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RESEARCH

Effects of exercise on some hemostatic parameters in experimental diabetes model induced by streptozotosin (STZ) in rats

Canan Ceylan[1] · **Nurcan Dönmez**[2]

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Abstract

The aim of this study was to determine the effects of regular aerobic exercise on some hemostatic parameters in streptozotocin (STZ)-induced experimental diabetic rats. In the study, 36 six-week-old adult Wistar Albino rats were used. Animals were divided into four groups as control (C), diabetes (D), exercise (E), and exercise + diabetes (ED). Groups D and ED were injected intraperitoneally with a single dose of 60 mg/kg STZ. Groups E and DE were exercised on a treadmill at a speed of 20 m/min for 45 min per day for 4 weeks. Insulin levels were found to be lower in the ED group compared to the C and E groups and significantly higher in the D group ($p < 0.05$). Serum FIB, D-dimer, PAI-1, FVIII, t-PA, and TAT levels showed a significant increase in group D compared to group C ($p < 0.05$). In addition, FVIII and TAT levels were significantly higher only in group E compared to group C ($p < 0.05$). In group E, other parameters (FIB, D-dimer, PAI-1, t-PA, ATIII, aPTT, PT) were similar to the data obtained from group C ($p > 0.05$). In addition, serum PAI-1 and FVIII levels were significantly decreased in the ED group compared to the D group ($p < 0.05$). In conclusion, aerobic exercise for 4 weeks due to increased insulin sensitivity and improved glycaemic control because it suppresses excessive clot formation by providing both anticoagulant effect by regulating coagulation factors and activation of the fibrinolytic system can be considered as a complementary treatment strategy.

Keywords Coagulation · Diabetes mellitus · Exercise · Hemostasis · Insulin

Introduction

Diabetes mellitus (DM) is a metabolic, endocrine disease characterized by chronic hyperglycemia, resulting from decreased sensitivity of tissues to insulin due to impaired carbohydrate, protein, and lipid metabolism, insufficient insulin secretion, or excessive glucagon secretion, leading to a series of physiological dysfunctions on the organism (Achila et al. 2020; Salgıntaş et al. 2021). According to the 2025 atlas of the International Diabetes Federation (IDF), 589 million people aged 20–79 years are estimated to be diabetic worldwide, and this number is expected to reach 853 million by 2050. DM, which is associated with acute and chronic complications, causes significant morbidity and mortality by causing micro and macrovascular damage, such as retinopathy, nephropathy, neuropathy, hypertension, atherosclerosis, cardiovascular disease, ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (Özsan et al. 2025; Uygur & Gogas Yavuz 2017).

Type 2 diabetes mellitus (T2DM) triggers vascular dysfunction in two different ways. The first of these is associated with diffuse vascular diseases, while the other is the development of thrombotic tendency (Rydén et al. 2013). Therefore, most of the increased morbidity and mortality in this patient group is associated with dysfunction of hemostatic mechanisms (Gatot et al. 2019). Hemostatic changes in T2DM are positively correlated with various pathophysiological

Key messages It causes a deterioration in the activation of hemostasis, coagulation, and fibrinolysis, which are among the complications of diabetes. However, chronic exercise practices contribute to both the improvement of diabetes complications and the activation of the fibrinolytic system without causing hypercoagulability.

✉ Canan Ceylan
canan.ceylan@izu.edu.tr

Nurcan Dönmez
nurcandonmez@selcuk.edu.tr

[1] Istanbul Sabahattin Zaim Unıversity, Department of Physical Education and Sports, Istanbul, Turkey

[2] Selcuk University, Veterinary Faculty, Department of Physiology, Konya, Turkey

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processes such as insulin resistance, endothelial dysfunction, dysglycemia, and systemic inflammation. Thus, hyperreactivity of platelets, increased expression of prothrombotic markers, and decreased fibrinolytic activation significantly increase the thrombotic burden (Oguntibeju 2019).

Physical exercise is central to the treatment of T2DM because of its therapeutic effect in improving quality of life and vascular complications (Balducci et al. 2014; Ceylan et al. 2023). It has been reported that exercise provides blood glucose regulation in diabetic patients, increases the sensitivity of cells to insulin, reduces lipid levels, facilitates weight loss, and improves cardiovascular system and metabolic control (Donmez et al. 2020a; Kim et al. 2004; Sigal et al. 2004).

