

Correlation between CRP and IL-6 Serum Levels after Induction of Diabetes and Eight Weeks Resistance Training in Rats

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Abstract

Introduction: Systemic low-grade chronic inflammation is considered to be one of the significant characteristics of diabetes mellitus. This study aimed to investigate the correlation between C-reactive protein (CRP) and interleukin-6 (IL-6) serum levels, after induction of diabetes and eight weeks of resistance training in rats.

Methods: For the purpose of this experimental study, 24 streptozotocin induced diabetic rats were divided into three groups of 8 including (1) first week diabetic control, (2) last week diabetic control and (3) resistance training. Moreover, 8 healthy rats were chosen as the first week healthy control groups to assess the effects of diabetes induction on CRP and IL-6 serum levels. Rats of group 3 were subjected to an eight-week resistance training (3 days/week). Kolmogorov-Smirnov, independent-samples t-test, and Pearson correlation coefficient, were used for data analysis ($p \leq 0.05$).

Results: Induction of diabetes had a significant effect on the increased serum levels of CRP ($p = 0.01$) and IL-6 ($p = 0.01$). However, after 8 weeks of resistance training, a significant decrease was observed in CRP ($p = 0.001$) and IL-6 ($p = 0.01$) serum levels of streptozotocin induced diabetic rats. Also, there was no significant correlation between CRP and IL-6 serum levels, after the induction of diabetes ($p = 0.23$) and eight weeks of resistance training ($p = 0.65$).

Conclusion: It appears that there is no correlation between CRP and IL-6 serum levels, after the induction of diabetes and eight weeks of resistance training in rats.

Keywords: Diabetes, Resistance Training, IL-6, CRP

Introduction

The prevalence of diabetes mellitus, which is a deficiency in endocrine glands or a metabolic syndrome, is increasing all around the world. Based on the global statics, the number of diabetics, since 1980 until 2014, has dramatically increased from 108 million to 422 million patients (1). In long-term, diabetes may cause disorders such as neuropathy, retinopathy, nephropathy, cardiovascular diseases, immune system deficiencies, vascular injuries and impairment of tissue repair, which in turn, have significant effects on patient as well as society (2, 3). With the progress of diabetes, cytokines which can

influence insulin resistance and adipokins associated with lipid and carbohydrates metabolism are secreted from adipose and muscle tissues; therefore, production of some adipokins during obesity can cause more pain and suffering for diabetic patients and patients with metabolic syndrome (4). Secretion of macrophages may result in inflammation of adipose tissue. In this case, different kinds of innate immune receptors have the ability to regulate the disturbed function of adipose tissue and insulin resistance (5). A large body of literature showed that C-reactive protein (CRP) and pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis

factor- alpha (TNF- α) serum levels of diabetic patients, is higher than healthy people and, thus, the risk of cardiovascular diseases in diabetic patients is higher, too (6, 7). Additionally, in many studies, the significant effect of IL-6 serum levels on insulin resistance has been shown. On the other hand, one of the important functions of IL-6 is the stimulation of CRP production. CRP is a biomarker, which is produced by cytokines, when the systemic inflammation reaches its final stages. High levels of CRP, has been associated with high blood pressure, body mass index, metabolic syndrome, and diabetes (8). Increased systemic levels of pro- and anti-inflammatory cytokines, has been shown in many studies. Moreover, it has been suggested that the anti-inflammatory effects of regular exercise, has many beneficial impacts on many different diseases (9). The moderating effects of physical activity can also cause positive changes in innate immune system. Such effects, has been attributed to the production of IL-6, during contractile activity of skeletal muscle; thus, any activity that can change the abnormal levels of these factors in blood circulation, somehow, may prevent cardiovascular diseases. Physical activity is known to have positive role on decreasing obesity in individuals; however, available data about the effects of physical activity on inflammatory markers, such as TNF- α , IL-6 and CRP, are inconsistent (7). In this regard, it has been shown, that following a 3-days-a-week resistance circuit training protocol for 12 weeks, has been significantly decreased CRP, IL-6, and leptin, and increased adiponectin serum levels of obese non-athletic men, in comparison to their serum levels before beginning the training program. Eight weeks of resistance swimming training (three 60 minutes sessions per a week), resulted in decreased serum levels of TNF- α , IL-6 and CRP in rats with diabetic neuropathy (1); however, Molanouri Shamsi *et al.* (2014), reported that following an eight-week resistance training (3 days/week), with weights

