Effects of Moderate-intensity Exercise on Serum Proinflammatory Cytokine Levels in Obese and Non-obese Men

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Abstract: To date, limited and often controversial data concerning modulation of pro-inflammatory cytokines by exercise in obese individuals. In order to assess this possibility, 37 healthy untrained volunteers were selected and divided in two groups, obese and non-obese. Before and after three months of an aerobic training program, the plasma concentrations of leptin, IL-1α, IL-2, TNF-α, IL-1β, IFN-α and IL-6 by an enzyme-linked immunosorbent assay. Before exercise, obese volunteers exhibited higher concentrations of IL-6 ($p=0.07$), leptin ($p<0.005$) and lower IL-1α ($p<0.05$) than non-obese group. Following exercise, a significant decrease in IL-2, IL-6, IL-1α, IL-1β and leptin levels were observed in non-obese individuals ($p<0.05$). Obese volunteers showed a significant reduction only in IL-1α, IL-1β and leptin after exercise ($p<0.05$). Our results indicate moderate long term exercise induce a major reduction in pro-inflammatory cytokines in obese and non-obese individual, however, adipose tissues probably refines and modulates these alterations.

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1. Introduction

To date, It is becoming increasingly evident that moderate exercise enhances the immune system ,whereas intense or strenuous exercise may suppress host defense functions.(Gabriel and Kindermann 1997; Simonson 2001; Starkie and others 2005). There are also some evidences indicating that moderate exercise decrease the risk of infectious disease (Drela and others 2004; Gleeson 2007). Several studies have demonstrated exercise promotes release of in pro-inflammatory and anti-inflammatory cytokines (Petersen and Pedersen 2005) and results in catecholamines, corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol release. The hormones from the HPA axis, in particular cortisol, return to pre-exercise resting baseline within several hours to days. Contrary to this, catecholamines rapidly declines to the normal value (Santos and others 2007). In this context, many studies showed that exercise without any muscle damage induces IL-6 gene transcription in contracting muscle(Keller and others 2003). It appears that adrenaline has minor impact on the exercise-induced increase of IL-6 gene expression(Steensberg and others 2001b). Likewise, Steensberg and co-workers pointed out that low level of muscle glycogen enhances elevation of plasma IL-6 and thus indirectly stimulates the hepatic synthesis of glucose. Taken together, it assumed that IL-6 release may be playing a glucose modulator role during prolonged exercise. Other data also introduced IL-6 as a potent modulator of fat metabolism in man, increasing lipolysis and fat oxidation without causing hypertriacylglycerolaemia (Pedersen and others 2001). Exercise also induce production of both IL-1 receptor antagonist and IL-10 and inhibit TNF production. Other proinflammatory cytokines, IL-β and IL-1α, in general do not increase with exercise (Ostrowski and others 1999).

In accompany with the elevation of serum IL-6, IL-10 and IL1ra levels, increase of cortisol and epinephrine, as well as prostaglandin E2, may all contribute to immune deviation to a predominance of Th_2 response. A Th_2 cell response leads to suppression of cell-mediated immunity, rendering the athlete susceptible to infection(Lakier Smith 2003). In the other hand, moderate exercise training could improve Th cell-mediated immune functions and result in a reduction in the risk of infections and autoimmune diseases in elderly people(Shimizu and others 2008). There is a variety of factors involved in the influence of exercise on immune responses include changes in circulating levels of cytokines, nutritional status, intensity, duration and obesity (O'Kennedy 2000). In the later case, several studies confirm the association of immune functions with adipose tissue. Recent investigations demonstrated that adipose tissue is not only an energy store, but also an active endocrine organ which produce a number of hormones and

cytokines. Adipose-secreted proteins include a variety of immune-related proteins such as leptin, TNF-α, IL-6, acylation stimulation protein that are collectively referred to as adipocytokines. In addition, It is known that obesity induces decreases in both T and B-lymphocyte responses (Berggren and others 2005).
Although many studies focus on exercise-induced alterations in pro-inflammatory cytokines, however, limited and often controversial data concerning modulation of pro-inflammatory cytokines by exercise in obese and non-obese objects, which is considered as the main purpose of this paper.

