Medit Vet J, 9(1): 247-253, 2024
DOI: 10.24880/maeuvfd.1439770

Research Article

The effects of exercise on vascular responses in rats with type 1 diabetes

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Key Words:
acetylcholine
aorta
exercise
phenylephrine
rat
type 1 diabetes.

Received : 21 February 2024
Revised : 03 April 2024
Accepted : 16 April 2024
Published : 12 June 2024
Article Code : 1439770

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This research was supported by Research Fund the Aydın Adnan Menderes University. Project number: VTF-15021.

ABSTRACT

Diabetes causes dysfunctions and damages in different tissues over time. It has been known that exercise has beneficial effects on the pathologies associated with diabetes. This study was aimed to evaluate the effects of moderate swimming exercise on vascular responses in rats with type 1 diabetes. The groups in the experiment were conducted as diabetes, diabetes exercise, exercise, and control. Streptozotocin (50 mg/kg) was intraperitoneally given to induce type 1 diabetes. The rats in group diabetes exercise and exercise were subjected to a swimming protocol was applied 5 days a week and 1 hour a day for 4 weeks after streptozotocin injection. The initial and final blood glucose levels and weekly body weights were measured. At the end of the study, *in vitro* thoracic aorta responses were recorded. A reduction in body weight of rats with type 1 diabetes was determined from week 1 to week 4 ($p<0.001$). Blood glucose levels were significantly ($p<0.001$) higher in both diabetic groups than those of controls and group exercise. The 4-week swimming exercise had no effect on blood glucose levels of diabetic rats. The responses of the thoracic aorta to norepinephrine and sodium nitroprusside were not different between groups. The control rats showed the highest relaxation response of the thoracic aorta to acetylcholine while this response gradually decreased in groups diabetes exercise, exercise, and diabetes. In conclusion, it was observed that 4-week moderate swimming exercise regimen corrected endothelium-dependent relaxation responses in rats with type 1 diabetes.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder with multiple etiologies characterized by disturbances in carbohydrate, fat, and protein metabolism due to the defects in insulin secretion or insulin action or both. Patients with diabetes also have an increased risk of developing cardiovascular, peripheral vascular and cerebrovascular diseases (Alberti and Zimmet, 1998). Hypotheses for the mechanisms of hyperglycemia-induced damage have been included increased flow in the polyol pathway, increased advanced glycation end products (AGEs), activation of protein kinase C isoforms and increased flow in the hexosamine pathway (Brownlee, 2001). The causes of vascular dysfunction leading to defective angiogenesis in diabetes are complex. Some of these factors include increased reactive oxygen species and AGEs, decreased growth factors and cytokines, and altered cellular immune responses. Endothelial dysfunction is primarily caused by a reduction in nitric oxide bioavailability and may be caused by or contribute to various disease processes, such as in diabetes mellitus, hypercholesterolemia and hypertension (Kolluru et al., 2012).

The endothelium is essential for maintaining vascular wall integrity and locally regulating vascular tone, structure, and hemostasis. Regular exercise can improve endothelial function through several mechanisms. For example, it increases blood flow and laminar shear stress, resulting in increased nitric oxide production and bioavailability (Di Francescomarino et al., 2009).

Aerobic exercise also increases mitochondrial density, insulin sensitivity, oxidative enzymes, compliance and reactivity of the blood vessels, pulmonary function, and cardiac output (Garber et al., 2011). Moderate and high levels of aerobic activity lead to significant reductions in cardiovascular and overall mortality risks in both type 1 and type 2 diabetes (Ratamess et al., 2009). In type 1 diabetes, aerobic training increases cardio-respiratory performance, reduces insulin resistance, and improves lipid levels and endothelial function (Chimen et al., 2012). The aim of this study was to investigate the effects of moderate swimming exercise for 4 weeks on vascular response in male rats with type I diabetes mellitus.

