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THE EFFECT OF MODERATE-INTENSITY TRAINING PROGRAM ON INTERLEUKIN-6 AND GLUCOSE IN DIABETES SUBJECTS

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ABSTRACT
Adipocytokines has emerged over the last decade as a key factor in insulin resistance and type II diabetes. To assess the effects of aerobic training on inflammatory profile, pre and post training (aerobic training program: 3 session per weeks for 3 months) of serum interleukin-6 (IL-6) as well as glucose were measured in 12 adult men with type II diabetes or control subjects (no training) matched for age (37 - 48 years) and body weight (82 - 106 kg). All participant were sedentary and non-smokers. Data analysed by T test in SPSS software. Anthropometrics variables improved significantly after training intervention in exercise group. Despite improve in fasting glucose, aerobic training resulted in significant increase in serum IL-6 in exercise group, but not significant trend in control subjects. It appears that the beneficial effects of long-term training programs are more closely associated with IL-6 receptor in skeletal muscles not its serum levels. Further studies are necessary to elucidate the significance of exercise training on inflammatory profile in these patients.

KEYWORDS: Aerobic training, Cytokine, Glucose, Inflammation.

INTRODUCTION

Over the past two decades, obesity has been the focus of health sciences researchers as one of the most prominent non-communicable diseases. The increased prevalence of obesity and its consequences, along with the industrialization of societies and changes in lifestyle, highlights the prevention and treatment of obesity as a key challenge for health systems (Julia et al., 2010). Studies have always stressed that peptide or hormonal mediators secreted by the adipose tissue and other tissues strongly affect the homeostasis or the energy equilibrium (Takizawa, 1998; de Salles et al., 2010). Researchers have also noted that, the impaired secretion of these biochemical mediators, such as the inflammatory or anti-inflammatory adipocytokines, is associated with the occurrence of obesity and obesity-related diseases, such as type 2 diabetes, cardiovascular diseases, respiratory diseases, and other diseases such as the metabolic syndrome, kidney disease, and cancer (Arnson et al., 2010). In this regard, although the pathophysiological mechanisms of insulin resistance and impaired insulin secretion, as a major determinant of type 2 diabetes (Reaven et al., 1988; DeFronzo, 1988; Bergman, 1989), is still unknown, clinical studies have frequently suggested the fundamental role of increased pro-inflammatory markers or cytokines such as Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-A) in the pathogenesis of type 2 diabetes and insulin resistance (Zhang et al., 2002; Aruna et al., 2001). Among the inflammatory cytokines, IL-6 injection results in an increased gluconeogenesis, and thereby, and increased blood glucose (hypoglycemia), and ultimately, increased blood insulin (hyperinsulinemia) (Stith, 1994). Similar metabolic responses have also been observed in humans after subcutaneous IL-6 injection (Tsigos et al., 1997). Several studies support the role of inflammation in the etiology of diabetes and increased IL-6 in individuals with insulin resistance syndrome (Ye, 2008; Weiss, 2005).

A number of studies have examined the interventions such as exercise, weight loss, diet or taking antioxidants to reduce inflammatory cytokines in diabetics (Michael, 2008; Beavers et al., 2013). Among the environmental interventions, exercise and weight loss have been suggested as an important non-pharmacological measure in controlling blood sugar and inflammatory markers in diabetics. Although there are some contradictory findings about the inflammatory cytokines response to different types of exercise (Klöting et al., 2010; Su et al., 2010), in a recent study, for example, exercise reduced the IL-6 plasma levels along with the insulin resistance (Monzillo et al., 2003). In another study, exercise reduced the serum levels of TNF-α and CRP (Kondo et al., 2006). In contrast to these findings, several recent studies have shown that, exercise interventions do not change the IL-6 or CRP levels (Hammett et al., 2006; Bautmans et al., 2005). Given the inconsistent findings in this regard, the present study aimed at determining the effects of three months of aerobic exercise on IL-6 levels in type 2 diabetics.

