Original Article

Investigating the Relationship between Serum Glucose and Inflammatory Markers in Diabetic Rats with Progressive Resistance Exercise

Vatandoust Maryam[1*], Zare Banaadkouki Ali[2]

1. Department of Exercise Physiology, Payame Noor University (PNU), Tehran, Iran
2. Department of Exercise physiology, Faculty of Physical Education, Payame Noor University, Alborz, Iran

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Abstract

Background & Objective: Diabetes Mellitus (DM) is a condition that is associated with an increase in inflammatory markers and studies show that resistance exercise with appropriate intensity can reduce inflammation generally. The aim of this study was to investigate the relationship of serum glucose with Interlekin18 (IL-18) and Tumor Necrosis Factor-alpha (TNF-α) in Diabetic rats with progressive resistance exercise.

Materials & Methods: In this experimental study, 32 Wistar male rats were distributed to sedentary control, trained control, sedentary diabetic, and trained diabetic groups of 8. Diabetes was induced by Streptozotocin (55 mcg/bw-i.v.). The resistance training protocol consisted of elevating upward from a ladder with weight, supporting an overload equivalent to 5% of body weight, during 6 weeks. The data obtained were analyzed by ANOVA and Tukey's posthoc multiple comparison tests, and a significance level of 5% was considered.

Results: According to results, serum concentrations of TNF-α and IL-18 decreased significantly in trained diabetic group compared to sedentary diabetic group after resistance training. While in the amount of TNF-α in the trained control group compared to the sedentary control group, a significant increase was observed, and in the amount of IL-18 in trained control group compared to the sedentary control group, a significant decrease was observed. But regarding the correlation between serum IL-18 concentration and glucose, only in sedentary control group, a significant correlation was observed.

Conclusions: Resistance training was able to reduce TNF-α and IL-18 inflammatory markers in trained diabetic rats and improve metabolic and immune aspects in diabetes mellitus.

Keywords: Resistance Training, Tumor Necrosis Factor-alpha, Interleukin-18, Diabetes Mellitus

Introduction

Many chronic diseases are now in pandemic proportions and are increasingly a major cause of morbidity and mortality worldwide. Diabetes mellitus plays a starring role in this problem (1). The major forms of diabetes can be categorized as type 1 or type 2. In type 1 diabetes, which accounts for 5–10% of cases, the cause is an absolute deficiency of insulin secretion resulting from autoimmune destruction of the insulin-producing cells in the pancreas. Type 2 diabetes (90–95% of cases) results from a combination of the inability of muscle cells to respond to insulin properly (insulin resistance) and inadequate compensatory insulin secretion. Less common forms include gestational diabetes mellitus (GDM), which is

***Corresponding Author: Vatandoust Maryam,** Department of Exercise Physiology, Payame Noor University (PNU), Tehran, Iran
Email: Maryam.Vatandost@pnu.ac.ir
https://orcid.org/0000-0002-5623-8101

Zare Banaadkouki Ali: https://orcid.org/0000-0003-4822-994X

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associated with a 40–60% chance of developing type 2 diabetes in the next 5–10 years. Diabetes can also result from genetic defects in insulin action, pancreatic disease, surgery, infections, and drugs or chemicals and also its risk increases with age, obesity, and physical inactivity (2). Recently, the effect of physical activity on immune function has been studied intensely in diabetic patients (3). This is an important area of study because exercise may modulate the immune system's ability to monitor and protect the individual from disease and to repair the damage. In most of these studies, aerobic exercise (AEX) and aerobic conditioning (ACO) have been the independent variables. Consequently, the functional immune response to ACO seems relatively clear. However, the immune response to resistance exercise (REX) is not as clear because few studies have been published. The immune response to REX may be different from that to AEX because of the different physiological demands of these 2 types of exercise. Resistance conditioning (RCO) does not have a significant effect on heart rate, blood pressure, cardiac output, stroke volume, vascular resistance, or the arteriovenous oxygen saturation difference during submaximal treadmill exercise (4).

The extent to which these changes occur in patients with a chronic inflammatory disease is important to address to ensure that exercise is performed in a safe manner where inflammation is not being further amplified. In an almost paradoxical way, however, participation in regular exercise (i.e. resistance training) can reduce resting levels of many inflammatory markers (5).

