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The Effects of Regular Treadmill Exercise on Some Blood Parameters in Diabetes Mellitus

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Abstract: This study aims to determine the effects of regular treadmill exercise on some blood parameters in rats with an experimental diabetes model. In the study, 36 Wistar Albino rats were divided into four groups Control (C), Exercise (E), Diabetes (D), and Diabetes+Exercise (DE). A single dose of 60 mg/kg STZ solution was injected intraperitoneally (i.p) into the D and DE groups to create a diabetes model. After diabetes induction, E and DE groups were given running exercises at 20 m/min and 45 minutes daily for four weeks. According to the data obtained, while lipid profile (TC, LDL, TG) and liver enzyme (ALT, AST) levels increased significantly in group D compared to group C, HDL and TP levels were found to decrease. However, a decrease was observed in parameters other than HDL and TP in the DE group. It was also observed that the mineral and vitamin (Vit D, Ca, Mg, and Zn) levels decreased in the D group compared to the C group, while these values tended to increase in the DE group. As a result, the experiment shows that a four week regular exercise program in rats with diabetes has a therapeutic, preventive, and protective effect on lipoprotein levels, liver enzyme markers, and micronutrient levels.

Keywords: *Diabetes Mellitus, Exercise, Lipid profile, Liver enzymes, Micronutrients.*

Diabetes Mellitus'ta Düzenli Koşu Bandı Egzersizinin Bazı Kan Parametreleri Üzerindeki Etkisi

Özet: Bu çalışma, deneysel diyabet modeli oluşturulan sıçanlarda düzenli koşu bandı egzersizinin bazı kan parametreleri üzerindeki etkilerini belirlemeyi amaçlamaktadır. Çalışmada 36 adet Wistar Albino rat Kontrol (K), Egzersiz (E), Diyabet (D) ve Diyabet+Egzersiz (DE) olmak üzere dört gruba ayrıldı. D ve DE gruplarına diyabet modeli oluşturmak için tek doz 60 mg/kg STZ solüsyonu intraperitoneal (i.p) olarak enjekte edildi. Diyabet indüksiyonu sonrası, E ve DE gruplarına dört hafta boyunca, 20 m/dk hızda ve günlük 45 dk. koşu egzersizi yaptırıldı. Elde edilen verilere göre, K grubuna göre D grubunda lipid profil (TK, LDL, TG) seviyeleri ile karaciğer enzim (ALT, AST) düzeyleri önemli ölçüde artış gösterirken, HDL ve TP düzeylerinin azaldığı tespit edildi. Ancak DE grubunda HDL ve TP dışındaki parametrelerde bir düşüş gözlendi. Yine K grubuna oranla D grubunda mineral ve vitamin (Vit D, kalsiyum, magnezyum ve çinko) seviyelerinin azaldığı gözlenirken, DE grubunda bu değerlerin artma eğiliminde olduğu belirlendi. Sonuç olarak, deneysel diyabetli sıçanlarda dört haftalık düzenli egzersiz programının lipoprotein seviyeleri, karaciğer enzim belirteçleri ve mikro besin seviyeleri üzerinde terapötik, önleyici ve koruyucu bir etkiye sahip olduğunu göstermektedir.

Anahtar Kelimeler: *Diabetes Mellitus, Egzersiz, Karaciğer enzimleri, Lipid profili, Mikro besinler.*

Introduction

Diabetes Mellitus (DM) is a significant public health problem with an increasing prevalence worldwide and is among the primary causes of morbidity and mortality. DM, characterized by chronic hyperglycemia, is a metabolic disease mainly caused by the inability of pancreatic β cells to produce sufficient insulin hormone, resulting in impaired insulin secretion, the resistance of peripheral tissues to insulin, or both (Kilincarslan and Donmez, 2019).

The liver plays a vital role in lipid metabolism by mediating lipid metabolite production, storage, and transport (Hatipoğlu and Kahraman, 2021). Cholesterol plays an essential role in the pathogenesis of diabetes because of its effect on the structure and function of the pancreatic β-cell membrane (Perego et al., 2019). An increase in total cholesterol, triglycerides, and LDL levels in DM and a decrease in HDL levels cause dyslipidemia (Jialal and Singh, 2019). In addition, hyperlipidemia leads to liver enzyme abnormalities (Kathak et al., 2022).