MATERIAL and METHODS

Animals and experimental design

Thirty-six adults male Wistar albino rats with an average weight of 350 g were used in the study. The rats were housed in a room under a 12/12 light/dark cycle, at 22 ± 2 °C, and 50 to 70% of humidity with ad libitum access to food and water. The rats were divided into four groups: diabetes (n=10), diabetes and exercise (n=10), exercise (n=8) and sedentary

To cite this article:
Can Z, Ünsal C. The effects of exercise on vascular responses in rats with type 1 diabetes. Medit Vet J. 2024; 9(1): 247-253.

control (n=8). For induction of type 1 diabetes, a single dose (50 mg/kg) of streptozotocin (2-Deoxy-2-(3-methyl-3-nitrosoureido D-glucopyranose - S0130 1G, Sigma Aldrich®) was administered intraperitoneally. For this purpose, STZ was weighed into Eppendorf tubes (50 mg each), wrapped with aluminum foil, and stored at -20 C. Freshly prepared 0.1 M sodium citrate buffer (pH: 4.5) was added 1 ml to the tubes, STZ-dissolved and immediately administered to the animals. Seventy-two hours after streptozotocin injection, the rats with 250 mg/dl blood glucose levels or higher were considered diabetic and included in the experiment. An additional blood glucose measurement was done at the end of the experiment. A glucometer and test strips (Bayer Contour Plus®, Germany) were used to measure blood glucose levels from tail vein. Rats were weighed at the beginning of the study and weekly thereafter.

Swimming protocol

Eight days after diabetes induction, a swimming protocol was applied 5 days a week and 1 hour a day for 4 weeks. This intensity of exercise protocol is considered as moderate exercise in rats (Kregel, 2006). Rats were individually swum in plastic containers with a 70 cm of diameter and a 90 cm of height in temperature controlled (31±1°C) water with a 50 cm of depth (Ünsal et al., 2017).

Preparation of aorta rings

Four weeks after swimming exercise, rats were anesthetized with a combination of ketamine and xylazine (50 mg/kg ketamine-10 mg/kg xylazine Alfamine®, Alfazyne® EGE-VET, Turkey, respectively) and placed supine position on a thermal pad. After skin incision, upper midline median thoracotomy was done. The surrounding organs were then carefully dissected, and the thoracic aortas were separated from the connecting tissues and placed in Krebs bicarbonate solution. Krebs bicarbonate solution was prepared (mM/l) at pH 7.4 (NaCl: 128; KC1: 4.5; $CaCl_2$: 2.5; $MgSO_4$: 118; KH_2PO_4: 1.18; $NaHCO_3$: 125; D-glucose: 5.55). Vascular rings were made and kept in Krebs bicarbonate solution at +4 °C until use. The vascular rings were connected to the isometric transducer in the chamber of the organ bath and washed every 15 minutes with the Krebs bicarbonate solution in order to allow the tissues to adapt to the environment. The vessels were pre-tensioned (1 g) and left for 1 h. After each experimental protocol, the vessels were given a 30-minute rest period, and the washing process was repeated every 15 minutes (Keegan et al., 1995; Turgut et al., 2008).

For assessment of vascular integrity, phenylephrine (10^{-5} mM) was added into the bath and vascular contraction was recorded. Endothelial integrity in the vessel reaching submaximal contraction was evaluated by measuring the relaxation response to acetylcholine (10^{-5} mM). Additionally, at the beginning of the experiment, KCl (80 mM) was added into the organ bath to assess vascular smooth muscle contractility and the response to phenylephrine. Phenylephrine was applied cumulatively at the concentrations ranging from 10^{-9}-10^{-4} mM. Endothelium-dependent relaxation responses were evaluated by the cumulative application of acetylcholine (10^{-9}-10^{-4} mM) in vessels that were pre-contracted with 10^{-5} mM phenylephrine. Smooth muscle-dependent relaxation responses were evaluated by the cumulative application of sodium nitroprusside at the concentrations ranging from 10^{-9}-10^{-4} mM in vessels pre-contracted with 10^{-5} mM phenylephrine (Turgut et al., 2008).

Statistical analyses

The data was analyzed using the SPSS 19.0 package program. The arithmetic mean ($\bar{x}$) and standard error of the mean ($S\bar{x}$) were determined for each variable. Normal distribution was assessed by Shapiro-Wilk test and homogeneity of variance by Levene's test. Repeated measures analysis of variance was performed for body weight, blood glucose levels, and aortic responses, except for the KCl responses, for which a one-way analysis of variance was performed. Post-hoc Bonferroni and Duncan tests were performed.

RESULTS

Blood glucose levels in the diabetic groups continued to increase significantly ($p<0.001$) compared to the beginning of the experiment. Although exercise tended to lower blood glucose levels in rats with diabetes, the effect did not reach to the statistically significant level (Figure 1).

