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The effect of endurance training on serum glucose levels, weight changes and IGF-1 protein expression in the hippocampus of diabetic rats.

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Original Research
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Abstract

Purpose: Diabetes mellitus is the most common metabolic problem worldwide, which is associated with hyperglycemia and structural and functional disorders of the nervous system. The aim of the present study was to investigate the effect of endurance training on serum glucose levels, weight changes and Like Growth Factor 1 (IGF-1) protein expression in the hippocampus of diabetic rats. **Method:** For this study, the samples included 48 male Wistar rats (8 weeks old), which were divided into 4 groups: control (C), the diabetes control (DC), diabetes-training (DT) and exercise (T). In order to induce diabetes, streptozotocin injection was used. 5 sessions per week of endurance activity were performed for 6 weeks. 48 hours after the completion of the exercise program, hippocampal tissue was dissected and extracted. ELISA method

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and one-way variance test were used to analyze the data. **Resalts:** Based on the results, serum glucose levels decreased after six weeks of endurance training (p=0.001). The amount of IGF-1 in group DC was significantly lower compared to all groups DT, T, and C (P≤0.05). But the DT group had no significant difference with the C and T groups (P=0.210 and P=0.226, respectively). On the other hand, the amount of IGF-1 in group T was only significantly different from group D (P=0.001). The correlation between blood glucose and IGF-1 was significant (p=0.001, r=0.820). **Conclusion:** Diabetes reduces IGF-1 and hyperglycemia, but exercise moderates the effect of diabetes on IGF-1. Considering the appropriate duration of training and the correlation of this protein with blood glucose, maybe endurance training can reduce the negative effect of diabetes.

Keywords: Diabetes, Endurance Training, Hippocampus, IGF-1.

Introduction

Diabetes Mellitus is a persistent hyperglycemia caused by reduced production or dysfunction of insulin (Mukhtar, Galalain, & Yunusa, 2020). Due to its widespread prevalence, it is considered one of the most important threats to human health globally (Abdul Basith Khan et al., 2020). Therefore, (Awuchi, Echeta, & Igwe, 2020). However, today the third type has also been identified, in which cognitive, memory and learning problems occur due to the accumulation of amyloid beta proteins in the brain. It arises (M Ashraf et al., 2014). Hyperglycemia occurs in all types of this disease and this is considered the main cause of the secondary effects of this disease in the body (Daryabor, Atashzar, Kabelitz, Meri, & Kalantar, 2020). It has also been well shown that long-term hyperglycemia caused by diabetes causes capillary disorders, is the foundation of damages such as retinopathy, nephropathy, and neuropathy, and destroys many important tissues of the body, including nerves (Demir, Nawroth, Herzig, & Ekim Üstünel, 2021). On the other hand, objective observations also indicate the presence of cognitive, memory and learning disorders widely in most diabetic patients. The reason for this is due to damage to areas of the brain, such as the hippocampus, which is responsible for these processes (Ortiz et al., 2022).

Insulin is primarily a metabolic hormone that acts on muscle, fat, and liver through activation of its cognate receptor, although it also acts in tissues not classically considered metabolic, such as the vasculature and brain (Daryabor et al., 2020). It has been shown that there is a close relationship between insulin resistance and neurodegenerative diseases (Barone, Di Domenico, Perluigi, & Butterfield, 2021). Accordingly, diabetes has been mentioned as one of the risk factors and in a way a precursor to the occurrence of other neurodegenerative diseases such as Alzheimer's and Parkinson's (Tomić, 2020). In addition, it has been proven in animal models that disruption of the messenger pathway of insulin-like factor 1 is a characteristic of diabetes (Duran, PANCUR, & Bahadori, 2022). And the dysfunction of insulin-like growth factors has been identified as one of the mechanisms involved in nerve damage. Insulin-like growth factor is a protein encoded by the IGF-1 gene in humans. IGFs have a more mitogenic role both during fetal development and after birth. As a nutritional factor, IGF-1 is important for growth and metabolic

