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The effect of an interval training course on nitric oxide levels, insulin resistance, and some blood lipid factors in type 2 diabetic male rats

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Abstract

Background: Diabetes is a metabolic and vascular disorder characterized by endothelial dysfunction. Physical activity, particularly intermittent exercise, may offer therapeutic benefits. This study examined the effects of six weeks of intermittent exercise on serum nitric oxide (NO), insulin resistance, and lipid profiles in male diabetic rats.

Methods: Sixty Wistar rats (8 weeks old, 200 ± 20 g) were divided into six groups (n=10): healthy control, sham, interval training, interval training + saline, diabetic control, and diabetic + interval training. Diabetes was induced via nicotinamide-streptozotocin injection. The exercise groups underwent treadmill training (5 sessions/week for 6 weeks). Post-intervention, glucose, insulin, NO, LDL, HDL, triglycerides, and cholesterol were measured.

Results: Diabetes induction significantly increased glucose and insulin resistance while reducing insulin and NO levels compared to controls ($P < 0.001$). After six weeks, the diabetic + exercise group showed significant reductions in glucose and insulin resistance ($P < 0.001$) and increased NO levels ($P < 0.001$) versus the diabetic group. Insulin levels did not differ significantly among the groups ($P = 0.11$). Lipid profiles (LDL, HDL, triglycerides, cholesterol) remained unchanged ($P > 0.05$).

Conclusion: Six weeks of intermittent exercise improved glucose metabolism and vascular function in the diabetic rats by reducing insulin resistance and increasing NO levels, suggesting its potential as a non-pharmacological therapy for diabetes-related endothelial dysfunction.

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Diabetes

Introduction

As one of the major health problems, diabetes, mostly type 2 diabetes, has affected more than 400 million people worldwide (1). Various studies have shown that diabetes is not only a metabolic disease but also a vascular disease due to its effects on small and large vascular beds, and the relationship between diabetes and increased prevalence of cardiovascular disease has been well proven (2). High blood pressure and type 2 diabetes seem to be the main factors that increase the risk of death from cardiovascular diseases (3). Diabetic patients face endothelial functional disorders and damage. These disorders include functional changes in the endothelium (Impaired vasoconstriction) and increased inflammatory activity that is related to cardiovascular diseases (4). The most active vasodilator produced by endothelial cells is nitric oxide (NO) (5). NO is the cause of vascular dilation; it is a regulatory molecule with extensive metabolic, vascular, and cellular effects, which originates from the oxidation of the guanidine group of L-arginine. It is found in almost all tissues. It is also secreted in response to stimuli such as lack of oxygen in the tissue and shear stress of endothelial cells (6). Reducing the amount of NO inhibits vascular dilation, and its amount in the blood of diabetic patients is lower than in healthy people (7). Another characteristic of type 2 diabetes is insulin resistance, which seems to cause vascular endothelial dysfunction through increased fat, insulin, and oxidative stress. In addition, increased fatty acids stimulate endothelial apoptosis. As a result, it increases vascular oxidative stress and reduces the amount of NO (8). Therefore, increasing NO by reducing vascular tone, reducing blood pressure, and improving insulin sensitivity has been recognized as a suitable treatment for patients with type 2 diabetes (9). Sports activity through successive changes in shear stress and its increase leads to an increase in the biological activity of NO and improvement of vascular endothelial function (10). In a study, Farzanegi showed that 30 minutes of swimming training had significantly reduced blood glucose, insulin, and NO in diabetic rats (11).

Many other risk factors increase cardiovascular complications in these patients. The most common of these factors are increased levels of TG, decreased levels of HDL, increased levels of LDL, obesity, weight gain, and high blood pressure, which lead to atherosclerosis (12).