At the beginning of the experiment, the body weights were not different among the groups. Induction of diabetes caused a time-dependent reduction in mean body weights of groups diabetes exercise and diabetes over four weeks when compared to the controls and exercise group ($p<0.001$). The 4-week swimming exercise did not prevent rats from body weight loss caused by diabetes (Figure 2).

In all groups, contraction responses of the aorta rings were obtained in response to KCl (80 mM) which the differences between groups were not statistically significant ($p=0.918$, Figure 3).

Phenylephrine responses for each concentration were obtained by proportioning the contractile responses to the responses that were obtained with KCl. Therefore, the results were given as % contraction of KCI (Figure 4). The contractile responses of the thoracic aorta to the phenylephrine increased in a dose-dependent manner for each group. However, the changes were not statistically significant ($p=0.802$).

Sodium nitroprusside responses were calculated from the ratio of the obtained submaximal responses to phenylephrine and given as % relaxation (Figure 5). The relaxation responses increased in a dose-dependent manner. The highest relaxation responses were obtained in the control and exercise groups. However, the differences between groups were not statistically significant ($p=0.452$).

Acetylcholine responses were obtained from the ratio of the results for each concentration to the submaximal phenylephrine response and given as % relaxation (Figure 6).

The relaxation responses to acetylcholine increased in a dose-dependent manner. Vessels from the rats with diabetes had the least relaxation responses which was found to be sig-

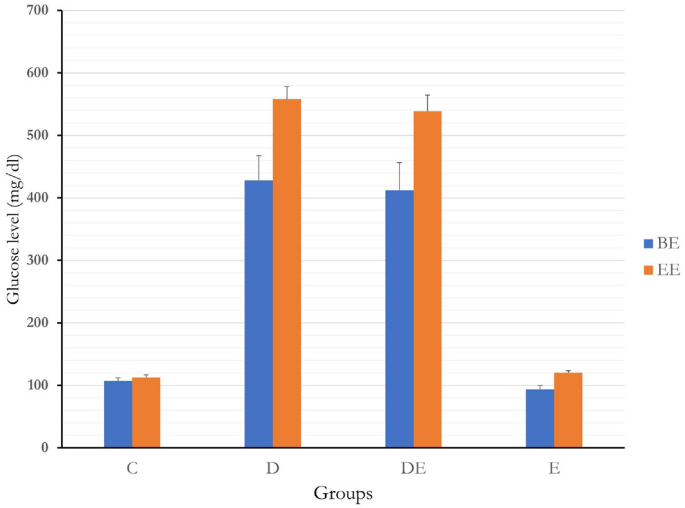
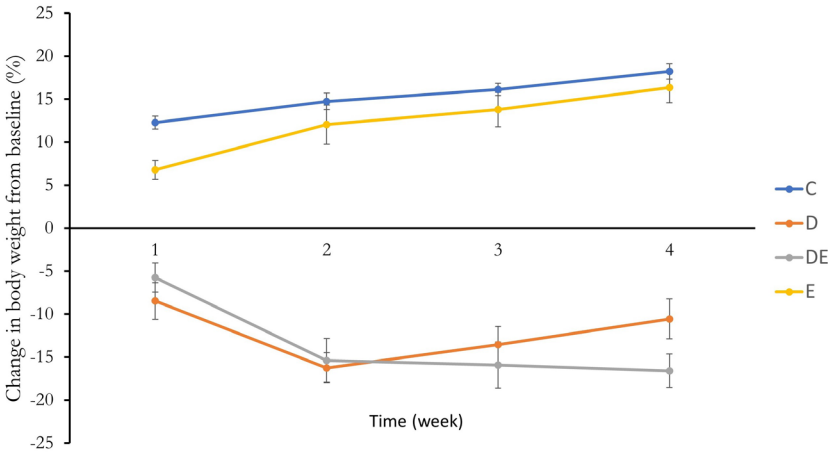


Figure 1. Blood glucose levels in rats (mg/dl).
D: Diabetes, DE: Diabetes exercise, E: Exercise, C: Control.