Chronic hyperglycemia, which is the main symptom of DM, causes serious changes in the condition of micronutrient elements (vitamins, minerals, and trace elements) in the body. Micronutrients increase the efficiency and sensitivity of insulin by providing hormonal control with the activation of insulin receptor sites and acting as cofactors or components for enzyme systems involved in glucose metabolism. It also shows an antioxidant effect preventing tissue oxidation (Gürbüz and Çelik, 2019). Many trace elements are involved in the organism at physiological and biochemical levels. Changes in element levels vary depending on the type, duration, intensity of exercise, and nutritional behavior (Pourvaghar and Shahsavar, 2010).

Regular exercise central to improving glucose homeostasis by increasing glucose uptake by tissues by increasing insulin sensitivity and response in insulin-dependent tissues such as adipocytes and myocytes (Yaribeygi et al., 2019). With the exercise protocols applied, blood cholesterol and triglyceride plasma levels decrease; it decreases fatty acid oxidation in pancreatic β cells by expressing lipogenesis enzymes in the liver by reducing LDL and increasing HDL levels. This therapeutic efficacy of exercise on the organism is offered as a treatment option for lowering metabolic and cardiovascular risk factors (Balducci et al., 2014; O'hagan et al., 2013).

This study aims to determine the effect of regular aerobic exercise training on serum lipid parameters, liver enzyme levels, and some micronutrient levels in rats with an experimental diabetes model.

Materials and Methods

Animal Study Design: In the study, 36 Wistar Albino rats with similar live weights and six weeks old were used. The subjects were obtained from Selçuk University Experimental Medicine Application and Research Center (SUDAM). Selcuk University Faculty of Veterinary Medicine Experimental Animal Production and Research Center Ethics Committee (SUVDAMEK) approved the research plan and project with the number 2023-50. Subjects in the SUDAM unit were housed in plastic cages at 23±2 °C room temperature and 50±10% humidified environment with 12/12 night/day light cycles. Standard rat chow and daily fresh water were given ad libitum to the subjects during the study. Animals were divided into Control (C), Exercise (E), Diabetic (D), and Diabetic+Exercise (DE) groups.

Experimental Diabetes Procedure: A single dose of 60 mg/kg STZ (Sigma S0130-1G) solution was dissolved in 0.1 M citrate buffer (pH 4.5) and injected intraperitoneally (i.p) to form a diabetes model in the D and DE groups. After fasting for 72 hours, blood glucose was monitored from the tail with a blood glucose meter (plusMED). Subjects with blood glucose above 250 mg/dl were considered diabetic (Dönmez et al., 2020).

Running Exercise Protocol: Subjects started the treadmill exercise program after diabetes induction. The groups (E and DE) who were taken to the SUDAM experimental treadmill exercise practiced for two days at a speed of 15m/min and for 15 minutes as a process of adaptation to the exercise. They then started the experimental phase for 45 minutes daily at 20 m/min for four weeks (Ugurlu et al., 2022). After the four-week trial, enough blood was taken from the subjects under anesthesia (thiopental anesthesia, 40 mg/kg) by heart puncture and into anticoagulant tubes.

Hematological Analysis: In the serums obtained from the blood samples taken at the end of the trial total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), total protein (TP), alanine aminotransferase test (ALT), aspartate aminotransferase test (AST), vitamin D (vit D), calcium (Ca), magnesium (Mg) and zinc (Zn) the levels were determined by chemiluminescent method on the Abbott C8000 device in accordance with the commercial kit (Abbott) protocol.

Statistical Analysis: Statistical analysis of the data obtained at the end of the experimental study and the determination of the importance of the differences between groups were carried out by using the SPSS 26.0 package program and by using Duncan's Multiple Range tests in the analysis of variance ($p<0.05$).

Results

The data obtained at the end of the experimental study are presented below in Table 1 and 2.

Discussion

Type 2 DM, associated with hyperglycemia and hyperinsulinemia, causes diabetic dyslipidemia by causing some disorders in the production and metabolism of plasma lipoproteins (Tangvarasittichai, 2015). Evidence from existing studies highlights a strong association between hyperlipidemia and diabetes. Many studies on this subject

Table 1. The effect of exercise training on lipid profiles and liver enzyme levels in experimental diabetic rats.

	C (n=6)	E (n=10)	D (n=10)	D+E (n=10)
TC (mg/dl)	95,00±0,97[b]	91,42±0,85[b]	140,20±1,35[a]	105,70±1,86[ab]
HDL (mg/dl)	39,83±1,33[b]	48,63±1,48[a]	24,60±1,07[c]	34,42±1,21[bc]
LDL (mg/dl)	53,30±1,21[b]	40,21±0,88[c]	116,72±2,14[a]	72,12±1,39[ab]
TG (mg/dl)	66,34±0,63[b]	61,50±0,62[b]	109,90±6,18[a]	95,53±1,02[ab]
TP (g/L)	68,65±0,26[b]	70,92±0,31[a]	57,22±0,44[c]	61,52±0,34[bc]
ALT (U/L)	53,15±1,18[c]	60,51±0,52[b]	111,60±1,72[a]	89,35±2,49[ab]
AST (U/L)	84,90±1,38[c]	89,80±0,56[b]	144,84±0,73[a]	112,70±0,98[ab]
Vit D (ng/ml)	3,77±0,17[a]	3,98±0,20[a]	1,90±0,17[b]	2,57±0,11[ab]

a, b, c; The difference between the mean values shown with different letters for the same parameter on the same line is significant. ($p<0.05$).

