Indian Journal of Fundamental and Applied Life Sciences ISSN: 2231-6345 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/jls.htm
2015 Vol. 5 (2) April-June, pp.146-155/Namazi
Research Article

THE EFFECTS OF SHORT TERM CIRCUIT RESISTANCE TRAINING ON SERUM LEVELS OF IL-8, IL-6, AND TNF-A IN ACTIVE AND INACTIVE FEMALE

***Asieh Namazi**
Department of Physical Education and Sport Science,
Iran University of Science & Technology (IUST), Tehran, Iran
**Author for Correspondence*

ABSTRACT
Elevated levels of serum biomarkers such as cytokines are independently associated with cardiovascular risk. However, the prevalence of concurrent changes of these biomarkers and their relationship with cardiovascular disease after short-term circuit resistance training in females is unknown. This study aims to compare the effects of short-term circuit resistance training on some cytokines in active and inactive females. Serum concentrations of IL-8, IL-6, and TNF-α in 43 healthy female university students were calculated (mean age 22/74±3/9 y, weight 59/91±9/8 kg, height 165/9±0/04 cm, BMI21/73±3/1 (kg/m2), PBF 26/47±5/01, and Vo2max 38/65±5/43 (ml/kg/min)). Our subjects were randomly divided into four groups: Active test (n=8), Active control (n=8), inactive test (n=13), and inactive control (n= 14).Participants took part in a two-week short-term circuit resistance training including 5 sessions per week (10 sessions). The exercises include chest press, leg extension, sit-ups; pull down, front row, foot raising, back extension, and leg curl with free weights and machines. During the first week the training was done at 40% 1RMfor 15 repetitions and 3 sets. During the second week the intensity of training was increased to 50% 1RM, while other features of training remained constant. Before starting the training program and 48 hours after the last training session, fasting and resting blood samples were collected and measured using ELISA Test. Finding show that IL-6 and IL-8 decreased in all groups. The same goes with TNF-α, except in inactive test. Comparison among groups reveals that changes in IL-8, IL-6, and TNF-α were significant ($p \leq 0.05$). It seems that short-term circuit resistance training may improve the inflammatory condition in body. It also may lower the risk of diseases related to cytokines.

Keywords: *TNF-α, IL-6, IL-8, Circuit Resistance Training, Cytokine*

INTRODUCTION
Cytokines are soluble glycoproteins that are produced by immune and non-immune cells within and between organs and systems (Haahr *et al.*, 1991; Behr, 2007; Mackinnon, 1999, Moldoveanu *et al.*, 2001 & 2000; Nieman *et al.*, 1997; Nosaka *et al.*, 2002). Cytokine synthesis is activated by a broad range of stimulants including free radicals, physical activity, trauma, tissue injury, and infection factors. Regarding function, they are classified into two groups: pro-inflammatory and anti-inflammatory (Behr, 2007; Pedersen *et al.*, 1998; Elenkov *et al.*, 2000; Fa´bio *et al.*, 2009). They are produced periodically by immune cells. They act both locally and generally (Remick *et al.*, 1997; Phillips, 2001; Mackinnon, 2003). Mild chronic inflammation is identified with higher than normal level of few cytokines including Tumor Necrosis Factor (TNF-α), Interleukin-6 (IL-6), and C-reactive protein (CRP). They are independent predictors of such chronic diseases as coronary heart, stroke, and diabetics. Chemotactic cytokines such as Interleukin-8 (IL-8) is able to recruit and activate neutrophils to the site of tissue injury or infection. It also can appear in any tissue and produced in response to tissue injury due to IL-1 and TNF-α. In case of injury, endothelial cells are able to produce excessive amounts of cytokines, inflammatory materials, including IL-1 α, IL-1 β, IL-6, IL-8, and various Colony Stimulating Factor (CSF), (Phillips, 2001; Sukovich *et al.*, 1998). Exercise or physical activity is a potent activator of the immune system resulting in changes in the pro-inflammatory cytokine concentrations (Rohit *et al.*, 2007; Pedersen, 2000) that is related to exercise intensity, duration, the mass of muscle recruited, and one's endurance capacity (Rohit *et al.*, 2007; Pedersen *et al.*, 2003; Febbraio *et al.*, 2002; Pedersen *et al.*, 2001;