MATERIALS AND METHODS

Subjects

Subjects were aged 37–78 years, sedentary, overweight/obese (BMI 26–35 kg/m2, n=24) with type 2 diabetes that participated in this study by accessible sampling. Participants were randomly assigned to either an exercise group (n=12) that performed 3 months aerobic training program or a control group (n = 12) that rested. Anthropometric measurements of height, weight, percent body fat, and circumference measurements were taken study. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m). Body weight and height were measured with the subject wearing light clothes. Abdominal obesity was determined as waist circumference measured in a standing position. An informed consent was obtained from all participants before the studies were carried out, and the Ethics Committee of Islamic Azad University approved this study.

Inclusion and exclusion criteria

Patients were non-athletes, non-smokers. On the other hand, they had not been involved in regular physical activity/diet in the previous 6 months. Subjects with a history or clinical evidence of recent myocardial infarction, congestive heart failure, active liver or kidney disease, or other chronic diseases were excluded. Those patients who were not able to avoid using hypoglycemic drug at night before blood sampling were excluded.

Exercise Training Intervention and biochemistry

As mentioned previous, patients divided in exercise or control groups. Patients in exercise group trained three times per week for 12 weeks. Exercise intensity was set at 55–75% of maximal heart rate. Each session included warm up, main exercise (15-40 min) and cool up at the end. Warm-up and cool-down periods consisted of 5 min. Main exercise began at 15 min for first weeks, and then systematically increased by 5 min every 2 weeks thereafter to 40 min for weeks 10–12. Exercise physiologists supervised the exercise sessions, and monitored heart rate. The control group did not train, and were asked not to begin a structured exercise program. To reduce attrition, the control group was offered the intervention after the trial. Fasting blood samples were collected after overnight fast at 8 a.m. before and after exercise program. Blood samples used to measure glucose and serum IL-6, glucose was determined by glucose-oxidase method (pars Azmoon-Tehran). Serum IL-6 was measured by ELIZA (Enzyme-linked Immunosorbent Assay for quantitative detection of human IL-6, Austria)

Statistical analysis

Data were expressed as mean ± SD individual variables were compared using the student independent "t" test and paired "t" test. Statistical analysis was done with SPSS 15.0 for Windows. Normal distribution of data was analyzed by the Kolmogorov-Smirnov normality test. Significance was accepted at $P < 0.05$.

RESULTS

In present study, fasting serum IL-6 was compared between before and after exercise intervention. Anthropometrical and biochemical markers were similar at baseline.

Table 1: Pre and post training characteristics of anthropometrical and clinical for 2 groups

Variables	Exercise group		Control group	
	Pretest	post-test	Pretest	post-test
Age (year)	43 +/- 4.3	-----	42.7 +/- 2.56	-----
Height (cm)	173 +/- 5	-----	173 +/- 3	-----
Weight (kg)	91.2 +/- 6.99	88 +/- 7.9	90.7 +/- 6.9	**90.6 +/- 6.4**
Waist circumference (cm)	101 +/- 6.7	97 +/- 6.1	97.6 +/- 4.7	**97.5 +/- 4.4**
Hip circumference (cm)	102 +/- 3.9	100 +/- 5.7	99.3 +/- 6.4	**99.2 +/- 5.9**
Abdominal to hip ratio	0.98 +/- 0.05	0.97 +/- 0.03	0.98 +/- 0.03	**0.98 +/- 0.02**
BMI (kg/m2)	30.56 +/- 2.66	29.49 +/- 2.87	30.28 +/- 2.36	**30.25 +/- 2.22**
Body fat (%)	29 +/- 3.3	25.7 +/- 4.3	30.3 +/- 2.06	**30.2 +/- 2.04**
Visceral fat	13.3 +/- 1.8	11.3 +/- 1.5	13.3 +/- 1.37	**13.3 +/- 1.23**
Fasting glucose (mg/dl)	233 +/- 70	162 +/- 45	229 +/- 39	**225 +/- 34**
Insulin resistance	4.64 +/- 1.18	233 +/- 69	4.94 +/- 1.51	**4.81 +/- 1.37**
Serum IL-6 (pg/ml)	**2.09 +/- 0.65**	**8.13 +/- 5.27**	**2.51 +/- 0.93**	**2.60 +/- 1.08**

On the other hand, no significant difference in each variable was observed between two groups at pre training. Table 1 shows pre and post training characteristics of anthropometrical and clinical for the subjects of two groups. Aerobic training resulted in significant decrease in anthropometrical markers such as body weight and body fat (%) or BMI in exercise groups ($p < 0.05$) but not in control individuals ($p > 0.05$). Serum IL-6 increased significantly after aerobic training intervention when compared with pre test ($p = 0.0.027$). Compared with pre training, fasting glucose concentration ($p = 0.001$) and insulin resistance ($p = 0.001$) decreased significantly by exercise program.