reactions (Al-Samerria & Radovick, 2021). The main sources of IGF-1 production are the growth hormone activity dependent on the liver and local production in muscle, fat tissue, intestine, cartilage, bone and including the brain. IGF-1 is primarily produced by the liver (Rosen & Yakar, 2020). But its production is stimulated by growth hormone (GH). Most IGF-1 binds to one of six binding proteins that are regulated by insulin. Factors that change the level of IGF-1 in the blood circulation include: the amount of insulin, growth hormone, binding proteins, genetic make-up, time of day, age, gender, exercise status, stress level, nutrition level and body mass index (BMI), race and disease (Moham, 2010). In addition, this factor has the role of neuronal protection and has many effects on the functioning of the nervous system. Also, as a neuroprotective hormone, IGF-1 has autocrine and paracrine functions in the nervous system and enters the brain through the bloodstream (Frier, 2009). As explained before, this messenger pathway is involved in the control of nerve stimulation, metabolism, and the life of neurons (Barcelos, Lima, Carvalho, Bresciani, & Royes, 2020). In the past, it has been shown that its level decreases in a disease of nerve destruction. It is reported that physical activity increases the expression of this factor in the body (Pedersen, 2019). But the mechanisms involved are still not well understood. On the other hand, considering that chronic hyperglycemia is the main cause of the harmful consequences of diabetes and this disorder has also been observed in other neurodegeneration diseases, perhaps the increase in blood sugar caused by diabetes is the cause of the increase in IGF-1 (Borges et al., 2017). Therefore, it seems necessary to investigate the relationship between blood glucose level and this factor (Alizadeh, Rahmani-Nia, Mohebbi, & Zakerkish, 2016). Today, many drugs are discovered and used to prevent and deal with diabetes, which, despite their high efficiency, have many side effects and impose a lot of costs on the patient (Wu, Ding, Tanaka, & Zhang, 2014). Therefore, non-pharmacological solutions have been the focus of researchers. One of these methods, whose efficiency has been well demonstrated, is physical activity (Gillett et al., 2012). The result of the previous research also shows the positive effect of exercise on preventing and reducing the complications of diabetes, and carrying out appropriate exercise programs helps to regulate blood sugar (Colberg et al., 2010). Therefore, in order to use this method more effectively, researchers have investigated the mechanisms involved in

the effect of exercise on diabetes (Zanuso et al., 2017). In this regard, past results have clarified that endurance exercise moderates inflammatory and oxidative reactions (Slattery, Bentley, & Coutts, 2015). It also plays a role in improving nerve plasticity, learning, memory, learning and cognitive activities in improving the performance of the central nervous system (Zalouli et al., 2023). Such mechanisms are useful in the prevention and treatment of most neurodegenerative diseases such as Alzheimer's, Parkinson's and stroke (Liu et al., 2019). However, the mechanisms of the beneficial effects of exercise on the nervous system of diabetic patients are still not clear. Therefore, the aim of this study was the effect of six weeks endurance training on serum glucose levels, weight changes and IGF-1 protein expression in the hippocampus of diabetic rats.

Method:

The current research was conducted experimentally with a pre-test, post-test and control group design. The samples used in this experimental study were Wistar rats. For this purpose, 32 male rats (weight 165 ± 5 grams) were selected from the Pasteur Institute of Iran. After two weeks of familiarization with the laboratory environment, all samples were randomly divided into four groups: Diabetes-control group (DC): This group included 8 male rats that were made diabetic by intraperitoneal STZ and did not participate in any exercise program. Exercise Diabetes Group (DT): This group included 8 male rats that were given intraperitoneal injection of streptozotocin (STZ). became diabetic and from the twelfth week of life, for 8 weeks and 5 sessions of endurance training every week, training group (T): this group included 8 male rats that participated in the training program like the DT group. This group was dissected at the same time as the rest of the groups and all procedures and tests were performed on them, and the control group (C): this group included 8 male rats that did not perform any sports activities. All the samples were kept in a room in the animal shelter of the research center. Mice were kept in special cages in groups of three and in an environment with an average temperature of 22±2°C and a light-dark cycle of 12:12 hours. All mice had free access to water and special mouse food. Since the transfer of animals causes stress and as a result leads to physiological changes in them, after transferring them to the research environment, first, to acquaint the rats with running on a

treadmill, for one week at a speed equal to -3 5 meters per minute for fifteen to twenty minutes of training was considered.

Induction of diabetes

After completing the familiarization protocol, after 12 hours of food deprivation, by intraperitoneal injection of STZ solution (Sigma, St. Louis, MO; 50 mg/Kg dissolved in fresh citrate buffer 0.5 mol/L, pH 4.5:) diabetes was induced. Non-diabetic mice were also injected with a volume equivalent of citrate buffer. 48 hours after the injection, by making a small wound on the tail vein with a lancet, a drop of blood was placed on a glucometer strip and the strip was measured by a glucometer device (Glucotrend 2, Roche, Germany). Then, the mice whose blood sugar was higher than 300 mg/dL were considered as diabetic. To ensure that the blood sugar does not return at the end of the training program, the blood sugar of the mice was also measured.