Pedersen *et al.*, 2000). A recent study investigating an ultra-distance foot race showed markedly elevated IL-6 Plasma (Rohit *et al.*, 2007; Alexandra *et al.*, 2005). On the other hand, intensive and prolonged exercise training does not have a significant impact on the adaptive immune system at the resting state (Rohit *et al.*, 2007; Baj *et al.*, 1994; Nieman *et al.*, 1995). Another researches showed; chronic exercise decreases cytokine production in healthy rat skeletal muscle (Fa´bio *et al.*, 2009). In other words, Physical activity and exercise can make a lot of changes in the immune system and affect local and systemic cytokine production at different levels, often exhibiting striking similarity to the cytokine response to trauma and infection and lead to release of cytokines (Behr, 2007) which is a protective mechanism to fight and inhibit general immune responses after physical training. Long-term and regular exercise slows or stops the production of atherogenic cytokines in people with high risk of cardiovascular disease (Smith *et al.*, 1999). It may have anti-inflammatory and protective effects against cardiovascular diseases. Nakajaki *et al.*, (2001) find that regular exercise reduces the level of cytokines. Also changes in life style such as losing weight and getting more exercise can lead to a decrease in inflammatory factors (Ryan *et al.*, 2004). Significant decrease in IL-8 and CRP is followed by decrease in and prevention of atherogenisis and cardiovascular diseases (Solini *et al.*, 2006). Haghighi *et al.*, (2006) report that 13 weeks of resistance training in overweight male participants decreases the level of IL-6 and TNF-α (Haghighi, 2006). Philips (2001) state that after 10 weeks of resistance exercise during menopause, the release of TNF-α and IL-6 in monocytes decreases (Phillips, 2001). In addition, it is evidently suggested that high-intensity eccentric exercise caused a more pronounced increase in the plasma level of IL-6 (Bejeh, 2002; Bruunsgaard *et al.*, 1997), and moderate and vigorous endurance exercises cause a significant decrease in IL-6 and TNF-α (Moldoveanu *et al.*, 2000; Ullum *et al.*, 1994; Nemet *et al.*, 2003). Literature review reveals that there are limited reports regarding exercise and the level of IL-8 which suggests endurance training decreases the level of IL-8 (Nieman *et al.*, 2003a; Nieman *et al.*, 2004a; Timmons, 2005). It is also reported that moderate exercise has no effect on IL-8. It suggests that produced IL-8 is a local response to exercise (Timmons, 2005; Belperio *et al.*, 2000). As the effect of training and exercise with different intensity, severity and duration on cytokines and inflammatory factors has been investigated in prior studies, further research is required to investigate the effects of resistance training particularly short-term training, on cytokines. This paper, therefore, aims to determine the effects of short-term circuit resistance training on serum levels of IL-8, IL-6, and TNF-α in active and inactive female after two weeks (10 sessions) of training.

MATERIALS AND METHODS

Methodology

Subjects

Having released an invitation for participation in the research, 43 Volunteered female students at Tehran Azad University were selected randomly and divided into active and inactive groups. Inclusion Criteria were being healthy and had no infection , being on no special diet, no use of drug, no smoking, no menstruation during the training course (to control some hormonal factors), had no regular sport or exercise in inactive group, undergoing training or exercise for a minimum period of 6 months for active group, and aged 20-30. In order to control the effective factors on results, the training program and what participants were expected to do were explained in detail for them. Moreover, a written approval letter was asked from the participants. Our subjects were randomly divided into four groups: Active test (n=8), Active control (n=8), inactive test (n=13), and inactive control (n=14). Demographic features and 1RM were determined a week before the training started. Blood samples were collected 48 hours before the training and repeated at the end of the training course. Subjects performed circuit resistance training, including 5 one-hour training sessions a week at the gym. The course lasted for two weeks (10 sessions). All environmental conditions – temperature, machines, weights, time and length of sessions- were the same over the period of study. Every session included warm-up (10 minutes of stretching), resistance training, and cool-down exercises. The exercises include such station resistance exercises as chest press, leg extension, sit-ups, pull down, front row, foot raising, back extension, and leg curl with free weights

and machines. During the first week the training was done at 40% 1RMfor 15 repetitions and 3 sets. 1 minute rest between sets and 3 minutes between circuits were allowed. During the second week the intensity of training was increased to 50% 1RM, while other features of training remained constant.

Blood Samples

Resting blood samples were collected 48 hours before the training and repeated at the end of the training course. Subjects were asked to eat nothing for 12 hours before collecting the samples. Samples were taken between 8-8:30 A.M. and collected samples were centrifuged for 5 minutes at 2000rpm. The separated serum was distributed in eppendorfs and stored in freezer at -80c for later analyses. The serum samples was used to estimate the levels of cytokines IL-6 and TNF-a, IL-8, by using ELISA method and Bender med highly sensitive kits (Bender med Co. Germany). Reading was carried out with Biohit ELISA reader.

Statistical Methods

Descriptive statistics was used to identify the main factors and distributions. The normal distribution of data was tested by Kolmogorov-Smirnov. In order for variance homogeneity between groups, Levin test was applied. By using Correlated t-test, the effectiveness of training in groups was estimated. ANOVA was used to compare the measured variables. In case of significant difference in variance analysis, LSD test was used to analyze and compare the variances (Vincent, 1999). Significance level was $p \leq 0.05$ for all statistical results. The Statistical software namely SPSS 11.0 used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables, etc.

