous 6 months. After the nature of the study was explained in detail, informed consent was obtained from all participants. This study was performed in order to evaluate serum IL-6 response to acute exercise and to determine the relationship between changes in its levels with changes in glucose concentration in response to a single bout cycling exercise.

Inclusion and exclusion criteria
Subjects included individuals with no cardiovascular diseases, gastrointestinal diseases, kidney and liver disorders or diabetes. In addition, if any of the people had been participating in regular exercise or diet program during the past 6 months, they were excluded study. In addition, exclusion criteria included inability to exercise and supplementations that alter carbohydrate-fat metabolism. The subjects were advised to avoid any physical activity or exercise 48 hours before the exercise test.

Anthropometrical and biochemical measurements
The weight and height of the participants were measured by the same person when the participant had thin clothes on and was wearing no shoes. 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 (BMI) was calculated using the formula body weight/height² in terms of kg/m². Venous blood samples were obtained before and after a single bout incremental cycling test in order to measuring serum IL-6 and glucose concentration. Cycling exercise test was a YMCA
standard test on leg ergometry cycle (Tunturi, made in Finland). This protocol was performed in 5 continues stage without rest between stages. Each stage lasted 3 minute (Mullis et al., 1999). Glucose was determined by the oxidase method (Pars Azmoun, Tehran, Iran). Serum IL-6 was determined by ELISA method ((Enzyme-linked Immunosorbent Assay for quantitative detection of human IL-6)) using a Bender Medsystems GmBH made in Austria. The Intra- assay coefficient of variation and sensitivity of the method were 3.4% and 0.92 pg/mL, respectively.

**Statistical analysis**
Data were analyzed by computer using SPSS software version 15.0. Normal distribution of data was analyzed by the Kolmogorov-Smirnov normality test. Student’s t-tests for paired samples were performed to determine whether there were significant within-group changes in the outcomes. The bivariate associations between changes in serum IL-6 and glucose concentration were examined with the Pearson rank correlation analysis in studied subjects. All statistical tests were performed and considered significant at a P ≤ 0.05.

**Results**
Anthropometrical measurements showed that all participants are overweight or obese. In this study, at first we determined serum IL-6 in relation to glucose concentration at baseline. A borderline significant negative association was observed between serum IL-6 and glucose concentration in pretest condition (p = 0.56, r = 0.25). Single bout cycling exercise resulted in significant increase in serum IL-6 in studied subjects (3.73 ± 0.69 vs 6.23 ± 1.44 pg/ml, p = 0.021).

Compared to pre-training, glucose concentration decreased significantly after exercise test (105 ± 12 vs 97 ± 11 mg/dl, p = 0.033). The statistical analysis by Pearson showed that changes in serum IL-6 after training was significant negatively related to changes in glucose concentration (p = 0.00, r = -0.74, Fig 1).

We also observed decreased glucose concentration by exercise test. The protective of exercise training was reported 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 (Petersen et al., 2006). IL-6 is the first cytokine present in the circulation during exercise and the appearance of IL-6 in the circulation is by far the most marked and its appearance precedes that of the other cytokines (Petersen et al., 2006). Obesity is associated with a chronic inflammatory response characterized by abnormal cytokine production, increased synthesis of acute-phase reactants and activation of
inflammatory signaling pathways (Moschen et al., 2010).

Serum IL-6 levels as inflammation cytokine are elevated in obese, diabetic patients (Ontana et al., 2004; Kopp et al., 2003). Recent findings demonstrate that Regular physical activity, independently of BMI, is associated with lower risk of all cause mortality (Hu et al., 2005). But, the response of inflammation cytokines to acute exercise is not fully understood. A marked increase in circulating levels of IL-6 was reported after exercise without muscle damage (Petersen et al., 2006). Plasma-IL-6 increases in an exponential fashion with exercise and is related to exercise intensity, duration, the mass of muscle recruited, and one's endurance capacity (Pedersen et al., 2003; Nishimoto et al., 2004). In present study, serum IL-6 levels were also significantly increased in response to acute exercise when compared with baseline levels. This data were observed in some previous studies (Ostrowski et al., 1998; Philippou et al., 2009). On the other hand, Single cycling test resulted in significant decrease in glucose concentration compared to pre-exercise.