Although the available evidence suggests that regular physical exercise significantly modulates thrombotic tendency on hemostatic parameters in DM, limited data on the subject strengthens the conclusion. The type of exercise has different effects on the hemostatic system. Although acute exercise causes a short-term increase in thrombotic activation, regular aerobic exercise has been reported to be effective both by decreasing the activation of the coagulation cascade and by increasing the capacity of the fibrinolytic system (Nagelkirk et al. 2021). Exercise contributes to the reduction of the risk of hypercoagulability by prolonging aPTT and PT times (Menzel & Hilberg 2011). It has been observed that factor VIII, which has an important role in the coagulation cascade, increases transiently with acute exercise, but its levels do not change or decrease after regular exercise (El-Sayed 1996). It has been shown that exercise-mediated increased FVIII is associated with beta-adrenergic stimulus and that this increase varies depending on the intensity of exercise (Posthuma et al. 2015). In addition, the increase in ATIII levels with exercise is involved in the formation of anticoagulant response, while TAT levels tend to decrease in the long term (Hilber et al. 2003).

Chronic exercise in T2DM contributes to a decrease in fibrinogen levels (El-Sayed et al. 2004; Schneider et al. 1988). This suggests that it is associated with decreased systemic inflammation and improved endothelial function. It has also been reported that chronic exercise improves the fibrinolytic system by decreasing D-dimer levels (Rezaeimanesh 2020). Furthermore, regular exercise contributes to fibrinolytic activation by increasing tissue plasminogen activator (t-PA) and plasminogen activator-1 (PAI-1). This suggests that exercise may configure the antithrombotic aspect in diabetic individuals.

A review of the available scientific evidence reveals that there is a significant lack of research in this field due to the multivariate underlying causes of markers reflecting coagulation and fibrinolytic profiles in patients with diabetes. This study aims to evaluate the potential protective and regulatory effects of exercise in chronic diseases by simultaneously examining different markers affecting the hemostatic profile of regular and moderate aerobic exercise in an STZ-induced experimental diabetes model.

Materials and methods

Animal care

In the study, 36 healthy adult 6-week-old Wistar Albino rats with similar average body weights were used. Subjects were obtained from Selçuk University Experimental Medicine Research and Application Center (SUDAM). The research design was approved by the SUDAM Animal Studies Ethics Committee (Code of ethics: 2021–38). During the study period (30 days), the rats were housed in plastic rat cages under a 12/12-day-night light period, 23 ± 2 °C room temperature, $50 \pm 10\%$ relative humidity, and provided with the living conditions (temperature, humidity, and light) prescribed for rats. Animals were given standard rat chow and fresh water ad libitum daily. Animals were divided into control (C, $n = 6$), diabetes (D, $n = 10$), exercise (E, $n = 10$), and exercise + diabetes (ED, $n = 10$) groups.

Diabetes induction

A single-dose solution of streptozotocin (STZ) (60 mg/kg, Sigma S0130-1G) was dissolved in 0.1 M citrate buffer (pH 4.5), and rats were injected intraperitoneally (i.p), and diabetes model was established in diabetic groups (D, ED). Fasting blood glucose levels were determined in the D and ED groups 72 h after STZ injection using a glucometer (PlusMED) from tail capillary blood. Rats with blood glucose levels above 250 mg/dl were considered diabetic (Donmez et al. 2020). After the 4-week trial, adequate blood was collected from rats by cardiac puncture under anesthesia (thiopental anesthesia, 40 mg/kg), with and without anticoagulant (citrate).

Egzersiz Protokolü

In the SUDAM experimental treadmill, E and ED groups were exercised for 15 m/min and 15 min for 2 days as an acclimatization period to aerobic exercise, followed by 45 min of 20 m/min running daily for 4 weeks (Ugurlu et al. 2022).

Determination of insulin levels and coagulation parameters

Insulin levels in plasma stored at − 80 °C until the time of analysis were determined on a Siemens Centaur XP

Immunoassay System using a commercial kit (BT Lab) according to the package insert.

Hemostatic system parameters from serum samples, factor VIII (FVIII), thrombin-antithrombin complex (TAT), D-dimer, tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen (FIB), and antithrombin III (ATIII) concentrations were determined by ELISA method (ELX800) according to the protocol of a commercial kit (BT Lab).