equivalent to 30 %-120 % of rat's body weight, had no significant effects on the TNF- α and IL-6 levels of fast-twitch muscle tissue, but, a significant and positive correlation between the levels of these cytokines, were detected (9). High intensive training, for 6 weeks, on the treadmill resulted in decreased fat mass and TNF- α levels, in over-weighted and diabetes type 2 women, but no significant difference in IL-6 levels, were observed (6); Mardanpour -shahr-e-kordi *et al.* (2017), which is investigated the effects of different training modalities, such as endurance-strength, strength-endurance and interval endurance-strength training, on TNF- α and IL-6 levels, showed that there is no significant difference between training modality and changes in inflammatory factors. Although, by comparing pre and post-test results, a significant decrease of these factor levels, were indicated, in all groups (11). It seems, there are major differences between the behavior and function of systemic and tissue IL-6. Also, the observed effects of IL-6 released in skeletal muscles, in response to the exercise, are clearly different. Up to this date, no appropriate resistance training protocols has been developed for patients with diabetes type 1, although increased muscle cross-sectional area, following resistance training, were observed, in these patients. In addition to this, literature shows that resistance training improves the action of insulin in skeletal muscle and increases the level of glucose tolerance in diabetic patients (12). Considering the observed inflammatory effects of diabetes, and since a large portion of systemic glucose is send and stored into the skeletal muscles, investigating the effects of resistance training in diabetic animals, can play an important role in establishing effective training protocols for diabetic patients (11). Moreover, studying the alterations in IL-6 and CRP levels, in response to resistance training and analysis of these variables in different types of diabetes, can provide answers to some questions concerning the metabolic effects of these factors.

Therefore, the present study sought to investigate the correlation between serum levels of CRP and IL-6, after induction of diabetes and eight weeks of resistance training in rats.

Methods

In this experimental study, 32 adult male Sprague-Dawley rats, were obtained from the animal resources center of Azad Islamic University of Marvdasht, and transported to animal maintenance room of Sport physiology laboratory (with ambient temperature of $22\pm 2^{\circ}$ Celsius, controlled light, and 12-hour cycle of light and darkness) for an 8-day acclimatization. During this time, animals' access to water and food was free. In the 8th day, after one fasting night, 24 rats were injected intraperitoneally with 60 mg/kg of streptozotocin (manufactured in Sigma Inc.) dissolved in citrate buffer. Four days after the injections, the necessary blood samples for assessing blood-glucose with Glucometer were obtained from animal tails by using punching method. Rats with blood-glucose more than 300 mg/dL were chosen as research subjects. Streptozotocin induced diabetes rats were subjected to a one-week resistance training program. Diabetic rats were randomly divided into three groups (8 rats for each group): (1) first week diabetic control, (2) last week diabetic control, and (3) resistant training. Also, for assessing the effects of inducing diabetes on IL-6 and CRP levels, at the same time with Group (1), and after a 16-hour fasting period, 8 healthy rats, were put down to sleep (by using euthanasia methods), and blood-samples were obtained. Based on the study protocol, by the end of acclimatization week, rats were positioned at the lowest step of ladder and were thought to climb the ladder without any additional weights, in order to be familiarized with resistance training and learn how to climb the ladder. Rats were conditioned to continue their climb by touching their tails and making noises.

Familiarizing of rats with the process of climbing, lasted every other day for a week and during each session, the rats were guided through four sets of exercises without weights. Resistance training protocol included eight weeks of climbing a one meter ladder with 4 cm distance between each step in a vertical position. In order to familiarize rats with the climbing process, before actual training course, they were forced to climb the ladder 3 to 5 times, without attaching any additional weights. Before the beginning of training course, rats were warmed up by climbing the ladder 3 times, without any weights or rests in between climbs. At the beginning, the chosen lift was equivalent to 30 % of rats' weight and, by the last week, it was a 100 % of their weights. According to study protocol, weights were attached to rats' tails with leukoplast plaster (before training, the sensitivity of rats' tails to this glue was assessed) and each rat was forced to climb the ladder 2 times, after which a new weight would replace the old one. Training load included 50, 75, 90 and 100 % of the heaviest weight that were successfully carried to the top. In the last session of each week and after the end of training and resting time, the maximum transferable weights of each rat was determined; for this purpose, new weights were added to the last weights, until the rats were unable to climb (13). Then, blood samples were obtained from remaining last week diabetic control (group 2) and resistance training (group 3) rats. Using commercially available Rat ELISA-kit (Ra-01, manufactured by Eastbiopharm Co. Ltd, Hangzhou, China), serum levels of IL-6 (ng/L, and sensitivity of 1.03 ng/L) and CRP (mg/L, and sensitivity of 2 mg/L), were assessed. All of the ethical and legal aspects of this research have been reviewed and approved at Azad Islamic University of Marvdasht. All collected data in this study, are described as mean and standard deviation. Also, Kolmogorov-Smirnov test was used for evaluating normal distribution of the findings, whereas for inferential analysis of findings, independent t-test and Pearson

correlation coefficient test were performed ($p \leq 0.05$).