High-intensity interval training (HIIT) is an effective training method in cardiovascular rehabilitation, which has been confirmed to have positive effects on health and disease. HIIT (13), compared to continuous training, has a greater effect on improving parameters related to cardiovascular health (14). Despite the cardiovascular protective effects of HIIT and its role in the management of diabetes, information about its cellular mechanisms is incomplete and sometimes contradictory, and more studies are needed on how HIIT affects. In this regard, this study investigated the effect of six weeks of HIIT on some factors related to cardiovascular diseases including hyperglycemia, insulin resistance, NO and some lipid factors in diabetic rats.

Methods

Analysis method

The present experimental study used 60 male Wistar rats (8 weeks old, 200 ± 20 g), obtained from the Ahvaz Physiology Research Center. The tested animals were kept in groups of five in polycarbonate racks and had free access to standard food and water. The ambient temperature was 22±3°C, the light-dark cycle was 12:12 hours, and the humidity was 55.6±4%. After one week of familiarization with the environment, all animals were introduced to running on the treadmill for one week (10 minutes at a speed of 10 meters per minute, five days a week). Then, the rats were randomly divided into six healthy and diabetic groups: 1) Healthy groups: These groups included 40 rats, which were randomly divided into four groups - control, intermittent exercise, sham, and intermittent exercise + saline. 2) Diabetic groups: This group included 20 rats, randomly divided into two groups - diabetes and diabetes + interval training.

To induce type 2 diabetes, first nicotinamide (120 mg/kg) was injected intraperitoneally into the rats, and 15 minutes later, a single dose of streptozotocin (STZ) (60 mg/kg) dissolved in 0.1 M normal citrate buffer was injected intraperitoneally into the animal. Then, to ensure that the animal became diabetic, the level of blood sugar increase was evaluated 72 hours after STZ injection using a glucometer. Rats whose fasting glucose was more than 250 mg/dl were considered diabetic. Due to the risk of hypoglycemia caused by STZ, the rats received a 10% glucose solution after 6 hours of STZ administration until 24 hours later.

Exercise protocol

One week after the induction of diabetes, rats in the exercise intervention group performed intermittent exercise on the treadmill for six weeks, five days a week. Before starting the main exercises and for familiarization, the rats started running on the treadmill for 10-15 minutes at a speed of 5-7 meters per minute with a zero-degree slope for two consecutive days. Two days after the familiarization exercises, the main intermittent exercises began and the rats performed activities on a special treadmill for six weeks. The interval training program was such that the speed of the training program in the first week started from 10 meters per minute. From the second to the sixth week, the weekly training speed increased by 2 meters per minute, reaching 20 meters per minute in the last week. The duration of training in the periodic group increased daily from the first to the sixth week, from 15 minutes on the first day to 40 minutes in the sixth week. The interval training group performed the training for the specified duration in two sessions in the first week, four sessions in the second to fourth weeks, and six sessions in the fifth to sixth weeks. Four minutes of exercise and 1 minute of active rest (Running at a speed of 3 meters per minute) was considered active rest (Table 1). At the beginning of each training session, each training group ran for 3 minutes at a speed of 1 m/min to warm up, and then to reach the desired speed, 2 m/min was added to the speed of the treadmill. At the end of the training, they ran for 3 minutes at a speed of 1 meter per minute to cool down. Rats in the intermittent training group were encouraged to continue running in all training sessions using a weak electric shock (Intensity 0.5 mA) that did not cause much stress in the animal (15).

Table 1. Intermittent exercise implementation protocol

Week	Exercise duration (Minutes)	Training speed (Meters per minute)	Type of rest
First	10	2×7.7	Active
Second	12	4×5	Active
Third	14	4×6.25	Active
Fourth	16	4×7.5	Active
Fifth	18	6×5.83	Active
Sixth	20	6×6.66	Active

Blood sampling and laboratory analysis

Twenty-four hours after the final training session, rats from both the healthy and diabetic groups were anesthetized via intraperitoneal injection of ketamine-xylazine. Blood samples were then collected via cardiac puncture and transferred into Falcon tubes. After coagulation, the blood samples were centrifuged at 4000 rpm for 15 minutes to separate the serum. The serum was then aliquoted and stored at -70°C until further analysis for the target variables.