Groups		C	D	DE	E
Time (week)	0	343,17 ± 13,31	329,14 ± 16,62	343,86 ± 13,31	373,13 ± 11,61
	1	385,00 ± 12,41	301,43 ± 17,14	323,86 ± 12,41	398,13 ± 11,95
	2	393,67 ± 9,97	275,57 ± 14,74	290,00 ± 9,97	416,38 ± 7,03
	3	398,67 ± 13,68	284,43 ± 15,45	289,14 ± 13,68	423,13 ± 7,84
	4	405,33 ± 14,15	294,00 ± 15,15	287,29 ± 14,15	432,88 ± 9,01

Figure 2. Body weight changes and change in body weight from baseline (%).
D: Diabetes, DE: Diabetes exercise, E: Exercise, C: Control.

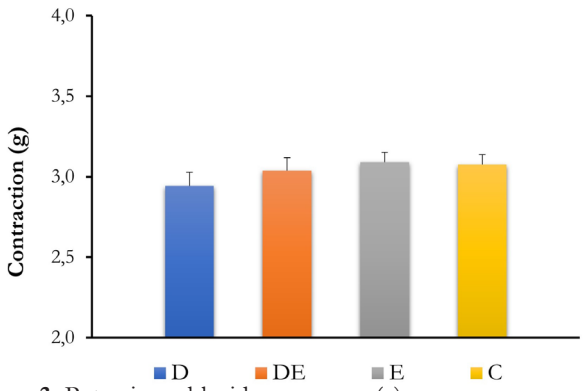


Figure 3. Potassium chloride responses (g).
D: Diabetes, DE: Diabetes exercise, E: Exercise, C: Control.

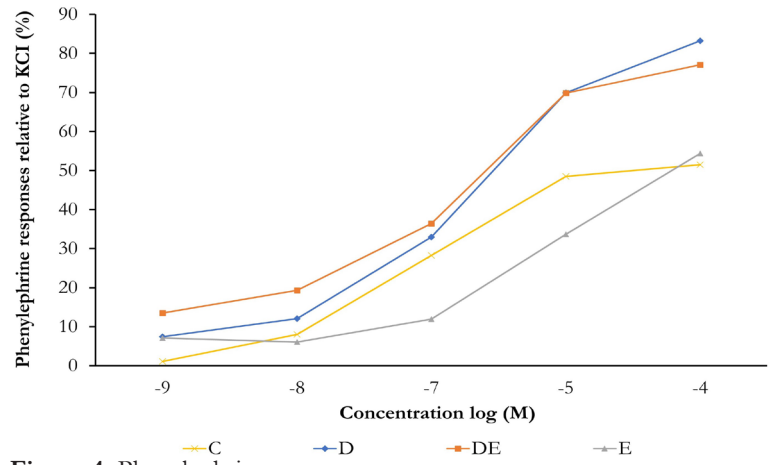


Figure 4. Phenylephrine responses.
D: Diabetes, DE: Diabetes exercise, E: Exercise, C: Control

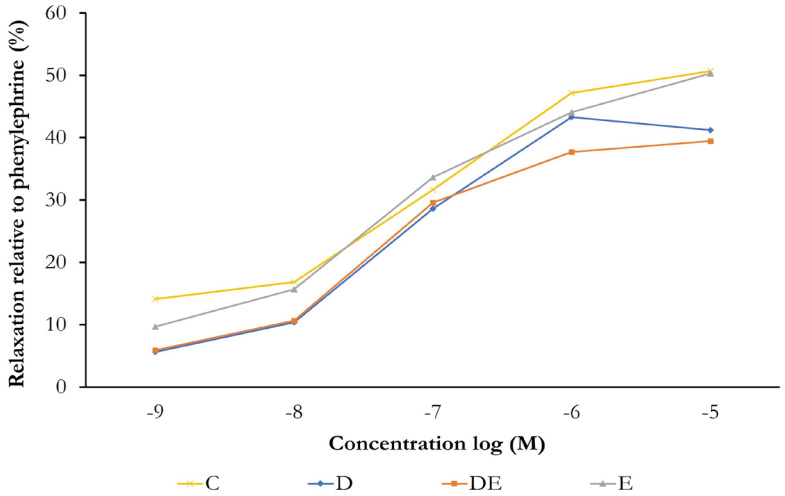


Figure 5. Sodium nitroprusside responses.
D: Diabetes, DE: Diabetes exercise, E: Exercise, C: Control.
The difference between the groups was not statistically different (p=0.452).