Results

Serum levels of CRP and IL-6 of all 4 study groups are, respectively, shown in figure (1) and (2). Based on the independent t-test results (table 1), it could be suggested that induction of diabetes has significant effects on increased CRP and IL-6 serum levels, in rats ($p = 0.001$); however, after 8 weeks of resistance training a significant decrease was observed in CRP ($p = 0.001$) and IL-6 ($p = 0.01$) of serum levels in diabetic rats. Results of Pearson correlation coefficient test are summarized in table 2; based on this table, there is no significant correlation between CRP and IL-6 serum levels, after the induction of diabetes ($p = 0.23$) and eight weeks of resistance training ($p = 0.65$).

Discussion

Based on the results of this study, induction of diabetes can increase the serum levels of CRP and IL-6 in rats. Similar to our results, scientists have shown that induction of diabetes with 50 and 55 mg/kg streptozotocin, can cause a spike in protein (9) and serum levels (3, 12-14) of inflammatory factors, such as IL-6, TNF- α and CRP. CRP serum levels of 737 diabetic patients were significantly higher than 785 healthy individuals (17); moreover, according to the results of a prospective study with 5 years of follow-up, comparison of 127 diabetic patients with the total of 5245 participants in the study, showed that CRP levels of middle-aged men can be considered as a predictive factor for diabetes (18). Since human studies are restricted due to ethical and moral considerations, the best way to gain better insight into this disease is the utilization of animal models for conducting animal studies. One of the prominent diabetic-inducing chemical agents which are widely used in vitro studies on animal models is streptozotocin. This agent is gathered by pancreas β -cells via GLUT 2 and, then, enters different cells to cause tissue damage. The main cause of streptozotocin toxicity is methylation in pancreas β -cells DNA. One way or another, the simultaneous function of

NO and ROS, can directly affect division or fragmentation of cell DNA and, thus, cause complete cell destruction (19). Diabetes mellitus is one of the main problems of public health, which in turn may cause acute diseases and increase mortality rate; some of the long-term and most dominant complications of this type of diabetes include neuropathy, nephropathy, and retinopathy (20). In this case, increased serum levels of inflammatory factors (6,8) in diabetic male and female patients and obese men (7) points to the role of diabetes and obesity on increased levels of IL-6 and CRP; in other word, diabetic individuals are more inclined to experience cardiovascular diseases (6). Results of the present study indicate that eight weeks of resistance training, can significantly decrease CRP and IL-6 serum levels in diabetic rats. Similar to our study, 16 weeks of 3-days-a-week concurrent endurance and resistance training, resulted in the significant increase of IL-6 and TNF- α in middle-aged women with diabetes type 2 (21); After 4 weeks of 3-days-a-week resistance training with ladder, the levels of CRP were decreased, while vaspin was increased in diabetic and non-diabetic rats (3); 8 weeks, three 60- seconds sessions a week of mixed training (endurance-resistance, in comparison with resistance-endurance group) resulted in decreased levels of hs-CRP and IL-6 for elderly healthy women, while there was no significant difference in training modality (11); 8 weeks, three sessions a week, of endurance training with medium and high intensity had significant effect in decreasing CRP levels of diabetic rats, however there was no correlation between training intensity and the obtained results (22); 3 sessions a week of endurance training with 60 % to 70 % of maximum heart rate for the duration of 12 weeks could significantly decrease CRP in middle-aged diabetic women (23); 6 weeks of physical activity in form of rehabilitation (3 weeks) and controlled physical training (3 weeks) at home resulted in the significant decrease of CRP in patients with coronary artery disease (24); After 12 weeks of physical activities a significant decrease of CRP levels was observed in middle-aged women (25); Comparison of aerobic trainings and flexibility-resistance trainings effects showed that three 45-minutes sessions-a-week of aerobic training for 10 months can decrease