RESULTS AND DISCUSSION

Findings

Table 1 shows the demographic features of participants for each group.

Table 1: Demographic features of participants for each group

Variety	Groups	Inactive control	Inactive test	Active test	Active control	Total
Height(m)		163.25±0.05	167.31±0.00	166.25±0.1	168±0.00	165.9±0.04
Weight (kg)	before test	55.5±9.8	62.04±8.8	62.45±10.3	61.54±9.7	59.91±9.8
	After test	56.07±9.9	62.2±8.6	61.7±9.5	61.5±9.2	60.00±9.4
	%changes	0.93	0.27	-1.1	-0.04	0.15
%BF	before test	24.86±6.05	27.6±4.7	27.35±4.9	26.52±3.5	26.47±5.01
	After test	24.58±5.6	26.9±4.9	26.1±5.10	26.5±3.4	25.95±4.9
	%changes	-1.14	-2.39	-4.6	0.19	-1.95
BMI (kg/m^2)	before test	20.82±3.3	22.21±3.4	22.58±3.2	21.71±2.1	21.73±3.1
	After test	20.99±3.3	22.27±3.4	22.25±2.9	21.71±2.1	21.74±3.01
	%changes	0.79	0.28	-1.4	0.11	0.06
Vo_{2max} (ml/kg/min^{-1})	before test	38.08±4.6	37.15±3.2	40.09±9.4	40.64±4.4	38.65±5.43
	After test	38.96±4.3	37.38±2.8	41.47±5.8	40.34±4.2	39.34±4.3
	%changes	2.3	1.8	3.4	-0.7	1.79

Findings show that the levels of IL-8, IL-6, and TNF-α decreased in active test group which was significant for IL-6 and TNF-α. No significant change is observed in IL-8 and TNF-α show in inactive test group. Comparison between changes in resting levels of cytokines reveals significant differences between the groups (IL-8 ($p=0.03$); IL-6 ($p=0.0003$); TNF-α ($p=0.001$). These differences are in IL-8 between active test group and inactive control group ($p=0.05$) and inactive test and inactive control ($p \leq 0.006$); IL-6 between active test and active control ($p=0.001$), inactive control ($p=0.0001$), and inactive test ($p=0.0001$); TNF-α between active test and active control ($p=0.003$), active and inactive control ($p=0.022$), active and inactive test ($p=0.0001$), and inactive test and control ($p=0.0004$).

Table 2: Statistical results for IL-6 concentration (pg/ml) in the studied groups before and after the test

Statistical indices groups	Before test	After test	Mean variance	Significance level	F
Active test	1.92±0.65	1.21±0.43	-0.7125	0.0003	8.121
	P = 0.001, t = 5.206				
Active control	1.21±0.34	1.36±0.53	-0.1500		
	P = 0.307, t = 1.101				
Inactive test	1.31±0.7	1.32±0.33	-0.0333		
	P = 0.691, t = 0.408				
Inactive control	1.38±0.71	1.48±0.77	-0.0971		
	P = 0.230, t = 1.260				

Table 3: Statistical results for IL-8 concentration (pg/ml) in the studied groups before and after the test

Statistical indices groups	Before test	After test	Mean variance	Significance level	F
Active test	8.11±1.1	7.79±1.27	-0.3250	0.033	3.217
	P = 0.305, t = 1.106				
Active control	8.92±0.99	8.01±1.04	-0.9125		
	P = 0.103, t = 1.876				
Inactive test	7.66±1.13	7.66±0.66	-0.0083		
	P = 0.870, t = 0.167				
Inactive control	8.45±1.48	7.01±0.99	-0.4429		
	P = 0.005, t = 3.406				

Table 4: Statistical results for TNF-α concentration (pg/ml) in the studied groups before and after the test

Statistical indices groups	Before test	After test	Mean variance	Significance level	F
Active test	4.57±2.27	2.31±0.68	-2.2625	0.001	6.579
	P = 0.007, t = 3.720				
Active control	2.52±0.79	2.33±0.5	-0.1875		
	P = 0.555, t = 0.620				
Inactive test	2.44±0.65	2.44±0.68	0.00		
	P = 0.368, t = 0.935				
Inactive control	3.36±1.66	1.76±0.56	-1.5929		
	P = 0.003, t = 3.645				

Discussion

IL-6

IL-6 is one of the most important cytokines. It has prominent metabolic and anti-inflammatory roles in adults (Timmons, 2005). findings from studies on animals (mice) suggest that increase in IL-6 leads to decreased muscle growth and causes muscular atrophy due to increase in proteolytic enzyme function. It also leads to endothelial growth factor expression as an angiogenic factor (Cohen *et al.*, 1996). Physical activity, exercise and training decrease the inflammatory factors including IL-6 (Pitsavos *et al.*, 2005). Our findings show that after the training course, this factor decreases in active test group, which is statistically significant. Although the primary levels of this variable were higher (most probably due to

chronic inflammation or long-lasting effects of prior physical exercise program) the significant decrease in IL-6 shows that our training program had a stimulating role in creating changes. It is in consistency with Khaleghi *et al.,* (2007) and Ziyaee (2007). They reported that increasing the cardiovascular fitness is linked to increase physical activity and reduce levels of inflammatory markers such as IL-6 (Khaleghi *et al.,* 2007; Ziaee N *et al.,* 2007).