DISCUSSION

The findings of this study showed a significant increase in the serum levels of IL-6 following aerobic exercise. In other words, a three-month aerobic exercise led to a significant increase in IL-6 in diabetic men. However, the level of each anthropometric parameter such as weight, body mass index, and body fat percentage also increased. The molecular mechanisms responsible for the role of IL-6 in the pathogenesis of obesity and chronic diseases or diseases associated with metabolic disorders is not yet fully understood as the literature supports both its inflammatory and anti-inflammatory properties. Some studies that stress its inflammatory properties have noted that, the increased systemic levels of this inflammatory cytokine are a predictor of mortality in elderly patients (Reuben et al., 2002). Increased plasma concentrations of IL-6 are associated with reduced muscle mass and reduced muscle mobility (Ferrucci et al., 2002; Visser et al., 2002). Some studies have also reported its role in the glucose homeostasis as studies on animal models have shown that, its injection increases gluconeogenesis, and thus, increases blood glucose (hypoglycemia) and ultimately, increased blood insulin (hyperinsulinemia) (Stith et al., 1994). Evidence suggests an accelerated catabolism of skeletal muscle in response to increased IL-6 (Charles et al., 2008). Similar metabolic responses have been observed after subcutaneous injection of IL-6 in humans (Tsigos et al., 1997). In recent studies, researchers have noted the role of inflammation in the etiology of diabetes and increased IL-6 and CRP in individuals with insulin resistance syndrome (Festa et al., 2000; Frohlich et al., 2000). Evidence suggests that, the training program described in this study was associated with the inflammatory properties rather than the anti-inflammatory properties. The increased serum levels of IL-6 were observed, while the aerobic exercise program was associated with a significant reduction in body weight and body fat percentage. This is in contrast to those literature that support the direct relationship of IL-6 with obesity and obesity-related diseases (Weiss, 2005) because in the present study, the reduced weight and body fat was associated with an increased IL-6 in response to exercise.

However, some studies have pointed to the anti-inflammatory effects of IL-6. For example, in one study, researchers observed the anti-inflammatory effects of IL-6 in skeletal muscles and blood circulation (Gielen et al., 2003). Some other studies, reported the reduced IL-6 expression and other inflammatory cytokines in skeletal muscle, but not in their systemic levels (Gielen et al., 2003). It has been found that, those training programs that combined with diet are associated with weight loss led to a reduced IL-6 mRNA in skeletal muscle. However, it is unclear whether the reduced IL-6 expression is a result of exercise or diet (Brown et al., 2000). Therefore, it appears that the beneficial effects of long-term training programs are more closely associated with IL-6 receptor in skeletal muscles or other tissue rather than the systemic blood levels. Some researchers have also noted that the anti-inflammatory effects of IL-6 appear though inhibiting TNF-α and increasing IL-10 following training (Fiers, 1991). IL-6 has also been found to have anti-obesity effects and an increasing effect on insulin resistance so that the activation of AMPK pathway, and in turn, increase in the insulin signaling pathways leads to an increased glucose consumption (Glund et al., 2007). On the other hand, it has been reported that IL-6 increases glucose oxidation or glucose absorption without affecting the glucose production in muscles in hyperinsulinemia (Carey et al., 2006). Some researchers have noted that IL-6 alone increases both lipolysis and fat oxidation and supported IL-6 as an important lipolysis factor (Petersen et al., 2005). Based on these evidence, and considering the findings of the present study that indicate an increased IL-6 and a decreased glucose in response to aerobic exercise, it may be hypothesized that an increased IL-6 is an anti-inflammatory characteristic of long-term.

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