Cytokines are a group of pharmacologically active, low molecular weight polypeptides that possess autocrine, paracrine, and juxtacrine effects with characteristic features. These molecules cluster into several classes (i.e., interleukins, tumor necrosis factors, interferons, colony-stimulating factors, transforming growth factors and chemokines), which are relevant humoral mediators in a highly complex, coordinated network regulating inflammatory immune responses with the participation of different cytokine-associated signaling pathways (6). In addition, they exert important pleiotropic actions as cardinal effectors of injury (7).

Type 1 pro-inflammatory cytokines such as interferon (IFN)-γ, interleukin (IL)-1β, IL-12, IL-18 and tumor necrosis factor (TNF) release by macrophage and T lymphocytes in the vicinity of pancreatic beta cells have repeatedly been implicated in the pathogenesis of Type 1 (insulin-dependent) diabetes mellitus (8). Obviously, TNF-α effects have been reported, such as induction of apoptosis and necrotic cell death (9). IL-18 is another type 1 cytokine primarily produced by macrophages and closely related to the IL-1 family of cytokines. It has been shown that IL-18 plays a pivotal part in the generation of type 1 cytokine responses through its ability with IL-12 to up-regulated IFN-γ production from T cells and natural killer cells and leads to the destruction of pancreatic beta cells and diabetes development (6).

At the present time, it is recognized that chronic low-grade inflammation and activation of the innate immune system are closely involved in the pathogenesis of diabetes mellitus (10). Most evidence suggests that individuals who progress to diabetes mellitus display features of inflammation years before the disease onset Moreover, population-based studies suggest that inflammatory parameters, including inflammatory cytokines, are strong predictors of the development of diabetes (11,12).

However, there is little data about the impact of resistance exercise on inflammatory markers function and inflammation in type 1 diabetes.

The aim of this study was thus to investigate whether a 6-week supervised resistance exercise program could suppress the inflammatory cascade and trigger anti-inflammatory mediators in male rats with type 1 DM.

Materials & Methods

Laboratory animals

In this experimental study, 32 Male Wistar rats were used (250±30g; 40-day-old). In order to adapt to the new environment, they were

kept at 25°C with a 12/12 light/dark cycle for 1 week and fed with Purina rat food and water ad libitum. All experiments with the animals were performed in accordance with the specific Brazilian resolutions of the Bioethics of Experiments with animals.

For the study, the rats were randomly distributed into four groups (n = 8 per group):

1. Sedentary Control (SC): not trained and no drug treatment-induced 2. Trained Control (TC): resistance training is done with no drug treatment, 3. Sedentary Diabetic (SD): Streptozotocin (STZ) induced with no resistance training, 4. Trained Diabetic (TD): resistance training is done with STZ induced.

Diabetes induction

The animal was first anesthetized by intraperitoneal injection of a combination of ketamine (70 mg/kg B.W.) and xylazine (3mg/kg B.W.). Diabetes was induced by intravenous injection (55 mcg/kg B.W.) of Streptozotocin (STZ, Sigma, st, MO, USA). After two days, blood samples were obtained with animals in the after 6 hours of fed state to determine the plasma glucose concentration. Rats that were not diabetic (<14.7 mmol/L) or too severely diabetic (>35.5 mmol/L) were eliminated from the study.

Training protocol

Climbing of a ladder with a 2 cm grid ladder inclined with 26 steps at 85 degrees with weights attached to their tails was used as a resistance exercise. Rats were familiarized with the exercise for three days. Three days after familiarization, the resistance training was begun using cylinders containing weights that were attached to the base of the tail with foam tape (3M Conan), a Velcro strap and a hook. Briefly, the cylinders were fastened to the tail by wrapping the upper portion of the tail (2-3 cm from the proximal end) with Velcro on top of foam tape. Then, the appropriate weights were inserted into the cylinders. The rats were positioned at the bottom of the climbing apparatus and motivated to climb the ladder by grooming action to the tail. The initial weight attached was 30% of their body weight for the diabetic group and 50% of their body weight for the control group and increased gradually (5% overload/week) throughout the 6 weeks of the training period. The resistance training consisted of five sets of 4 repetitions with a 3 min rest interval between the sets and 30 to 60 seconds between the reps for 6 weeks period and 3 sessions per week. Electrical shock (0.2-3m Amp) was used to motivate the rat to climb when necessary.