Table 2. The effect of exercise training on Ca, Mg and Zn levels in experimental diabetic rats.

	C (n=6)	E (n=10)	D (n=10)	D+E (n=10)
Ca (mg/dl)	10,64±0,21[a]	11,04±0,71[a]	6,80±0,09[b]	7,41±0,08[ab]
Mg (mg/dl)	2,82±0,04[a]	3,00±0,18[a]	1,52±0,09[b]	1,90±0,04[ab]
Zn (ug/dl)	81,79±0,95[a]	83,46±1,80[a]	47,25±0,55[b]	54,20±1,23[ab]

a, b, c; The difference between the mean values shown with different letters for the same parameter in the same line is significant ($p<0.05$).

indicate that TC, TG, and LDL levels in diabetics show a significant increase compared to the control, but HDL levels decrease (Abdella Baragob et al., 2014; Amaechi et al., 2015; Hadi et al., 2023). In our findings, significantly increased lipid profiles (TC, TG, LDL) and decreased HDL levels were observed in the experimental diabetes group compared to the control group (Table 1). The lipoprotein lipase (LPL) enzyme, which provides lipoprotein regulators and hydrolysis of triglycerides, is activated by insulin. However, hyperlipidemia occurs due to the inability to activate the LPL enzyme due to insulin resistance in diabetic conditions. In addition, insufficient insulin secretion and/or insulin deficiency activates the hormone-sensitive lipase enzyme, increasing the transport of free fatty acids from adipose tissue and causing an increase in lipoprotein levels (TC, TG, and LDL) and a decrease in HDL (Makinde et al., 2020).

Disturbances in lipoprotein levels in DM also affect liver metabolism, causing hepatic dysfunction. ALT and AST, produced by the liver are specific markers used to determine liver damage (Kalas et al., 2021). Studies have reported that ALT and AST levels are significantly increased in diabetic subjects compared to the control group (Hadi et al., 2023; Kılıçarslan and Dönmez, 2016; Yazdi et al., 2019). Our results determined that liver enzymes (ALT, AST) were significantly increased in the diabetes group compared to the control group (Table 1). Chronically high glucose levels in DM increase hepatic enzyme levels due to oxidative stress and subsequent carbohydrate, protein, and lipid metabolism dysfunction. Therefore, the increase in enzyme levels causes cellular damage and destruction of liver tissue (Ahangarpour et al., 2018; Mohamed et al., 2016).

Although there are studies that report that total protein levels increase in diabetes (Malawadi & Adiga, 2016; Riaz et al., 2018), some studies indicate a decrease in these protein levels (Analike et al., 2019; Makinde et al., 2020). When the data obtained from the study were examined, it was determined that the total protein levels decreased significantly in the diabetes group compared to the control group (Table 1). In conclusion, it can be said that total proteins, which provide hemostasis and coagulation and play an important role in immunity, have a specific role in the pathology and complications of diabetes. In addition, a marked decrease in total protein levels indicates diabetes-induced liver tissue damage. Therefore, hyperglycemia associated with diabetes causes the breakdown of structural proteins by increasing the conversion of amino acids to glucose, negatively affecting the synthesis of total proteins such as albumin and globulin (Ekperikpe et al., 2019; Goboza et al., 2019).

In many studies, it has been reported that lipid profiles, including TC, TG, and LDL, decreased in the exercise-applied diabetes group compared to diabetic subjects, while HDL levels increased significantly (Aly et al., 2016; Eldin et al., 2021; Mohammad et al., 2019). This study observed an increase in HDL levels and a decrease in lipid profile parameters (TC, TG, LDL) in diabetic rats who underwent running exercise compared to the diabetes group (Table 1). Some researchers report that exercise can increase LPL enzyme activation and decrease hepatic triglyceride lipase (Liu & Wang, 2014). In conclusion, increased LPL activation with exercise causes an increase in the metabolism of lipoproteins, resulting in a decrease in LDL levels.