To check the NO index, the Promega (Promega Corp., USA) kit was used. To measure the amount of insulin, the ELISA kit (Diacolon, France) was used. The amount of glucose was calculated using the photometric method (Pars Azmoun, Iran), and insulin resistance was calculated using the homeostasis model evaluation method according to the following formula (11):

HOMA-IR = [Glucose] × [Insulin] / 22.5 × 18

The measurement of lipid profile (High-density lipoprotein, triglyceride (TG), and total cholesterol) was done by the enzymatic method using commercial biochemistry kits prepared by Pars Azmoun - Iran, and low-density lipoprotein was calculated using the equation of Friedwald et al.

Statistical method

In the descriptive statistics section, the dispersion indices of mean and standard deviation were used. In the inferential statistics section, the Shapiro-Wilk test was used to determine the normality of the data distribution, and the homogeneity of the variances was measured with the Levene test. To determine the significance of the difference between the variables and their interaction, one-way analysis of variance and Tukey's post hoc test were used. The findings were analyzed at the 95% confidence interval, and statistical analysis of the data was done using SPSS software.

Results

The average serum levels of glucose, insulin, LDL, HDL, TG, and cholesterol of the subjects are presented in Table 2. ANOVA test results showed that after six weeks, a significant difference was observed in the blood glucose level of the rats. The follow-up test showed that the blood glucose of the diabetes + interval training group had decreased significantly compared to the diabetes group after six weeks ($P = 0.001$). In addition, the amount of blood glucose in the interval training group was significantly reduced compared to the control group ($P = 0.001$). However, no significant difference was observed between the two intermittent training groups and the intermittent training + saline group ($P > 0.55$). Regarding lipid profile indicators, ANOVA test results showed that after six weeks, there was no significant difference in the LDL, HDL, TG and cholesterol levels between the groups (Respectively: $P > 0.12$, $P > 0.059$, $P > 0.059$, $P > 0.84$) (Table 2). The results of the ANOVA test regarding the insulin index also showed that after six weeks, no significant difference was observed between the groups ($P = 0.11$). A significant difference was observed only between the insulin resistance of the two diabetes groups with diabetes + interval training ($P = 0.001$) (Table 2).

The ANOVA test results showed that after six weeks, there was a significant difference between the groups regarding the insulin resistance index ($P = 0.001$). According to the follow-up test, the insulin resistance of the diabetes + exercise group was significantly reduced compared to the diabetes group ($P = 0.001$). A significant difference was also observed in insulin resistance between the diabetes group and the control, sham, intermittent exercise + saline, and intermittent exercise groups ($P = 0.001$). However, there was no significant difference between the insulin resistance of other groups ($P > 0.05$) (Figure 1).

Table 2. Mean and standard deviation results of glucose, insulin, LDL, HDL, TG and cholesterol groups

Variable (Unit)	Control	Sham	Interval training	Intermittent training + saline	Diabetes	Diabetes + interval training	P-value
Glucose (mg/dL)	110.11±4.64	105.74±4.58	91.41±4.08	94.4±6.35	271.81±23.52	182.57±12.82	0.001
Insulin (m/ml)	11.54±2.02	11.54±1.97	10.58±1.81	10.77±2.06	9/13±1/30	8.21±1.06	0.11
LDL (mg/dl)	37.13±3.32	36.89±5.14	34.50±4.36	34.76±4.55	39.11±2.68	36.67±3.27	0.126
HDL (mg/dl)	32.82±4.60	33.73±4.60	35.92±2.41	35.36±2.29	31.24±5.19	36.05±4.13	0.059
TG (mg/dl)	83.01±7.82	83.63±7.70	76.26±8.17	76.93±7.69	86.44±11.27	81.13±8.80	0.059
Cholesterol (mg/dl)	86.59±7.30	87.34±8.74	84.09±6.08	85.48±6.44	87.37±4.24	86.42±6.73	0.845

Repeating the letter symbol indicates a lack of significance between the two groups. Using the letter alone indicates a significance between the two groups.