Blood sampling

Rats were anesthetized in a chloroform chamber 24 hours after the last training session and after cutting the chest and abdomen, blood samples were taken directly from the animals' hearts at a rate of 6 cc. Then the samples were kept at room temperature for 30 minutes for clotting and then centrifuged for 20 minutes at 4000 rpm. The samples were kept at 20 ° C and laboratory assay was started immediately.

Cytokines detections

Serum TNF-α and IL-18 levels were measured by enzyme-linked immunosorbent assay (ELISA) technique (enzyme-amplified sensitivity immunoassay (ELISA) kits (from Bender Med Systems Co, BMS622 and Invitrogen Life Science Co, KRC2341, USA) respectively. These assays detected only Rat cytokines and the minimum detectable concentrations in our laboratory were 11 pg/mL for TNF-α and 15.6 pg⁄mL for IL-18.

Glucose was measured from whole venous blood with a glucose monitor (Glucometer; Bayer Diagnostics, New York, NY).

Glucose measurement

Serum glucose was measured by glucose oxidase (Zist Shimi) enzymatic method using a digital spectrophotometer (Spectronic-20, USA).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 16, was used for statistical analysis. All data are presented as mean ± SEM. Before statistical

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analysis, all variables were checked for normality and homogeneity of variance by using the Kolmogorov-Smirnoff and Levene tests, respectively. The data obtained were tested by ANOVA followed by Tukey's posthoc multiple comparison test and $P<0.05$ was considered statistically significant.

Results

The effect of progressive resistance exercise on serum levels of Glucose:

After the experimental period Streptozotocin-induced, diabetes increased serum glucose.

As shown in Chart 1, there was a significant difference between the mean of Sedentary Diabetic group with the mean of other healthy groups and also between the mean of Trained Diabetic group with the mean of other healthy groups in assessing plasma glucose concentration ($P = 0.000$). But there was no significant difference between the mean of Trained Diabetic and Sedentary Diabetic groups ($P=0.05$) (Chart 1).