There is also the question whether decreased glucose levels in response to exercise is caused by increased serum IL-6, and or changes in levels of these two parameters in this study in response to cycling activity, are independent of each other. It is possible that the increase in serum levels of IL-6 has somehow brought about a decrease in blood glucose concentration.

In present study, serum IL-6 was not significant related to fasting glucose in studied obese subjects in baseline. In this area, a number of studies have demonstrated that at resting conditions, acute IL-6 administration at physiological concentrations did not impair whole-body glucose disposal, net leg-glucose uptake, or increased endogenous glucose production in resting healthy young humans (Petersen et al., 2005). But, we observed a significant negatively correlation between them after cycling test. In other words, Changes in serum IL-6 was negatively correlated with change in glucose concentration in response to cycling exercise. Decreased plasma insulin was observed in response to IL-6 infusion, suggesting an insulin sensitizing effect of IL-6 (Petersen et al., 2005). Additionally, several studies have reported that IL-6 increased glucose infusion rate (Carey et al., 2006) and glucose oxidation without affecting the suppression of endogenous glucose production during a hyperinsulinemic euglycemic clamp in healthy humans (Petersen et al., 2006).

The contracting skeletal muscle is a major source of circulating IL-6 in response to acute exercise (Julia et al., 2010). Physiological concentrations of IL-6 stimulate the appearance in the circulation of the anti-inflammatory cytokines IL-1ra and IL-10, and inhibit the production of the pro-inflammatory cytokine TNF-α (Julia et al., 2010). Therefore, the anti-inflammatory effects of exercise may offer protection against TNF-induced insulin resistance (Julia et al., 2010). On the other hand, Several studies have suggested that Blocking IL-6 in clinical trials with patients with rheumatoid arthritis leads to enhanced cholesterol and plasma glucose levels, indicating that functional lack of IL-6 may lead to insulin resistance and an atherogenic lipid profile rather than the opposite (Nishimoto et al., 2004; Choy et al., 2002). It is reported that IL-6 alone markedly increases both lipolysis and fat oxidation identify IL-6 as a novel lipolytic factor (Petersen et al., 2006). The anti-inflammatory effects of IL-6 are also established that IL-6 stimulates IL-1ra and IL-10 production (Steensberg et al., 2003). However, it is not known whether the effects of IL-6 on glucose and lipid metabolism are mediated by activation of AMPK. A recent study has established that IL-6 increases AMP-activated protein kinase (AMPK) in both skeletal muscle and adipose tissue (Kelly et al., 2004). AMPK may increase glucose uptake (Fisher et al., 2002) via
mechanisms thought to involve enhanced insulin signaling transduction (Jakobsen et al., 2001).

In a general summary, this study showed that a single bout cycling exercise would lead to increased serum levels of IL-6. Increased serum IL-6 was observed while the reduction in glucose concentration was yet another favorable benefit of this exercise protocol. Although according to these findings it can not be stated with certainty that the reduction in blood glucose during exercise occurs in response to increased IL-6. But observation of a negative association between increased IL-6 serum and decreased blood glucose levels in response to exercise somehow supports direct or indirect role of IL-6 in blood glucose concentration. If so, we can conclude that although in most cases IL-6 has been recognized as an inflammatory cytokine, but increase in its serum levels after one session exercise has anti-inflammatory characteristics. Because some other studies too have reported that increased its levels after exercise would lead to increased levels of IL-10 which has anti-inflammatory properties. The potential role of IL-6 on the activity of AMPK, that is one effective factor in membrane transport of glucose, should not be ignored. In addition, some other studies have supported the role of IL-6 as an inhibitor of TNF-α secretion following a one-session exercise. According to the findings of this study and previous studies it may be concluded that changes in IL-6 in response to exercise, directly or indirectly leads to a decrease in blood glucose concentration. Despite all these findings, understanding the molecular mechanisms responsible for this process still requires extensive studies in this field.

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