In addition, the results of the ANOVA test regarding the NO index showed that after six weeks, there was a significant difference between the groups (P = 0.001). According to the follow-up test, the NO index significantly increased in the diabetes + exercise group compared to the diabetes group (P = 0.003). A significant difference was also observed in the NO level between the diabetes group and the interval training + saline and interval training groups (P = 0.001). The amount of NO was also significantly different between the control group and the diabetes, intermittent exercise, and diabetes + intermittent exercise groups (P = 0.001). However, there was no significant difference in the NO level between the other groups (P > 0.05) (Figure 2).

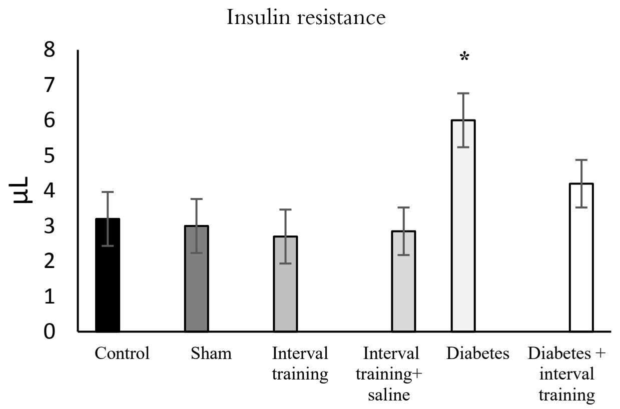

Figure 1. Comparison of the average levels of insulin resistance in different groups
*: There is a significant difference compared to the control group.

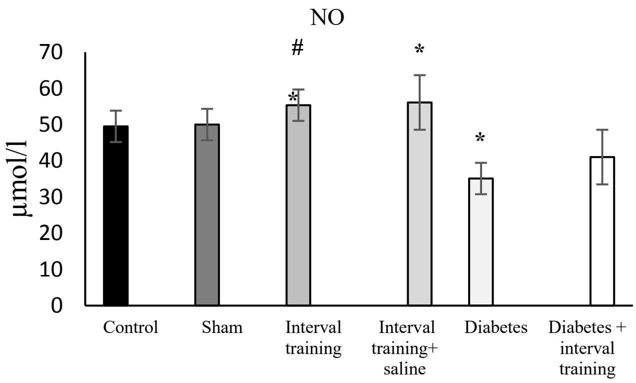

Figure 2. Comparison of mean NO serum levels in different groups
*: There is a significant difference compared to the control group.
#: There is a significant difference compared to the diabetes group.

Discussion

The present study was conducted to investigate the effect of six weeks of intermittent training on NO levels, insulin resistance, and some lipid factors in type 2 diabetic male rats. The results of this study showed that the induction of diabetes caused a significant decrease in the serum levels of NO and a significant increase in the blood glucose level and insulin resistance in the diabetic group. Thus, six weeks of intermittent training in the diabetes group + intermittent training caused a significant increase in the serum NO level compared to the diabetes group. Also, in the present study, the blood glucose level and insulin resistance after six weeks of intermittent exercise in the diabetes group + intermittent exercise decreased significantly (P < 0.008), which is similar to the studies of Farzanegi (11), Asarzadeh et al. (16) and Mohebi et al. (17), and it is consistent with the studies of Wang et al. (18) and Shad et al. (19). Probably, these different results are due to differences in the type, duration, intensity of training and different samples. Various studies have shown that exercise through 1) insulin receptors, 2) protein and mRNA of glucose transporter (GLUT4), 3) increasing glycogen synthetase and protein kinase-B, hexokinase, and 4) improving internal messengers. Insulin cells and their effect on intermediate molecules in the insulin signal, such as increasing the expression of ERK2, increasing the activity of PI3K or AKt/PKB and improving the AMPK signal (20), changes in muscle composition (Increasing capillary density in muscle fibers and converting muscle fibers into fast-twitch oxidative fibers), 6) increasing the delivery of glucose to the muscle, 7) reducing the accumulation of TGs in the muscle cell and 8) reducing the release of fatty acids and increasing their oxidation and clearing (21), modulating insulin resistance. In the present study, the NO level decreased significantly after induction of diabetes, but increased significantly after six weeks of intermittent exercise (P < 0.05), which is consistent with the studies of Mitranen et al. (22), Ghardashi Afousi et al. (23), Grijalva et al. (24), and Zhang et al. (25). In another study, Zhang et al. reported an increase in serum NO levels following 10 weeks of exercise (25). Research has shown that exercise increases myocardial NOx production and eNOS protein levels, as well as sensitivity to eNOS phosphorylation caused by insulin stimulation (26). As shown in this study, the induction of diabetes causes hyperglycemia, increase of LDL levels (In a non-significant way), and insulin resistance. Each of these factors in a way causes disruption in the endothelial function of the vessels of diabetic people (27).