2. Material and Methods

The volunteers were selected from volunteers recruited through a poster advertising campaign at the Mashhad Azad University. Body mass index of volunteers were measured using the body composition analyzer and 37 healthy untrained volunteers were selected and divided in two groups: 19 participants (weight 96.8±15.9kg, height 171.5±12.3cm, age 30±5years,BMI 32.3±2.1 kg/m²) in obese group and 18 participants (weight 57±3.3kg, height 177±4.47cm, age 30±5years, BMI 18.1±0/58 kg/m²) in non-obese group. None of the volunteers had a smoking history, medication or an illness or infection in the preceding months. All volunteers gave written informed consent after being provided with a description and explanation of the testing procedures. Approval for the study was obtained from the Ethics Committee of the Mashhad Azad University.

During three months of this study, each groups performed an aerobic training program consisted of running with 65-75% of individual maximum heart rate on treadmill (SportsArt® 6300, Taiwan) for three 30-min bouts per week. Blood samples were taken before and 37 hours after exercise to determine plasma cytokine concentrations. Serum and plasma samples were stored in aliquots at - 70°C until use. The plasma concentrations of IL-1, IL-2, TNF-α, IL-1β, IFN-α and IL-6 were measured by a high sensitivity enzyme-linked immunosorbent assay (Diaclone, Cedex, France). Leptin level was also determined using ELISA (Diagnostic Biochem Canada Ontario, Canada) according to the manufacturer's instructions. All measurements were performed in duplicate and the means of the two values were used in all analyses. Because data were not normally distributed, Non-parametric tests were used for statistical analyses using GraphPad Prism 5 for Windows (GraphPad Software Inc). Comparisons between two groups were carried out by Mann Whitney test. The Wilcoxon signed-rank test was used for paired values of cytokine before and after exercise. Correlations were performed by using Pearson's correlation coefficient. All results are given as mean±SEM. Significance was set at $P<0.05$.

3. Results

Table 1 summarized cytokine concentrations in non-obese and obese groups before and after exercise. Using Mann Whitney analysis, we found no significant differences between two groups on IL-1β, IL-2, TNF-α, IL-6 and IFN-α concentrations before exercise. However, volunteers in obese exhibited slightly higher concentrations of IL-6 ($p=0.07$). Obese group also had a significant higher leptin ($p<0.005$) and lower IL-1α ($p<0.05$) than non-obese group before exercise (Figure 1). Following exercise, a significant decrease in IL-2, IL-6, IL-1α, IL-1β and leptin levels were observed in non-obese individuals ($p<0.05$). Obese volunteers also showed a significant reduction in IL-1α, IL-1β and leptin after exercise ($p<0.05$), while IL-6 and IL-2 demonstrated no different after exercise ($p=0.37$, $p=0.27$, respectively).

In both obese and non-obese volunteers, plasma concentration of TNF-α and IFN-α indicated no significant changes following exercise.

In comparison of post-exercise cytokine in obese and non-obese groups, only plasma concentration of IL-6 was significantly different between two groups that tended to be higher in obese group after exercise. In addition, the ratio of IL-6 to TNF-α, as an anti-inflammatory index (Timmons 2006), was significantly higher in obese group than non-obese group ($p=0.007$). In contrast to baseline (pre-exercise) levels of Leptin and IL-1α, there were no significant difference between obese and non-obese groups in the plasma levels of leptin and IL-1α after exercise ($p=0.1$ and $p=0.066$, respectively).

The correlation coefficient between post-exercise plasma levels of TNF-α and IL-2 were 0.68 ($p=0.002$) in the non-obese and 0.48 ($p=0.042$) in obese groups. There was a positive correlation between post-exercise plasma levels of TNF-α and IFN-α in non-obese ($r=0.57$, $p=0.013$) and obese groups ($r= 0.5$, $p=0.035$). In obese group, post-exercise plasma level of IL-1a was correlated with the plasma levels of IL-2 ($r=0.62$, $p=0.006$) and IFN-α ($r=0.59$, $p=0.01$).

4. Discussions

Several studies within the past few years have demonstrated that pro and anti- inflammatory cytokine balance could be altered by exercise. It became of interest to determine the role other factors that might be involving influence of exercise on the cytokine balance, which may mediate some of the health benefits of regular exercise. Although several researchers examined the role of exercise duration and intensity on systemic release of pro and anti-inflammatory cytokines, much less is known about the effects of obesity on cytokine balance after exercise. This concept is based on the fact that several important mediators and cytokines are synthesized in adipose

tissue of obese and non-obese individuals including IL1β, IL-6, TNF-α leptin, complement system components and macrophage colony-stimulating factor and TGF-β,(Berggren and others 2005; Coppack 2001; Sopasakis and others 2005; Starr and others 2009). In consistent with this viewpoint, obese group showed a higher concentrations of leptin and IL-6 and a lower concentration of IL-1α than non-obese group before exercise.