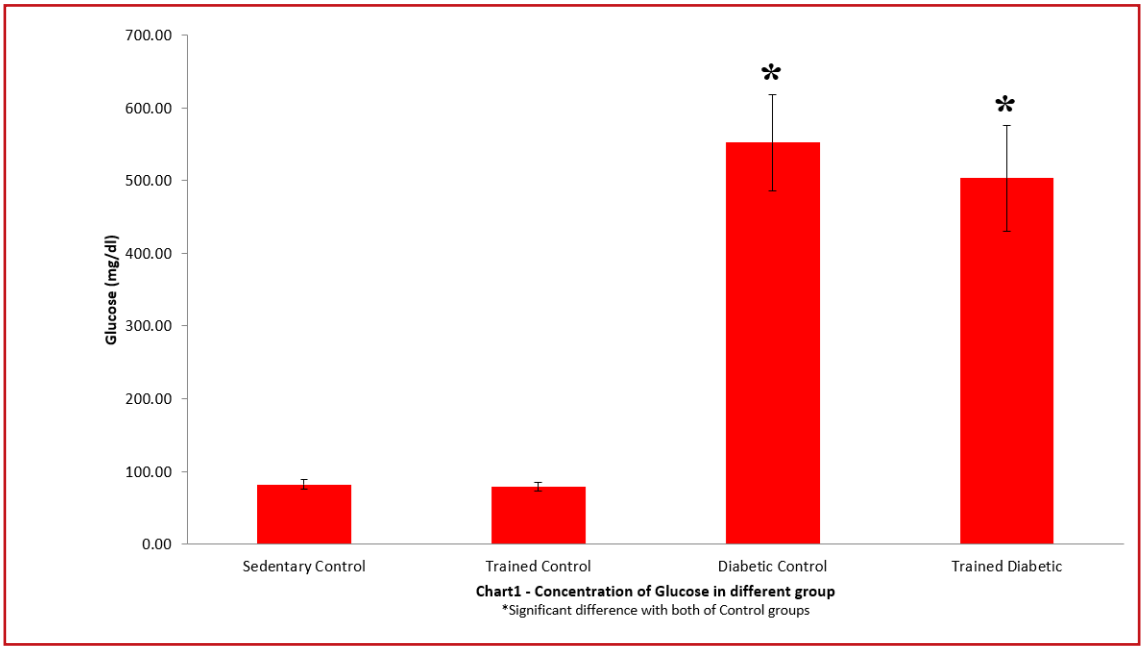

Chart 1. Concentration of Glucose in different groups

*Significant difference with both of Control groups

The effect of progressive resistance exercise on serum levels of IL-18 and TNF-α:

The mean plasma level of IL-18 in Sedentary Control and Sedentary Diabetic groups were 39.68±15.46 respectively and 46.24±5.92 that decreased after exercise to 30.79±8.70 and 30.79±6.60 respectively (as Trained Control and Trained Diabetic groups). There was a significant difference between the mean of Sedentary Diabetic and Trained Diabetic groups ($P=0.001$) (Chart 2).

The mean plasma level of TNF-α in Sedentary Control and Sedentary Diabetic groups were 27.65±6.11 and 46.28±9.64 respectively that increased into 40.38±5.14 in Trained Control group and decreased to 30.38±7.98 in Trained Diabetic group after exercise. There was a significant difference between the mean of Sedentary Diabetic and Trained Diabetic groups ($P=0.002$) and there was a significant difference between the mean of Sedentary Control and Trained Control groups ($P=0.013$) Chart 2).

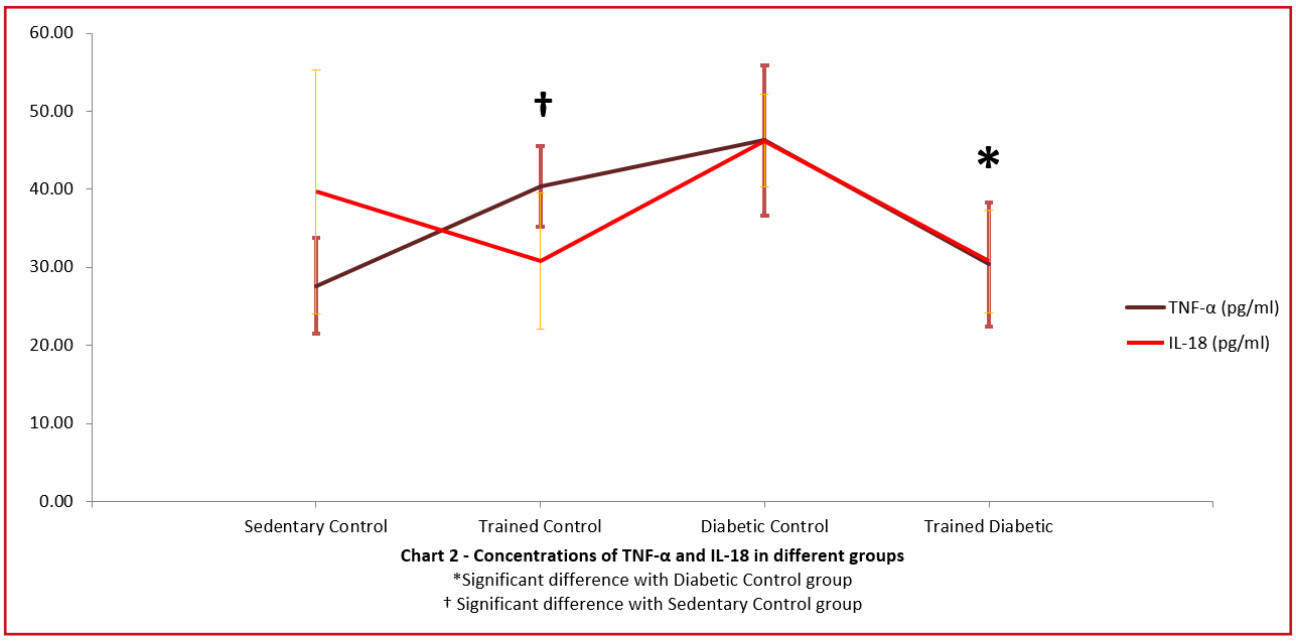

Chart 1. Concentration of Glucose in different groups

*Significant difference with Diabetic Control group
† Significant difference with Sedentary Control group

Relationship of serum concentrations of TNF-α and Glucose in trained and sedentary rats

According to Table 1, it was observed that there was no significant correlation between serum concentrations of TNF-α and glucose in any of the groups (Table 1).