Prior studies in the effect of resistance training on inflammatory cytokines reveal the same findings (Phillips, 2001; Haghighi, 2006). Due to limited number of related studies, mechanisms through which Physical activity, exercise and training influence inflammatory cytokines are unknown. Researchers believe that one of possible mechanisms is the decreases gene expression and serum levels in adhesive leukocyte molecules after resistance training. This reaction can synthesize Granulocyte macrophage colony-stimulating factor (MG-CSF) and consequently produce cytokines. Another likely mechanism may be the antioxidant effects of physical exercise. Human and animal evidence show that endurance training can decrease the oxidative stress by elevating the antioxidant defense capacity of body (Powers *et al.,* 1999 & 2008). Resistance training has probably the same effect, but not studied yet. Moreover, it may reduce the release of pro-inflammatory cytokines from mononuclear cells through strengthening the cardio respiratory system (Greiwe *et al.,* 2001) by decreasing daily hypoxia as the stimulator of gene expression in inflammatory cytokines through free radicals production (Ali MH *et al.,* 1999). In addition, resistance training decrease gene expression of cytokines in muscular tissues by increasing the protein synthesis (Greiwe *et al.,* 2001) through increasing the serum testosterone, resistance training may result in elevated protein synthesis and inhibited cytokines - induced atrophy. The partial effect of training on decreasing disease risk may be due to prevented or decreased inflammation. Releasing IL-6 is dependent on the intensity and duration of training (Behr, 2007; Sorichter *et al.,* 2006; Kasapis and Thompson, 2005; Petersen and Pedersen, 2005; Steensberg *et al.,* 2000).

Some findings show that in order to prevent and decrease the inflammation in skeletal muscles and fat tissues (Timmons, 2005; Pitsavos *et al.,* 2005) and due to anti-inflammatory function of IL-6, long-term training and exercise (> 1 hour, > 60% Vo2max), through which a large group of muscles are involved, requires increase in IL-6. More recent observations on IL-6 production and IL-6 release from contractions in muscles reveal that increase in IL-6 during physical exercise is related to regulation of glucose production (Pedersen *et al.,* 2001). Therefore, IL-6 increases during long-term and vigorous exercise and trainings with eccentric contractions, and more muscular damage, mechanical stress, and glycogen depletion. Considering the findings, our training program probably leads to less muscular damage, mechanical stress, and glycogen depletion. Findings from studies with non-resistance training show that playing tennis leads to no significant change in IL-6 level in male and female participants. Here, the researchers assumed that their training and exercise program would not create enough stress (Nieman *et al.,* 1997). In contrast, water polo causes a significant increase in IL-6 in female. In explaining the results is expressed that Contradictory findings may be due to the type of training or sport and individuals physical fitness (Nemet *et al.,* 2003). Rohit *et al.,* (2007) in their study about Cytokine response to strenuous exercise in athletes and non-athletes reported that majority of the athletes and non-athletes demonstrated a rise in IL-6 levels. Further, the athletes showed a lesser magnitude of change in the cytokine levels following a longer duration of exercise than non-athletes (Rohit *et al.,* 2007). Stewart *et al.,* (2007) found no changes in IL-6 in female (both young and old inactive females) after 12 weeks of aerobic and resistance training (Stewart *et al.,* 2007). Findings suggest that our training program has not created too much stress. Although several factors influence the findings including different methodology, age, physical fitness, training program, research protocol, measurement techniques, time of measurement and study, the primary levels of variable, sensitivity of measurement tools. Changes in the activity, production, and reproduction of cells and cytokines of immune system is highly relied on the intensity, duration, and the type of the trainings, as well as muscles contraction and timing of training.

IL-8

Our findings show that IL-8 decreases in active and inactive test groups which is not statistically significant. IL-8 is cleared from the injured tissues very slowly. It is probably one of the intermediates in

neutrophils accumulation in injured muscular cells during long-term intensive training, exercises, and eccentric contractions (Mackinnon, 2003). Accordingly, our resistance training program seems to have not caused any damage and perhaps can prevent and decrease atherogenisis and cardiovascular diseases (Solini *et al.,* 2006) (Although this factors no measured).