Exercise protocol

The endurance training used in this research consisted of 6 weeks, 5 sessions per week of running with an intensity equivalent to the speed of 22-25 m/min (equivalent to 80% of vo2 max) on a treadmill for rodents. The time and intensity of each training session is shown in the table below

Table 1: Training protocol in different weeks

Exercise variations	First week	Second week	third week	Fourth week	Fifth week	Sixth week
Exercise duration (minutes)	10	20	20	30	30	30
treadmill speed (m/min)	10	10	15	15	17-18	17-18
slope (degrees)	0	0	0	0	0	0
Repetition (day of the week)	5	5	5	5	5	5

Sample extraction

48 hours after the end of the last training session and after 12 hours of fasting, the subjects were anesthetized by intraperitoneal injection of a

combination of ketamine (75 mg/kg-1) and xylazine (5 mg/kg-1) and blood was taken and sampled. The texture was done as follows.
Sample collection from the hippocampus: after cutting the head of the mouse with a guillotine and under sterile conditions to measure IGF-1 protein expression, the hippocampus tissue was separated and kept in a freezer at minus 70 degrees Celsius for further analysis. To homogenize, 100 mg of the tissue was washed with saline buffer in a sterile beaker. The tissue was homogenized in one milliliter of saline buffer and kept at -20°C for 16 hours. Then the tissue was taken out of the frozen state and frozen again. In order to destroy the plasma membrane, this operation was repeated three times. The resulting mixture was centrifuged for 5 minutes at 5000 rpm at a temperature of 2 to 8 degrees Celsius. Then the supernatant was separated and stored at -80°C for further analysis. The amount of IGF-1 protein was measured by IGF-1 ELISA kit, sensitivity: 1.6 pg/ml, detection range: 15.62-1000 pg/ml, Antibodies) according to the instructions of the relevant company. .
Blood sampling: To measure the amount of serum glucose and insulin levels, blood sampling was done directly from the heart of the mouse and the blood was immediately poured into a tube containing ethylenediaminetetraacetic acid and to separate the blood serum of the samples for 15 minutes at 4 degrees Celsius. It was centrifuged at 3000 rpm and kept at minus 20 degrees Celsius. Glucose serum levels were measured using a glucometer made in Germany and insulin serum levels were measured with a rat special ELISA kit made in Germany with a sensitivity of 0.1.

Statistical analysis

The normality of the natural distribution of the data was evaluated using the results of the Shapiro-Wilk test. To investigate the possible difference in both variables between groups, one-way analysis of variance and then Tukey's post hoc test were used. All statistical analyzes were performed using SPSS version 24 statistical software. The significance level was considered $P<0.05$.

Results

The results of the present study indicate that at the end of the 6-week exercise program, the average weight of the diabetic groups compared to the non-diabetic groups showed a significant decrease ($P<0.05$), as

compared to the D group. C group (p=0.025) and DT group's weight was significantly lower than T group (p=0.014). While there was no significant difference between T and C groups (P=0.088). Also, DT and D groups had no significant difference (P=0.076) (Table No. 1). Also, the data of the present study stated that blood glucose levels were significantly lower in the DT group than in the D group (P=0.001). The blood glucose level of group D was significantly higher than groups C and T (p=0.001). Also, the difference between DT and C and T groups was also significant (P=0.001). Therefore, it can be said that STZ injection significantly increased blood glucose levels in diabetic groups compared to non-diabetic groups. In contrast, endurance activity with hyperglycemia modulation has reduced glucose levels in the DT group (Table 2).

Table 2: Fasting serum glucose levels and changes in body weight (Mean±SEM) in groups

variables	Control	Diabetes Control	Diabetes exercise	Exercise	P-Value
glucose (mg/dl)	75.23±15.45	517.7±125.4	320.7±109.87	74.14±16.46	0.001
Weight (g)	230.63±22.05	210.7±14.32	207.7±16.21	199.14±15.76	0.001

* indicates the presence of statistically significant differences between groups. (P<0.05)

The results showed that after 6 weeks of training, the amount of IGF-1 in group D was significantly reduced compared to all groups DT, T, and C (P=0.001, P=0.001, and P=0.001, respectively). Also, the levels of IGF-1 protein in DT group were significantly increased compared to group D (P=0.001), while this group did not show a significant difference with groups C and T (see The order of P=0.210 and P=0.226). On the other hand, the amount of IGF-1 in T group was significant only with D group (P=0.001) and the difference of this factor in T group with DT and C groups was not significant (P=0.226 and P=1.001 respectively). In fact, it caused a significant decrease in the amount of IGF-1 protein, while endurance training prevents the decrease of this factor (Figure 1).