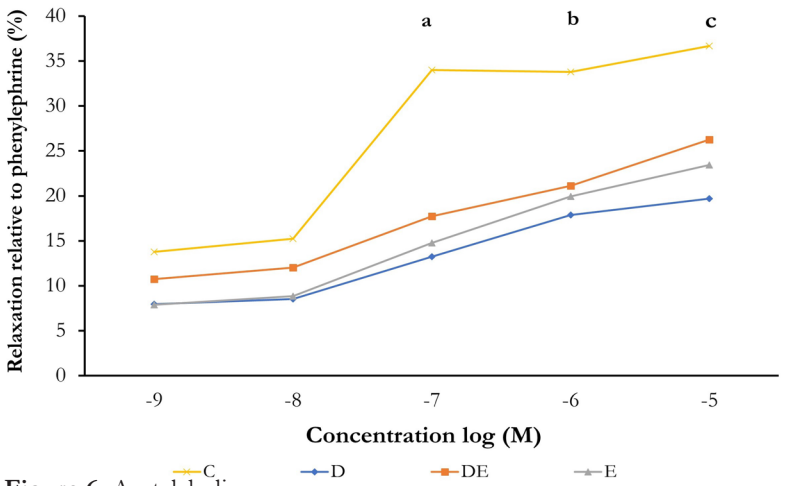


Figure 6. Acetylcholine responses.
D: Diabetes, DE: Diabetes exercise, E: Exercise, C: Control.
a: Diabetes, exercise and diabetes exercise groups were significantly different from the control group (p=0.037, p=0.006, p=0.043, respectively).
b: Diabetes group is significant with the control group (p=0,011)
c: Diabetes group is significantly different from diabetes exercise, exercise, and control groups (p=0.007, p=0.007, p=0.001 respectively).

nificant compared to the controls at the concentrations of 10^{-7}, 10^{-6} and 10^{-5} mM (p=0.001, p=0.037, p=0.011, respectively). The responses from the diabetes exercise group were found to be significant compared to the controls at 10^{-7} mM concentration of acetylcholine (p=0.043) and this difference disappeared in all other concentrations. The relaxation responses of the exercise group to acetylcholine were weaker than the control group and this difference was significant at 10^{-5} mM concentration of acetylcholine (p=0.037). The diabetes exercise group showed a stronger relaxation than the diabetic group and the difference was statistically confirmed for 10^{-5} mM concentration (p=0.007).

DISCUSSION

Previous studies showed that exercise did not cause changes in blood glucose levels of rats with type 1 diabetes (Mona and Allam, 2018; Nakos et al., 2018) which is consistent with this study. The type of the physical activity is considered important in terms of glycemic control through exercise. It has been reported that individuals with type 1 diabetes may experience higher glycemic variability during aerobic exercise as compared to the resistance exercise (Yardley et al., 2013). On the other hand, it is also emphasized that aerobic exercise is an appropriate method for chronic glycemic control specifically in humans, while resistance exercise does not have a significant effect on chronic glycemic control (Tonoli et al., 2012).

Compared to the controls, rats with type 1 diabetes lost 23-31% of body weight, while the diabetic exercise group lost 16-29%. The rats with diabetes showed a rapid weight loss and clinical symptoms of polydipsia, polyphagia, and polyuria, although data on these symptoms were not collected in this study. Similar to this study, Nakos et al (2018) observed a weight loss and symptoms of polydipsia and polyphagia in diabetic animals despite the eight-week exercise protocol provided only a partial improvement in body weights, suggesting that exercise alone is insufficient to reverse the effects of diabetes on body weight. However, significant improvements in insulin resistance were determined in exercising rats with type 1 diabetes (Hall et al., 2013) likely due to beneficial effects of long-term aerobic exercise on β-cell proliferation (Kiraly et al., 2007) and oxidative capacity (Torgan et al., 1993). Since insulin levels were not measured in this study, which is a limitation, it is hard to interpret the relationship between body weight change and insulin action.

Although diabetes caused a slight reduction, KCl-induced contraction of the thoracic aorta was not significant between groups. Consistent with this finding, Taylor et al. (1994) noted that KCl-induced contraction responses of mesenteric arteries remained unchanged in diabetic rats, but more recent evidence suggests that contraction responses to KCl increase under hyperglycemic conditions in vitro. Donmez et al. (2014) suggested that this increase may be due to elevated oxidative stress under hyperglycemic conditions. KCl-induced contraction is primarily mediated through voltage-gated calcium channels (Akata, 2007). In contrast to the studies mentioned above, there are also studies showing that KCI responses are reduced in diabetic rats (Fulton et al., 1991; Carmines et al., 1996) which may be due to a decreased density of voltage-gated L-type Ca^{+2} channels (Wang et al., 2000).