Mohammed et al. (2019) reported that ALT and AST levels of the moderate-intensity exercise program applied to diabetic subjects decreased significantly compared to diabetic subjects, but liver enzymes approached control after high-intensity exercise. Again, in studies on individuals with type 2 DM and on experimental animals, it has been reported that exercise reduces ALT and AST values (Akbari et al., 2020; RamzanPour et al., 2014). The data obtained from the study are compatible with these studies (Table 1), suggesting that regular and long-term exercise programs can minimize damage to various tissues and organs, such as the liver, skeletal muscle, and heart, and have a protective effect.

It is among the reports that physical exercise causes temporary increases in liver enzyme levels (Pettersson et al., 2008; Sjögren, 2007). There has been reported to be an increase in liver enzyme levels after various exercise protocols and competitions applied in both experimental animals and athletes in different branches (Kaynar et al., 2016; Lenaerts et al., 2005; Qureshi et al., 2022). Studies reported in the literature are similar to our findings (Table 1). In some studies, while no change is observed in the liver enzyme levels of exercise (Bürger-Mendonça et al., 2008; Lippi et al., 2011), it is stated that long-term aerobic exercise reduces these enzymes (Khaoshbaten et al., 2013; Yao et al., 2018). As a matter of fact, exercise duration and intensity may reveal different results in liver enzyme levels.

Although studies examining the effect of exercise on total proteins are limited, some studies indicate an increase in total protein levels after exercise (Ahmadizad & El-Sayed, 2005; Gailiūnienė et al., 2007). In the findings of the study, an increase in total protein levels was observed in the exercise group compared to the control group (Table 1).

Clinical studies report that micronutrient metabolism is a prominent factor in diabetes pathogenesis and progression (Khan and Awan, 2014; Mooren et al., 2011), leading to abnormal micronutrient concentrations in rodent models of diabetes (Ragbetli et al., 2014). Pittas et al. (2007) reported that changes in vitamin D and calcium levels play a role in the development of T2DM. Again, many studies in clinical and experimental animal models report that vit D and calcium levels are significantly reduced in subjects with DM compared to controls (Aly et al., 2016; Butola et al., 2020; Rana et al., 2016). Our results showed that diabetic rats had significantly lower vitamin D and calcium levels than the control (Tables 1 and 2). In conclusion, it can be said that the primary mechanism of action of vitamin D on insulin secretion and synthesis, calcium-dependent insulin secretion, and changes in calcium concentrations affect the secretion of β islets, leading to DM and related symptoms.

Data on low magnesium levels in the diabetic group in both human and experimental studies are supported by our results from the study (Table 2) (Dhavane and Dhavane, 2022; Gómez et al., 2017; Yang et al., 2011). Thus, although the cause of hypomagnesemia, which is common in diabetes, is not clear, it can be explained by increased urinary magnesium losses due to glucosuria and osmotic diuresis. In addition, hypomagnesemia resulting from chronic hyperglycemia in diabetes may lead to vascular complications of diabetes (Barbagallo and Dominguez, 2015). It has been reported that low plasma and serum zinc levels are associated with decreased insulin sensitivity and hyperglycemia (da Silva Bandeira et al., 2017). There are studies reporting that serum zinc levels are significantly reduced in experimental models and diabetic subjects compared to control subjects (Duzguner and Kaya, 2007; Gagandeep et al., 2015; Gómez et al., 2017; Kumar et al., 2014). Our data showed that serum zinc levels were significantly decreased in diabetic subjects compared to the control (Table 2). As a result, it suggests that the zinc deficiency observed in DM leads to a decreased zinc concentrations due to increased urinary excretion of zinc by transporting it to the kidney tubules.

Vitamin D and its receptors significantly affect muscle tissue by improving muscle fiber and muscle strength by providing the efficiency and transport of calcium, mediating muscle contraction. It has been reported that magnesium and zinc may have a significant effect on energy metabolism and performance (Aly et al., 2016; Huskisson et al., 2007). In the findings obtained from the study, the values of Vit D, calcium, magnesium, and zinc tend to increase after running exercise both in the exercise group and in diabetic rats (Tables 1 and 2). Parallel to these results, some studies have reported that these parameters increase after exercise (Aly et al., 2016; Baydil, 2013; Bicer et al., 2011).

Conclusion

The study suggests that a four-week regular exercise program has a therapeutic, preventive, and protective effect on lipoprotein levels, liver enzyme markers, and micronutrient levels in rats with experimental diabetes.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical Approval

Selcuk University Faculty of Veterinary Medicine Experimental Animal Production and Research Center Ethics Committee (SUVDAMEK) approved the research plan and project with the number 2023-50.

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