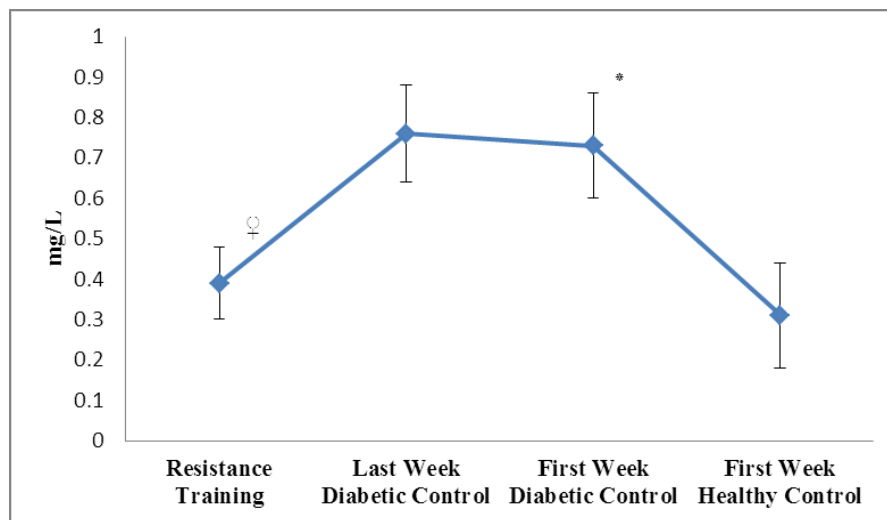


Figure 1. CRP serum levels of all four groups of the study; * significant increase of CRP serum levels in comparison with first week healthy control group; ♀ significant decrease of CRP serum levels in comparison with last week diabetic control group.

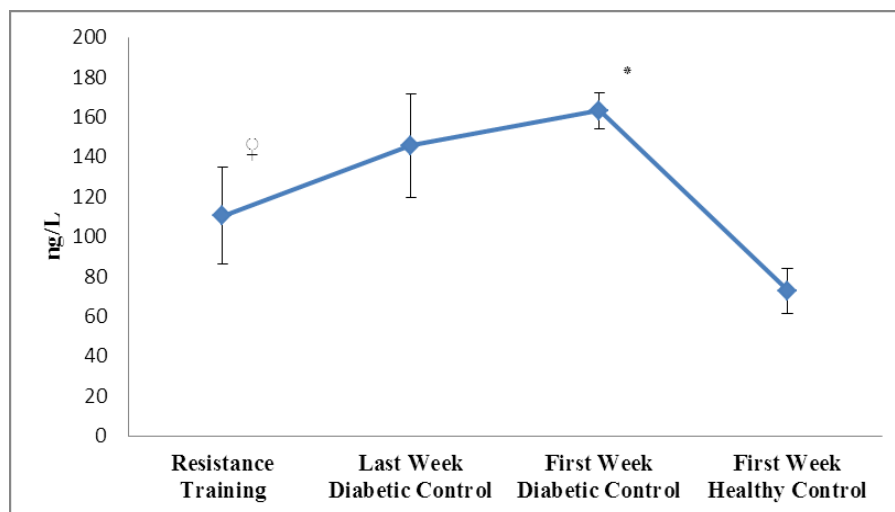


Figure 2. IL-6 serum levels of all four groups of the study; * significant increase of IL-6 serum levels in comparison with first week healthy control group; ♀ significant decrease of IL-6 serum levels in comparison with last week diabetic control group.

Table 1. Independent-samples t-test results, for assessing effects of induction of diabetes and resistance training on CRP and IL-6 serum levels of rats

Variable	Group	t	df	P
CRP	First week healthy control	-6.29	14	0.001
	First week diabetic control			
	Last week diabetic control	6.69	14	0.001
IL-6	Resistance training	-17.58	14	0.001
	First week healthy control			
	Last week diabetic control	2.78	14	0.01

Table 2. Pearson coefficient correlation results, for assessing correlation between CRP and IL-6 serum levels of rats, after induction of diabetes and an 8-week resistance training

Variable	
Factor	IL-6
Induction of diabetes	r=0.32, p=0.23
Resistance training	r=-0.12, p=0.65

CRP; however, these results were not significant for flexibility-endurance training (26). In addition, 6 weeks of 3-sessions-a-week endurance training at 45 % and 55 % of 1RM and 80 % to 90 % of 1RM, had significant effects on hs-CRP levels in young healthy men (27). However, inconsistent with the results of the present study, it has been shown that long-term and intensive physical activities may cause significant increase in CRP density (more than 20 folds) (28); Also, 18 months of mixed training (including walking and weight lifting) had no effect in decreasing CRP for elderly obese men (29). Different study sample and training protocols may be the cause of inconsistency between the results of the present study and the aforementioned research; 17 sessions of resistance training on a one meter ladder with 5 activity sets and 4 repetition in each set with 60-seconds rest-intervals and weights equivalent to 120 % of the rats' body weight, had no effect on protein levels of IL-6 and TNF- α , in diabetic rats (9). After 4 weeks, three session a week of resistance training on ladder, there was no difference on IL-6 levels in diabetic and non-diabetic rats (3); In this case, different training durations could be considered as the cause of distinguished outcomes; 6 weeks, three sessions a week of high intensity interval training had no significant effect on decreasing IL-6 levels of overweight women with diabetes type 2 (6); 8 weeks, three session a week of aerobic training and mixed exercises with 60 % to 80 % maximum heart rate intensity had no effects on IL-6 levels of type 2 diabetic patients (30); Moreover, after 6 weeks of three sessions a week resistance training with the intensity of 45 % to 55 % 1RM and 80 to 90 % 1RM, there was no difference in IL-6 levels of healthy young men (27). It is possible that the inconsistency between these results is due to different study samples and CRP basic levels.