Few studies on the effect of training and physical exercise on IL-8 reveal different findings which are not consistent with our findings. Evidence suggests that long-term and vigorous training and sports activities increase IL-8 (Timmons, 2005). Nieman *et al.,* (2003, 2004) show that resistance training leads to an increase in IL-8 (Nieman *et al.,* 2003a, 2004a). It seems that the slow clearance of IL-8 is the reason of increase in its level after training and sports activities. On the other hand, more recent studies document that muscular contraction which happens during moderate exercises can increase the IL-8 expression as a possible atherogenic factor (Belperio *et al.,* 2000) in muscle fibers (Akerstrom *et al.,* 2005). Henson *et al.,* (2000) report that moderate intensity and duration training has no effect on IL-8 (Henson *et al.,* 2000). Contradictory findings may be due to the effective factors on changes in cytokines such as intensity, duration, and type of the training or exercises, type of muscular contractions, timing of training, individuals' physical fitness, prior training and exercise, the place and methods of measuring cytokines.

TNF-α

The significant decrease in TNF-α in active test group shows that the intensity and duration of our training program is a good stimulator to create changes, while no change was observed in inactive test group which may be due to individuals' physical fitness (Khaleghi *et al.,* 2007; Ziaee *et al.,* 2007). Accordingly, considering the atherogenisis inflammatory background and the relationship between physical activity and exercise and low levels of inflammation, we may conclude that our training program decreases inflammation and creates cardiovascular protective effects in subjects. The impact of resistance training on cytokines has not studied broadly. Haghighi (2006) and Philips (2001) findings are consistent with our findings (Haghighi, 2006; Philips, 2001). It seems that in addition to possible mechanisms such as decrease in gene expression and serum level in adhesive leukocyte molecules, decrease in daily hypoxia and decrease in production of pro-inflammatory cytokines from mononuclear cells, protein synthesis that leads to gene expression in muscular tissue, possible increase in anti-oxidative defense capacity, and decrease of oxidative stress (Powers *et al.,* 1999 & 2008) which is attributed to resistance training, our training program and those used in more recent studies has reversed or changes the mechanisms related to skeletal muscles injury and inflammation. From suggested mechanisms we can mention the collision of broken proteins (released from injured muscles) with white cells and other cells such as fibroblasts and releasing cytokines.

This mechanism is relatively justifying, because intensive training and exercise and vigorous sports activities that lead to muscular damages (such as eccentric trainings and contraction) are followed by changes in cytokines concentrations (Mackinnon, 2003). Another suggested mechanism states that although physical exercise - induced incremental temperature cannot directly lead to releasing cytokines, it may release hormones like catecholamines. They mobilize and activate immune cells indirectly through releasing cytokines during and after exercise (Mackinnon, 2003; Phillips, 2001). Evidence show that some cytokines like TNF-α increase in response to high levels of stress hormones including catecholamines and corticosteroids during physical stresses like intensive exercises (Phillips, 2001). Therefore, our training program has not imposed vigorous mechanical stress on body. Evidence suggests that atherosclerosis plaque produced by endothelial cells in smooth muscles, oxidized lipids, and risky biomarkers and factors such as homocysteine and other losses, accumulate at the vascular walls and as a result IL-6, IL-8, and TNF-α are produced (Phillips, 2001). Produced inflammatory cytokines at the site of atherosclerosis, stimulate and activate leucocytes to produce more coordinating cytokines cascade (Phillips, 2001). In fact, the incremental production of leucocytes or cytokines is the indicator of atherosclerosis. Findings from the above-mentioned researches suggest that such training programs decrease the risk of disease by influencing the processes. Rohit *et al.,* (2007) found Majority of the athletes and non-athletes demonstrated a fall in TNF-α level. Further, the athletes showed a lesser magnitude of change in the cytokine levels following a longer duration of exercise than non-athletes

(Rohit *et al.,* 2007). Significant decrease in TNF-α in Ravasi, Slovan and Gharebagh are in consistency with partial of our findings (Ravasi, 2006; Slovan *et al.*, 2007; Gharebagh, 2007).

Although the adaptation have been mentioned as reason for achieving these results in these researches, but it seems that our findings are similar and identical with the above-mentioned researches. It is clear that moderate to vigorous long-term training and exercises such as marathon decrease the TNF-α (Sorichter *et al.*, 2006). Studies with short-term exercises and races show an increase in TNF-α. Releasing cytokines during and after physical exercises, therefore, is a protective mechanism to fight against immune responses.