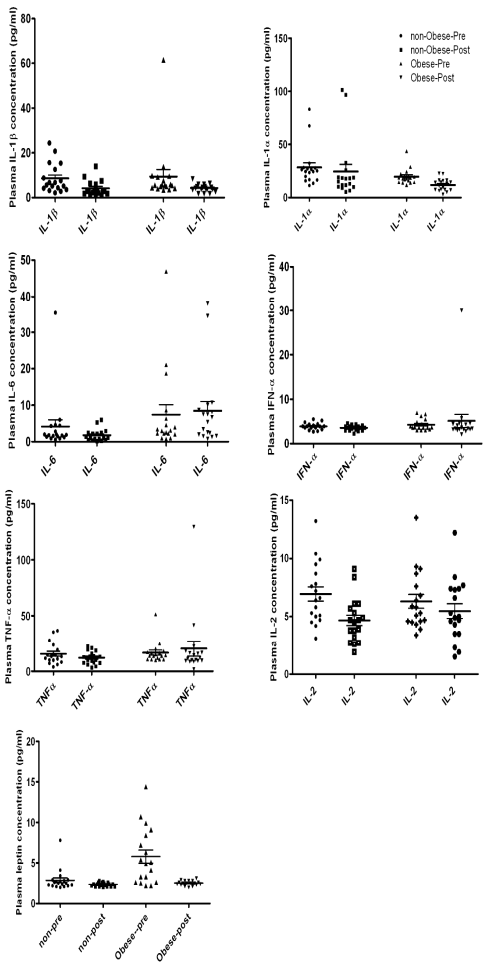

Figure 1: Mean plasma concentrations of leptin, IL-1α, IL-2, TNF-α, IL-1β, IFN-α and IL-6 in non-obese and obese groups before and after exercise. Values are expressed as the mean ± SEM.

After exercise, both groups showed a significant reduction in the plasma level of leptin. This could be related to the increase of noradrenaline and adrenaline (Trayhurn and others 1996) that occurs during exercise. These catecholamines have a major suppressive effect on leptin production. It has been reported that leptin increases the production of proinflammatory lymphokines such as IL-2 and interferon-γ, while it inhibits the secretion of IL-4 from the lymphoid cells (Marti and others 2001). In consistent with this notion, both groups indicated a decrease in the plasma level of leptin and IL-2. After a long-term moderate exercise that applied in our study, IL-1α and IL-1β plasma levels markedly reduced in both group in comparison with pre-exercise levels, while decrease in IL-2 and IL-6 plasma levels were observed only in non-obese group. Although, it has been well documented that acute exercise increases plasma levels of IL-6 (Fischer 2006; Keller and others 2003; Steensberg and others 2001a), several studies found a negative association between the amount of physical training and basal plasma IL-6 concentration (Fischer 2006). The reduction of this cytokine at rest as well as in response to exercise seems to be associated with the normal training adaptation. Our finding showed a post-exercise reduction of IL-6 plasma level in non-obese volunteers which was associated with a significant decrease in the ratio of IL-6 to TNF-plasma levels. This ratio has been suggested as a anti-inflammatory index (Timmons 2006). TNF-α is a proinflammatory cytokine secreted from a variety of cells including macrophages, monocytes, neutrophils, T-cells and nonfat cells present in adipose tissue (Fain and others 2004). In consistent with our results, several studies demonstrated that TNF-α is unchanged after prolonged (Saghizadeh and others 1996; Steensberg and others 2002). Contrary to this, other previous claim that TNF-α increase immediately after the end of exercise or later on, after a recovery period (Moldoveanu and others 2001). This discrepancy could be due to differences in exercise intensity, gender and fitness, nutritional state of the volunteers and time interval between the last exercise and blood sample collection.

Our results indicate moderate long term exercise induce a major reduction in pro-inflammatory cytokines in obese and non-obese individual, however, adipose tissues probably refines and modulates these alterations.

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