Table 1. Correlation between TNF-α concentration and serum glucose concentration in different groups

Parameter Groups	TNF-α concentration (pg/ml)	Glucose concentration (mg/dl)	Correlation coefficient	P value
Sedentary Control	27.65±6.11	82.22±6.81	0.045	0.933
Trained Control	40.38±5.14	79.00±6.18	0.186	0.659
Sedentary Diabetic	46.28±9.64	552.22±66.14	-0.180	0.733
Trained Diabetic	30.38±7.98	503.12±72.69	0.526	0.181

Relationship of serum concentrations of IL-18 and Glucose in trained and sedentary rats according to Table 2, it was observed that there was a correlation between serum concentrations of IL-18 and glucose only in Sedentary Control group and no significant correlation was found in other groups (Table 2).

Table 2. Correlation between IL-18 concentration and serum glucose concentration in different groups

Parameter Groups	IL-18 concentration (pg/ml)	Glucose concentration (mg/dl)	Correlation coefficient	P value
Sedentary Control	39.68±15.64	82.22±6.81	0.786	0.036*
Trained Control	30.79±8.70	79.00±6.18	-0.568	0.142
Sedentary Diabetic	46.24±5.92	552.22±66.14	-0.439	0.324
Trained Diabetic	30.79±6.60	503.12±72.69	0.072	0.865

*Significant correlation in sedentary control group

Discussion

In the present study, plasma glucose levels in the Trained Diabetic group were slightly lower than in the Sedentary Diabetic group.

The goal of treatment in type 1 diabetes is to achieve and maintain optimal Blood Glucose (BG), lipid, and blood pressure (BP) levels to prevent or delay chronic complications of diabetes (13). Many people with type 1 diabetes can achieve BG control by following a nutritious meal plan and exercise program, losing excess weight, implementing necessary self-care behaviors, and taking oral medications, although others may need supplemental insulin. Diet and physical activity are a central role in the management and prevention of type 1 diabetes because they help treat the associated glucose, lipid, BP control abnormalities, as well as aid in weight loss and maintenance. When medications are used to control type I diabetes, they should augment lifestyle improvements, not replace them (14).

It has been reported that 16 weeks of heavy resistance exercise in diabetic aged people leads to improving the glycemic condition (15). In a study conducted by Dunstan et al. in 1998, it was proved that circular resistance exercises have a role in controlling blood glucose and lipids profile and led to reducing these markers (16). In the present study, the length of the resistance training protocol was low and this can be a reason for the different results in blood glucose assessments.

Changes in serum levels of TNF-α and IL-18 showed significant differences obtained from our resistance exercise program. Serum concentrations of TNF-α decreased significantly in the Trained Diabetic group compared to the Sedentary Diabetic group but increased in the Trained Control group compared to the Sedentary Control group. Also, Serum concentrations of IL-18 decreased significantly in the Trained Diabetic group compared to the Sedentary Diabetic group and slightly decreased in the Trained Control group compared to the Sedentary Control group. Regarding the correlation between serum concentrations of IL-18 with glucose and a correlation between TNF-α with glucose, in trained and sedentary rats, the present study did not find a significant relationship between the groups but there was a correlation between serum concentrations of IL-18 and glucose only in the Sedentary Control group.

Cytokines are produced by a wide variety of cells in the body, playing an important role in many physiological responses that have therapeutic potential (7). The main cytokines involved in the pathogenesis of diabetes are IL-1, TNF-α, and IL-6 (17).