Several other studies have also shown that shear stress leads to the stimulation of increased expression of eNOS (28). In support of this hypothesis, it has been stated that HIIT is more effective in improving vascular function compared to moderate intensity continuous exercise training. This is probably due to the ability of HIIT to stimulate more blood flow through the vessels supplying oxygen to the working muscles, which increases the bioavailability of NO caused by shear stress (29). Thijssen et al. (30) confirmed this hypothesis and stated that with an increase in the intensity of sports activity, blood flow and shear stress also increase. Although the full effects of HIIT on endothelial function and NO release are not fully understood, it has been shown that HIIT can reduce the levels of catecholamines and the density of alpha-adrenergic receptors (31). Reducing the activity of sympathetic tone and increasing the activity of parasympathetic tone has a great effect on blood pressure regulation. As previously mentioned, an increase in TG, a decrease in HDL, and an increase in LDL and cholesterol can lead to atherosclerosis (12). Diabetes, especially type 2 diabetes, is often associated with lipid metabolism disorders, and increased serum levels of fatty acids play a major role in insulin resistance (32). This study showed that after the induction of diabetes, the levels of LDL, TG and cholesterol increased insignificantly while the HDL level decreased insignificantly. However, after six weeks of intermittent exercise in the diabetes group, the HDL level increased insignificantly, but the LDL, TG, and cholesterol levels decreased insignificantly (P > 0.05). This finding is inconsistent with the study of Niyazi et al. (33) and Ghasem Nia et al. (34), but consistent with the research of Gordon et al. (35). It can be stated that the difference between our findings and some studies' results can be attributed to the difference between the intensity, duration, training environment, type of samples, age and gender of the research samples. In general, the accumulation of excess fat from two separate main pathways causes insulin resistance, which includes the transformation of insulin signaling with cytokines secreted from adipose tissue and the damage or death of pancreatic beta cells due to the accumulation of free fatty acids. However, long-term exercise training, by reducing fat accumulation, probably improves insulin sensitivity and prevents insulin resistance (36,37).

Conclusion

According to the results of the present study, the time and intensity of sports activity according to the type of disease and the age of subjects can reduce blood glucose levels and factors related to cardiovascular disease (Lipid profile), increase NO, improve endothelial function, and consequently, decrease the occurrence of cardiovascular diseases in diabetes conditions. As a result, sports activity with appropriate intensity can be recommended as a non-pharmacological method for diabetic patients.

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Ethical statement

Ethical approval code: (IR.HSU.REC.1400.008).

Conflicts of interest

The authors declare no conflicts of interest regarding publication of this article.

Author contributions

Roohollah Mohammadi Mirzaei: Original draft, Methodology. Hamid Malekshahi: Writing, Review and Editing, Project Management. Halimeh Vahdatpoor: Methodology, Analysis.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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