Our findings show that the levels of TNF-α does not change due to circuit resistance training in inactive group. Training – induced stress, thus, has not created enough stimulator to change TNF-α in this group. Unlike IL-6 which is highly dependent on the intensity and duration of training, TNF-α increases only during long-term training exercises and more involved muscles (Steensberg *et al.,* 2000). It can be one of the causes of no change in inactive group. Different measurement methods; sensitivity and specialization of measurement tools, laboratory techniques, and measurement time are factors influencing the findings, because it is known that the timings of appearance, clearance, and excretion of cytokines are different. Intensity, duration, and the kind of training and contractions, the time of training, individuals physical fitness, different sports parameters, prior trainings, the place and the time of measuring cytokines are other reasons for different finding

Conclusion

Our findings related to the effect of training and exercises on immune indicators suggest that regular sports activities and changes in life style can lead to anti-inflammatory and protective effects against diseases (Stewart *et al.,* 2007; Khaleghi *et al.,* 2007). Regular training and sports activities are followed by lower amounts of inflammatory indices (Pitsavos *et al.,* 2005; Ziaee *et al.,* 2007). People with better physical fitness who are physically more active show lower levels of inflammatory indices (Mora *et al.*, 2006). Our findings show that resistance training with decrease in inflammatory indices improve the inflammatory condition of body. It probably decreases the risk of diseases related to cytokines.

REFERENCES

Akerstrom T, Steensberg A, Keller P, Keller C, Penkowa M and Pedersen BK (2005). Exercise induces interleukin-8 expression in human skeletal muscle. *The Journal of Physiology* **563** 507-516, PMID: 15618276.

Alexandra M, Katerina S, Maria T, Eugenia H and Antonia-Leda M *et al.*, (2005). Dramatic elevations of interleukin-6 and acute-phase reactants in athletes participating in the ultra distance foot race spartathlon: severe systemic inflammation and lipid and lipoprotein changes in protracted exercise. *Journal of Clinical Endocrinology and Metabolism* **90**(7) 3914–8.

Ali MH, Schlidt SA, Chandel NS, Hynes KL, Schumacker PT and Gewertz BL (1999). Endothelial Permeability and IL-6 production during hypoxia: role of ROS in signal transduction. *The American Journal of Physiology* **277** L1057-L1065, PMID: 10564193.

Baj Z, Kantorski J and Lewicki R *et al.*, (1994). Immunological status of competitive cyclists before and after the training season. *International Journal of Sports Medicine* **15** 319–24, PMID: 7822070.

Behr Melissa B (2007). The cytokine response to three days of intensive training. *University of North Carolina at Chapel Hill* fulfillment of the requirement for degree of Master of Arts in department of exercise and sport science (exercise physiology) UMI Number: 1445383.

Bejeh N (2002). The effect of eccentric and concentric exercise on inflammatory markers in female athletes, SID. *Research on Sport Sciences* **1**(3) 27-39 (Persian).

Bejeh N, Nazem F, Tavakol Afshari J, Nejat-Shokohe A, Mahmmoudi M and Rastein M (2001). The effect of two eccentric and concentric exercise pattern on given immune system parameters of athletic women**.** *Journal of Iranian Basic Medical Science* **3**(1).

Belperio J A, Keane MP and Arenberg DA *et al.*, (2000). CXC chemokines in angiogenesis. *Journal of Leukocyte Biology* **68** 1-8, PMID: 10914483.

Bruunsgaard H, Galbo H, Halkjaer – kristensen J, Johansen TL, MacLean DA and Pedersen BK (1997). Exercise – induced increase in serum interleukin-6 in humans is related to muscle damage. *Journal of Physiology* **499** 833-841, PMID: 9130176.

Cohen T, Nahari D, Cerem LW, Neufeld G and Levi BZ (1996). IL-6 induces the expression of vascular endothelial growth factor. *The Journal of Biological Chemistry* **271**(2) 736-741, PMID: 8557680.

Elenkov IJ, Chrousos GP and Wilder RL (2000). Neuroendocrine regulation of IL- 12 and TNF-alpha/IL-10 balance. Clinical implications. *Annals of the New York Academy of Sciences* **917** 94–105, PMID: 11268424.

Fa´bio S Lira, Cristiane H Koyama, Alex S Yamashita, Jose´ C Rosa, Nelo E Zanchi, Miguel L Batista Jr. and Marı´lia C Seelaender (2009). Chronic exercise decreases cytokine production in healthy rat skeletal muscle. *Cell Biochemistry Function* **27** 458–461, DOI:10.1002/cbf.1594.

Febbraio MA and Pedersen BK (2002). Muscle – derived interleukin -6: mechanisms for activation and possible biological roles. *The Journal of the Federation of American Societies for Experimental Biology (FASEB)* **16** 1335-1347, PMID: 12205025.

Ghodrat Gharebagh Z (2007). Effect of selective sub maximal aerobic training on homocysteine and TNF-α in health obese women. *Sixth International Conference of Physical Education and Sport Sciences*, Iran (Persian).

Greiwe JS, cheng B, Rubin DC, Yarasheski KE and Semenkovich CF (2001). Resistance exercise decreases skeletal muscle tumor necrosis factor α in frail elderly humans. *The Journal of the Federation of American Societies for Experimental Biology (FASEB)* **15** 475 -482, PMID: 11156963.