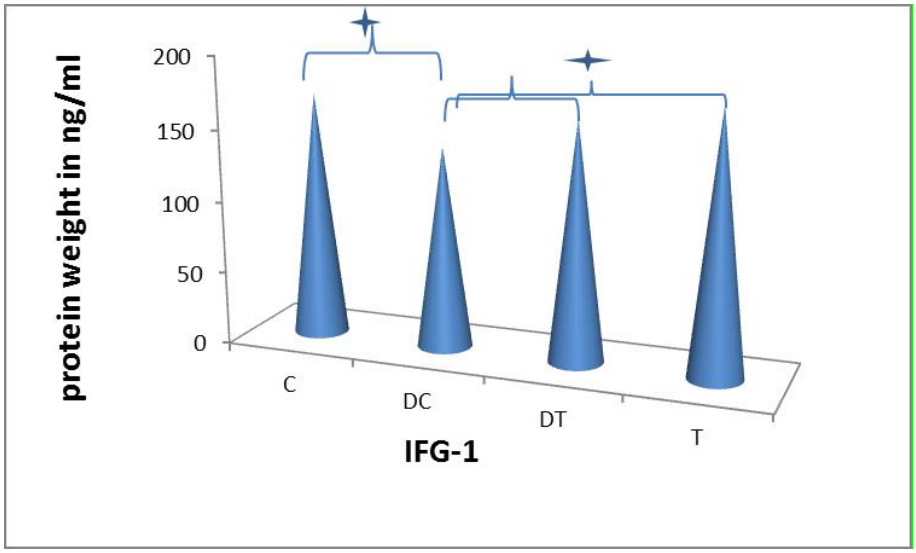

Figure 1: IGF-1 protein levels in the hippocampus

Discussion

The present study was conducted with the aim of investigating the effect of a period of endurance training on serum glucose levels, weight changes and IGF-1 protein expression in the hippocampus of diabetic rats. The results of measuring blood glucose levels showed that a period of endurance training caused a steady decrease in blood glucose levels in diabetic rats. In 2006, the American Diabetes Association investigated the effect of physical activity on plasma glucose levels in diabetic subjects, and they reported that long-term endurance exercise significantly reduced plasma glucose levels in diabetic subjects (Sigal, Kenny, Wasserman, Castaneda-Sceppa, & White, 2006). In the same way, Mohammadi et al. studied the effect of 12 weeks of endurance training on blood glucose levels, insulin and heart structure of type 2 diabetic rats (Mohammadi, Fathi, Chehel Cheraghi, & Nazari, 2023). They observed that mean blood glucose levels were higher in the diabetic control group compared to the endurance training group after 12 sessions of endurance training. Daneshyar et al investigated the effect of endurance training on blood lactate changes and plasma levels of calcitonin gene-related peptide in

type 2 diabetic rats (Daneshyar, Gharakhanlou, Nikooie, & Forutan, 2014). In their study, 50 rats were divided into four groups: healthy control, healthy exercise, non-exercise diabetic and exercise diabetic. Then the training groups performed the endurance training program on the treadmill. The research findings showed that resting blood glucose and lactate levels were higher in diabetic subjects compared to the healthy non-diabetic control group, while blood glucose and lactate levels were lower in exercising diabetic subjects than the non-exercising diabetic control group.

The results of our study have shown that diabetes causes a significant decrease in IGF-1 protein levels. Also, physical activity caused a significant increase in the amount of IGF-1 in DT and T groups. The results of most of the previous studies on nerve damage patients also show a decrease in IGF-1. Although several studies have investigated the role of exercise on this factor, the mechanisms involved in it are still unclear.

In addition, one of the mechanisms of researchers' interest in causing and aggravating the consequences of neurodegenerative diseases is the disturbance in the messenger pathway of insulin-like factors, in this context, IGF-1 is one of the most important factors of this family (Zemva & Schubert, 2014). In confirmation of these data, past studies have well shown the positive role of IGF-1 in the processes of neuronal protection and dealing with photo-damage in the central nervous system. Therefore, the overexpression of this factor can be a beneficial factor in modulating photo-damage caused by such diseases (Vardatsikos, Sahu, & Srivastava, 2009).