Decreased levels of CRP may be caused due to the potential influence of training on moderating diabetes inflammation; But, generally speaking, the direct role of physical activity in decreasing the production of cytokines in fatty tissue, muscle and mono-nuclear cells and the indirect role of these activities in increasing insulin sensitivity and improving endothelial performance, can lower the levels of CRP in blood circulation. However, how resistance training can decrease inflammation, remains unclear. The body of literature has shown that increased levels of intake calories can, in some ways such as losing weight, decrease CRP levels. Therefore, the resistance training courses of this study have also used the same mechanism to decrease CRP and IL-6 levels of rats (30). Also, it is believed that physical training is associated with increased pre-inflammatory cytokines, such as vaspin, which in turn have inhibitory effects on reactive oxygen species (ROS) and inflammatory factors in smooth and vascular muscle cells; this mechanism prevents the phosphorylation of nuclear factor kappa-light-chain-enhancer of activated B cells and protein kinase C θ transcriptional factors. Increased blood glucose during training, may cause oxidative stress, which in turn activates NF κ B and, thus, increases the levels of pre-inflammatory cytokines in blood circulation (31).

Moreover, the results of this study indicated the non-existence correlation between serum levels of CRP and IL-6 after the induction of diabetes and 8 weeks of resistance training. One of the main characteristics of diabetes mellitus is increased levels of inflammatory mediators, such as cytokines, and CRP which can cause cardiovascular problems. In cell, exposure of cells to high concentrations of TNF- α , IL-6 and IL-1 β , results in phosphorylation of insulin receptor serine sequences which can directly influence insulin

resistance (3). Interactional mechanism between inflammatory pathways and insulin resistance is known to be one of the most important influencing factors of diabetes. TNF- α can inhibit auto-phosphorylation of tyrosine sub-units of insulin receptor and induce phosphorylation of serine units of insulin receptor substrates, while IL-6 disrupts the signaling pathway of insulin by using suppressor of cytokine signaling-3 (SOCS-3) (32). Most studies suggesting a simultaneous increase in IL-6 and CRP serum levels (2, 32-34). Researchers believe that increased cholesterol, neutrophil accumulation and cells' hypoxia may be result in the production of inactive IL-1 β ; after that, Caspase-1 will mediate the activation of IL-1 β , and ultimately, IL-6 and CRP will be produced (35). Up to this date, CRP has been widely studied as a sensitive and non-specific factor. Some cytokines, especially IL-6, are responsible for the regulation of CRP levels. CRP is a member of Pentraxin family, which plays an important role in immune responses. Although, this substance is produced in liver, studies showed that vascular endemic layers with atherosclerosis can also be a source of CRP. Other than its role as an inflammatory marker, CRP can use different mechanisms, such as decreasing nitrite oxide (NO) production, increasing molecular adhesion and changing the absorption of low density lipoprotein into macrophages, to cause vessel destruction. Alternatively, IL-6 can simulate CRP synthesis (34). Results of human and animal studies on the effects of exercise on serum levels and correlation of IL-6 and CRP levels are very controversial. However, reviewing some of these studies showed that none of these studies report a significant relation between levels of IL-6 with CRP and serum vaspin in diabetes-induced rats after 4 weeks of physical training (3) and patients with diabetes type 2 (32). Based on the gathered information it could be said that physical activity can decrease the production of IL-6 and other cytokines of the involved muscles by increasing anti-oxidative protection and support; since TNF- α and IL-6 are released from adipose tissue and are involved in production of CRP, negative regulation of Sympathetic stimulation through physical activity can increase their release and, thus, decrease CRP levels (34).

Conclusion

It seems that resistance training can help diabetic patients in controlling their disease by lowering the serum levels of IL-6 and CRP. In addition, there is no significant correlation between serum levels of these factors, after the induction of diabetes and eight weeks of resistance training in rats.

Ethical issues

No applicable.

Authors' contributions

All authors equally contributed to the writing and revision of this paper.

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