Haahr PM, Pedersen BK and Fomsgaard A (1991). Effect of physical exercise on in vitro production of interleukin-1, interleukin-6, tumor necrosis factor-α, interleukin-2, and interferon-gamma. *International Journal of Sports Medicine* **12** 223-227, PMID: 1907258.

Haghighi AH (2006). Effect of resistance training on inflammatory cytokine and insulin resistance in obese man. *Olympic* **14**(3) 34 (Persian).

Henson DA, Nieman DC, Nehlsen-Cannarella SL, Fagoaga OR, Shannon M, Bolton MR, Davis JM, Gaffney CT, Kelln WJ, Austin MD, Hjertman JM and Schilling BK (2000). Influence of carbohydrate on cytokine and phagocytic responses to 2 h of rowing. *Medicine and Science in Sports and Exercise* **32**(8) 1384-9, PMID: 10949003.

Kasapis C and Thompson PD (2005). The effects of physical activity on serum C-reactive protein and inflammatory markers .*Journal of the American College of Cardiology* **45**(10) 1563-1569, PMID: 15893167.

Khaleghi Mahyar, Iftikhar J Kullo and Donald D Hensrud (2007). Markers of inflammation are inversely associated with VO2 max in asymptomatic men. *Journal of Applied Physiology* **102**(4) 1374-9, PMID: 17170204.

Mackinnon LT (1999). *Advances in Exercise Immunology* (Human Kinetics).

Mackinnon LT (2003). *Immunology and Exercise*, translated by Musavi T *et al., Imam Hosain University, Tehran Iran* (Persian).

Moldoveanu AI, Shephard RJ and Shek PN (2000). Exercise elevates plasma levels but not gene expression of IL-1β, IL-6 and TNF-α in blood mononuclear cells. *Journal of Applied Physiology* **89** 1499-1504, PMID: 11007588.

Moldoveanu AI, Shephard RJ and Shek PN (2001). The cytokine response to physical activity and training. *Sports Medicine* **31**(2) 115-144, PMID: 11227979.

Mora S, Lee IM, Buring JE and Ridker PM (2006). Association of Physical Activity and Body Mass Index with Novel and Traditional Cardiovascular Biomarkers in Women. *Journal of the American Medical Association (JAMA)* **295**(12) 1412 -9, PMID: 16551713.

Nemet D, Rose-Gottron CM, Mills PJ and Copper DM (2003). Effect of water polo practice on cytokine, growth mediators, and leukocytes in girls. *Medicine and Science in Sports and Exercise* **35**(2) 356-363, PMID: 12569228.

Nieman DC, Davis JM, Brown VA and Henson DA *et al.*, (2003a). Carbohydrate ingestion Influences skeletal muscle cytokine mRNA and plasma cytokine levels after a 3-h run. *Journal of Applied Physiology* **94** 1917-1925, PMID: 12533503.

Nieman DC, Davis JM, Brown VA and Henson D A, *et al.*, (2004a). Influence of carbohydrate ingestion on immune changes after 2h of intensive resistance training, *Journal of Applied Physiology* **96** 1292-1298, PMID: 14672962.

Nieman DC, Nelson-Cannarella SL, Fagoaga OR, Henson DA and Utter AMJ *et al.*, (1997). Influence of mode and carbohydrate on the cytokine response to heavy exertion. *Medicine and Science in Sports and Exercise* **30**(5) 1667-1667, PMID: 9588607.

Nieman DC, Buckley KS and Nehlsen Cannarella SL *et al.*, (1995). Immune function in marathon runners versus sedentary controls. *Medicine and Science in Sports and Exercise* **27** 986–92.

Nosaka Nosaka K, Newton M and Sacco P (2002). Muscle damage and soreness after endurance exercise of the elbow flexor. *Medicine and Science in Sports and Exercise* **34**(6) 920-927, PMID: 12048316.

Pedersen BK, Steensberg A, Fischer Kller C, Ostrowski K and Schjerling P (2001). Exercise and cytokines with particular focus on muscle –derived IL-6. *Exercise Immunology Review* **7** 18-31, PMID: 11579746.

Pedersen BK, Ostrowski K, Rohde T and Bruusgaard H (1998). The cytokine response to strenuous exercise. *Canadian journal of Physiology and Pharmacology* **76** 505-511, PMID: 9839076.

Pedersen BK and Anders DT (2000). Effects of exercise on the lymphocytes and cytokine. *British Journal of Sports Medicine* **34** 246–51.

Pedersen BK and Hoffman-Goetz L (2000*)*. Exercise and the immune system: regulation, integration and adaption. *Physiological Reviews* **80**(3) 1055–81.

Pedersen BK, Steensberg A and Fischer C *et al.*, (2003). Searching for the exercise factor: is IL-6 a candidate. *Journal of Muscle Research and Cell Motility* **24**(2-3) 113–9, PMID: 14609022.