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TNF-α is a pleiotropic inflammatory cytokine that is mainly produced by monocytes, macrophages, and T cells. In addition, and similar to other inflammatory cytokines, the expression and synthesis of TNF-α are not limited to hematopoietic cells. Furthermore, recent studies show that TNF-α can be stored within cells in a proactive form, and the TNF-α converting enzyme can rapidly increase levels of the active cytokine (9).

IL-18 plays a pivotal role in the inflammatory cascade and is also involved in innate immune and adaptive processes due to its ability to stimulate INF-y production in T lymphocytes and natural killer cells. An up-regulated production of IL-18 could therefore be an important pathogenic event in the dysregulated production of IFN-γ and other type 1 cytokines thought to predispose to immunoinflammatory diseases such as type 1diabetes (18).

According to the results of our study, diabetic rats have more resting levels of IL-18 and TNF-α than healthy rats. Researchers have identified inflammation as one of the main causes of IL-18 and TNF-α production (18). Diabetic rats have a higher inflammatory environment and also have higher levels of IL-18 and TNF-α. According to the result of this study, the reason for the decrease in IL-18 and TNF-α can be that following exercise, anti-inflammatory cytokines such as IL-10 and IL-4 are produced. These cytokines inhibit the production of inflammatory cytokines such as IL-18 and TNF-α.

Recently has been found that individuals with type 1 diabetes have increased serum IL-18 in the early stages of the disease (19). Several studies on humans and models showed that deficiency in IL-18 decreases T helper activities and levels of IL-18 in the sub-clinical stages of the disease is associated with an increase in antibody against beta cells and thereby the role of mentioned cytokines is known in the pathogenesis of these patients (20, 21). During acute exercise muscles release IL-6, and its levels can increase significantly. Inflammatory cytokines as well as plasma concentrations TNF-α, IL-1, IL-1ra, IL-10, IL-18 and sTNF-r can increase to various magnitudes during a bout of exercise (22).

Conforming to our findings, in a study, it had been shown that combined endurance/resistance training in patients with chronic heart failure has an anti-inflammatory effect through significant reduction in plasma TNF-α receptors. The patients had a four-month exercise program (three times/week) each session consisted of 30 min resistance and 20 min endurance training (23). Some studies investigated the effect of 6 and 12 weeks of strength training in men and had been found no significant change in the amount of TNF-α in the subjects (24). In conflict with our findings, in a study of the effect of 1 to 3 weeks of running wheel training for 30 minutes a day on mice, had been found that TNF-α expression increased after 2 to 3 weeks of training compared to untrained mice (25) that difference results of this study can be reasoned for the chronic effect of physical activity or high frequency of aerobic exercise in who had not any physical activity before the training protocol.

In an experimental study of 8 weeks of aerobic exercise, 3 times per week, subjects performed 30 minutes of rowing with the intensity of 70% Vo2max. Exercise reduced plasma IL-18 concentration in men by 14% and women by 25%, although these values were not significant (26). Conforming to our results, Yuan Liu et al (2015) in a study with 42 diabetic patients investigated the effects of 12 weeks of combined aerobic and resistance training and showed a significant decrease in serum levels of IL-18 (27).

Some researchers suggested that the type of exercise performed could have some effect on serum inflammatory mediators (22). Aerobic exercise reduces serum levels of IL-6, IL-18 and CRP, while strength training does not have the same positive effect (24, 28, 29).

In general, research shows that physical activity is inversely associated with levels of TNF-α and IL-18 (22). Regular physical activity has beneficial effects on all organs and tissues and effects on reducing inflammation. Inflammatory cytokines that reduce the body adapt to exercise in order to create an inflammatory environment

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(5). So doing at least one hour per week of physical activity has beneficial effects.

Conclusion

In the present study, we found the beneficial effect of resistance training on muscle strength and balance and the improvement of clinical signs in diabetic patients. This change will develop their fitness and quality of life. Besides reduction in the inflammatory cytokines, reduction of clinical disability of Diabetic subjects, demonstrate the performance of Resistance training as an exercise program. The present study suggests that the mentioned factors can be conducted in longer times and different intensities by future studies since an endurance exercise with high intensity maybe have some roles in changes of mentioned factors.

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Conflict of Interests

The authors declare no conflicts of interest.

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