In this study, although not statistically significant, phenylephrine responses fluctuated among groups as evidenced by the fact that an increase in rats with diabetes and a reduction in rats that were subjected to swimming exercise when compared to the controls. Overall, studies have shown that the response to phenylephrine can be unchanged (Fulton et al., 1991; Taylor et al., 1994; Kobayashi and Kamata, 1999), decreased (Oyama et al., 1986), or increased (Karasu and Altan, 1993) in diabetic states.

Sodium nitroprusside acts as an endothelium-independent relaxant, exerting its effect through direct action on vascular smooth muscle (Bonaventura et al., 2008). Previous studies showed that diabetes does not affect SNP-mediated relaxation responses (Oyama et al., 1986; Taylor et al., 1992) which is consistent with this study.

Studies have shown that vasorelaxation, induced by acetylcholine, is dependent on an intact endothelium which is mediated by endothelium-derived relaxing factors such as nitric oxide, prostanoids, and endothelium-derived hyperpolarizing factor (Leung et al., 2006). In this study, endothelium-dependent relaxation, caused by acetylcholine was impaired in the rats with type 1 diabetes. Importantly, the diabetic rats that were subjected to the swimming exercise showed an improved relaxation compared to the rats with diabetes per se and this difference was statistically confirmed at the concentration of 10^{-5} mM acetylcholine.

In rats with type 1 (Oyama et al., 1986; Dai et al., 1993; Taylor et al., 1994; Kobayashi and Kamata, 1999) and type 2 (Oyama et al., 1986) diabetes, endothelium-derived hyperpolarizing factor mediated vasodilation, the total oxidant capacity (Ünsal and Ünsal, 2016) and the production of free radicals and prostaglandin endoperoxidases is altered which may cause an impairment of nitric oxide-mediated endothelium-dependent relaxation (Dai et al., 1993). Although oxidative stress increases in the early stages of diabetes, the endothelial function is preserved. Nitrosothiol serves as an additional source of nitric oxide in this process, ensuring the continuity of endothelium-dependent relaxation (Leo et al., 2010; Joshi and Woodman, 2012). However, this compensatory mechanism may be impaired in the long term and endothelium-dependent relaxation may be damaged (Leo et al., 2010). Exercise seems like partially correct the impaired acetylcholine response in diabetic conditions. It has been shown that endurance exercise in rats with type 2 diabetes has beneficial effects on hyperglycemia and insulin resistance. It also prevents the impairment of endothelium-derived hyperpolarizing factor and endothelial derived relaxation factor (Minami et al., 2002) which suggests that exercise is thought to increase nitric oxide bioavailability and improve endothelial function (Di Francescomarino et al., 2009).

In conclusion, this study shows that type 1 diabetes negatively affects vascular properties of the thoracic aorta in rats. Exercise may have beneficial effects on the impaired processes. Longer duration of exercise could be more effective in ameliorating high blood glucose levels and endothelial dysfunction.

DECLARATIONS

Ethics Approval

The study was approved by the Aydın Adnan Menderes University Animal Experiments Local Ethics Committee (approval number: 64583101/2014/142).

Conflict of Interest

The authors state no conflict of interest.

Consent for Publication

Not applicable.

Author contribution

Idea, concept, and design: CU

Data collection and analysis: ZC, CU

Drafting of the manuscript: ZC, CU

Critical review: CU

Acknowledgements

This study was presented as an oral presentation at the 42nd National Physiology Congress of Turkish Physiological Sciences Association (Düzce University Congress Center 05-08 September 2016). The abstract of the presentation is published in the Congress Proceedings and ACTA Physiologica Volume 215, Issue S704. In addition, the serum samples obtained from the study were analyzed and presented (Oral Presentation) with the title "The Effect of Swimming Exercise on Lipid Profile and Oxidant-Antioxidant Status in Type I Diabetic Rats" in 10th The 10th International Conference in Physical Education, Sports and Physical Therapy (18-20 November 2016 Fırat University, Faculty of Sport Sciences, Elazig). This chapter was published in "F.Ü. Sağ. Bil. Tıp Derg. 2016; 30 (3): 119-123" as full text.

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