Pedersen BK, Steensberg A and Schjerling P (2001). Muscle-derived interleukin- 6: possible biological effects. *Journal of Physiology* (London) **536** 329–37.

Petersen AM and Pedersen BK (2005). The anti-inflammatory effect of exercise. *Journal of Applied Physiology* **98** 1154-1162, PMID: 15772055.

Phillips Melody D (2001). Cytokine response to acute and chronic resistance exercise in women aged 65-8yr. *A dissertation* submitted to the faculty of Purdue University for degree of doctor of philosophy, UMI Number 3075711.

Pitsavos C, Panagiotakos DB, Chrysohoou C, Kavouras S and Stefanadis C (2005). The associations between physical activity, inflammation, and coagulation markers, in people with metabolic syndrome: the ATTICA study. *European Journal of Cardiovascular Prevention and Rehabilitation* **12**(2) 151-8, PMID: 15785301.

Powers SK and Jackson MJ (2008). Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. *Physiological Reviews* **88**(4) 1243-76, PMID: 18923182.

Powers SK, Ji LL and Leeuwenburgh C (1999). Exercise training – induced alterations in skeletal muscle antioxidant Capacity: a brief review. *Medicine and Science in Sports and Exercise* **31** 987-997, PMID: 10416560.

Ravasi A (2006). The effect of endurance training on preinflamatory cytokines and insulin resistance in obese men. SID *Harkat Journal* **2**(28) 31-49 (Persian).

Remick DG and Fridland JS (1997). In: *Cytokines in Health and Disease*, second edition, edited by Remick DG and Friendland JS (Marcel Dekker, Inc. Publishers) New York.

Rohit Gokhale A, Chandrashekara BS and Vasanthakumar AKC (2007). Cytokine response to strenuous exercise in athletes and non-athletes—an adaptive response. *Cytokine* **40** 123–127.

Ryan AS and Nicklas BJ (2004). Reductions in plasma cytokine levels with weight loss improve insulin sensitivity in overweight and obese postmenopausal women. *Diabetes Care* **27** 1699-1705, PMID: 15220249.

Sloan R, Shapiro PA, Ronald E and Paula S *et al.*, (2007). Aerobic exercise attenuates inducible TNF production in humans. *Journal of Applied Physiology* **103** 1007 – 10110, PMID: 17626836.

Smith JK, Dykes R, Douglas JE, Krishnaswamy G and Berk S (1999). Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *Journal of the American Medical Association* **281**(18) 1722-1727, PMID: 10328073.

Solini A *et al.*, (2006). Effect of short – term folic acid supplementation on insulin sensitivity and inflammatory markers in overweight subjects. *International Journal of Obesity* **30** 1197-1202, PMID: 16491109.

Sorichter S, Martin M , Julius P, Schwirtz A and Huonker M *et al.*, (2006). Effects of unaccustomed and accustomed exercise on the immune response in runners. *Medicine and Science in Sports and Exercise* **38**(10) 1739 – 1745, PMID: 17019295.

Steensberg A, Osada T, Van Hall G, Scchetti M, Saltin B and Klarlund PB (2000). Production of interleukin-6 in contracting human skeletal muscles can account for the exercise – induced increase in plasma interleukin-6. *Journal of Physiology* **529**(pt 1) 237-242, PMID: 11080265.

Stewart LK, Flynn MG, Campbell WW, Craig BA and Robinson JP *et al.*, (2007). The Influence of Exercise Training on Inflammatory Cytokines and C - reactive protein. *Medicine and Science in Sports and Exercise* **39**(10) 1714–1719, PMID: 17909397.

Sukovich DA, Kauser K, Shirtey FD, DelVecchio V, Halks-Miller M and Rubanyi GM (1998). Experssion of interleukine-6 in atherselerotic lesions of male apoE-knockout mice:inhibition by 17β-estradiol. *Arteriosclerosis, Thrombosis, and Vascular Biology* **18** 1498-1505, PMID: 9743240.

Timmons BW (2005). Immunological changes in response to acute exercise, considering puberty and sex. *A dissertation* (thesis) submitted to the school of graduate in partial fulfillment of the requirements for degree Doctor of Philosophy (Kinesiology), Mc Master *University Hamilton, Ontario*.

Ullum H, Haahr PM, Diamant M, Palmo J, Halkjaer-Kristensen J and Pedersen BK (1994). Bicycle exercise enhances plasma IL-6 but does not change IL-1α, IL-1β, IL-6, or TNF-α pre-mRNA in BMNC. *Journal of Applied Physiology* **77**(1) 93-97, PMID: 7961280.

Vincent (1999). *Statistics in Physical Education and Sport Sciences*, translated by Minasian Vazgen (Published by Physical Education organization) (Persian).

Ziaee N *et al.*, (2007). Relationship of inflammatory indicators of heart disease with maximum oxygen consumption in women Athletes. *Sixth International Conference of Physical Education and Sport Sciences, Iran* (Persian).