The results of this study show a significant decrease in the amount of IGF-1 in group D compared to other groups, therefore it is suggested that diabetes is the cause of the decrease in the amount of IGF-1 in the hippocampal tissue of diabetic samples. Of course, the processes related to this matter are still not completely clear. However, according to the results of previous studies, hyperglycemia, reduction in capillary blood flow, insulin resistance, oxidative and inflammatory pressures can be mentioned as the mechanisms involved. In

confirmation of these results, Min et al. in their research on diabetic patients concluded that there is a high correlation between the amount of IGF-1 and insulin resistance, and that diabetes causes a decrease in IGF-1 levels through the increase of the IGFBP-3 factor (Min et al., 2023). Also, Zhou et al consider one of the important mechanisms of IGF-1 reduction in diabetic patients to be the increase of inflammatory factors such as IL-6, IL-1β and TNF-α (Zhou, Yan, Guo, & Tong, 2019). In addition, the results showed that the amount of IGF-1 in the diabetes exercise group is significantly higher compared to the diabetes group. Therefore, it has been suggested that aerobic training has probably compensated for the reduction of this factor due to diabetes in the hippocampal tissue. Although it has been well shown that exercise has a beneficial role in modulating nerve damage, the mechanisms involved are still not clear. However, it has been shown in the past that physical activity contributes to this process by reducing oxidative stress and inflammation, as well as improving cerebral blood flow and neuron protection processes (El Assar, Álvarez-Bustos, Sosa, Angulo, & Rodríguez-Mañas, 2022). In addition, the results show no significant difference in IGF-1 values in C and T groups. Therefore, it is suggested that endurance training could not increase this factor in the hypocampus of healthy samples. Now, considering the significant effect of this exercise in diabetic groups, maybe the reason is the low intensity of this exercise protocol (Colberg et al., 2016). Because the effect of exercise on this factor was significant in the diabetic groups, therefore, probably due to the pathological conditions of the disease, physical activity with a lower intensity was able to exert the necessary pressure to affect the mechanisms of reduction in IGF-1 values, while In order to create these effects in healthy samples, it is necessary to perform the exercise protocol with more intensity and duration (Colberg et al., 2016). In addition, perhaps exercise has moderated this factor in patient samples by modulating the mechanisms of oxidative, inflammatory and hyperglycemic pressures that are exacerbated by diabetes (Colberg et al., 2010).

On the other hand, the results show that blood glucose levels have a significant negative correlation with IGF-1 levels. So that the blood glucose level of DT group was lower than D group. Therefore, considering that it has been well shown in the past that the adjustment of blood glucose is beneficial in neuroprotective processes, and in this study, a strong correlation between blood glucose and IGF-1 is observed (Candeias et al., 2018). It can be said that this factor probably plays an important role in the neuronal protection of diabetic patients, besides, it has been clarified in the past that exercise also improves insulin sensitivity (Bertram, Brixius, & Brinkmann, 2016). Therefore, maybe the training protocol of the current research has caused an increase in IGF-1 due to the adjustment of blood glucose and in this way it has caused the adjustment of light destruction in the hippocampal tissue (Sonntag, Ramsey, & Carter, 2005). It should be noted that this opinion is in line with the findings of some previous researches, which showed that hyperglycemia is one of the main mechanisms of neuronal damage in STZ-treated diabetic animals, and insulin treatment is associated with the improvement of sensory nerve function. be The results of past researches have proven the effect of IGF-1 in mechanisms related to neuronal protection such as inflammation, amyloid plaque formation, synaptic plasticity, insulin resistance, oxidative stress on neurological disorders. In addition, the negative effects of diabetes on neuroprotective mechanisms are also well understood. Now, according to the previous findings that show the beneficial role of exercise in neuron protection mechanisms, such as modulating oxidative stress, inflammation, amyloid plaques and hyperglycemia, etc. It is possible that the increase in IGF-1 after completing the aerobic exercise protocol in this study is due to the modulation of oxidant pressure, hyperglycemia, inflammation, accumulation of amyloid proteins, IGFBP-3, and growth hormone increase. In addition, due to the existence of a significant correlation between this factor involved in neuroprotection in the hippocampus of healthy and diabetic samples, it can be concluded that exercise and diabetes have a significant effect on the level of IGF-1. So that

diabetes by reducing IGF-1 aggravates the mechanisms of nerve damage, while endurance physical activity moderates these processes.

Conclusions

The results of this study showed that endurance training reduces glucose levels and reduces IGF-1. On the other hand, exercise moderates the effect of diabetes on this factor. Also, due to the significant effect of the endurance training protocol on the desired factor and blood glucose in diabetic conditions, and at the same time, it has no effect on the samples of healthy groups. It can be concluded that the training intensity was not suitable for making the desired changes in non-disease conditions; Therefore, it is suggested to use protocols with more intensity as well as various sports disciplines in the next research.

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Conflict of Interests

The authors declare that they have no conflict of interests to disclose.

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