Statistical analysis

SPSS 17.0 package program was used to analyze the results obtained at the end of the study and to determine the significance of the differences between the groups. Comparison of the data obtained from the groups was performed by one-way ANOVA test. All values are shown as mean ± SD in the table. After assessing the homogeneity of variances, paired post-hoc comparisons (Tukey) were used to test the significance between groups when the p value was below 0.05, and Duncan's multiple range test was used in variance analysis.

Result

The effects of regular aerobic exercise on some hemostatic parameters and insulin levels in streptozotocin (STZ)-induced experimental diabetes model are shown in Table 1.

Discussion

The hemostatic system, which is clinically vital for human health, is a physiological defense mechanism that maintains the delicate balance between bleeding and coagulation in order to prevent blood loss due to impaired vascular integrity (Donga et al. 2015). Identification of factors associated with hypercoagulation and fibrinolysis, which are common in T2DM, is very important to clarify the risk factors and pathophysiologic causes in these patients. Available evidence suggests that exercise reduces the incidence of morbidity and mortality by preventing both metabolic diseases and the adverse effects of sedentary living (Khoury et al. 2021; Pedersen & Saltin 2015; Ceylan et al 2023).

When the findings obtained from our current study are examined, it is noteworthy that the decrease in plasma insulin level determined in diabetes groups (D and ED) compared to control groups (C and E) ($p < 0.05$) (Table 1) is remarkable in terms of revealing the damage caused by STZ in pancreatic β cells. These data are consistent with many studies supporting the mechanism of diabetogenic effect of STZ (Adewole et al. 2007; Kılıçarslan & Dönmez 2016; Lenzen 2008; Saygılı & Dönmez 2021; Özsan et al 2025). Regular exercise has been shown to improve glucose homeostasis and improve the vascular effects of insulin by increasing insulin sensitivity (Padilla et al. 2015).

The integrity of the coagulation cascade is maintained through intrinsic and extrinsic pathways. Screening tests that clinically evaluate the function of these pathways include prothrombin time (PT) and activated partial thromboplastin time (aPTT) (Ng 2009). When the data obtained at the end of the study were analyzed, it was found that aPTT and PT times were significantly shorter ($p < 0.05$) in the diabetes group (D) compared to the control groups (C and E) (Table 1). The findings are consistent with the results reported in the existing literature (Kulkarni et al. 2023; Li et al. 2021; Zhao et al. 2011). These shortened parameters in DM are attributed to increased expression of platelet surface proteins, increased plasma levels of coagulation factors, and decreased natural anticoagulant molecules (Al-Rubeaan et al. 2019; Lippi et al. 2009; Mina et al. 2010). In the ED group compared to the D group, the prolongation of aPTT and the tendency for prolongation of PT (Table 1) suggest

Table 1 The effect of exercise on Insulin, FIB, D-dimer, PAI-1, FVIII, t-PA, TAT, ATIII, aPTT and PT levels in rats with experimental diabetes

	C (n=6)	D (n=10)	E (n=10)	E+D (n=10)
Insulin (uU/mL)	0,70±0,03^{a}	0,30±0,05^{b}	0,69±0,01^{a}	0,60±0,07^{c}
FIB (ng/ml)	72,60 ± 12,58^{a}	97,20 ± 6,40^{b}	80,06 ± 4,80^{a}	87,80 ± 4,81^{ab}
D-dimer (ng/ml)	0,65 ± 0,02^{a}	0,75 ± 0,04^{b}	0,61 ± 0,03^{a}	0,70 ± 0,05^{ab}
PAI-1 (ng/ml)	2,68 ± 0,34^{a}	5,19 ± 0,47^{c}	3,46 ± 0,44^{ab}	4,28 ± 0,75^{b}
FVIII (IU/ml)	25,08 ± 3,95^{a}	97,65 ± 7,89^{c}	81,34 ± 7,60^{bc}	52,42 ± 8,84^{ab}
t-PA (ng/mL)	0,50 ± 0,14^{a}	1,00 ± 0,17^{b}	0,72 ± 0,08^{ab}	0,88 ± 0,08^{ab}
TAT (pg/ml)	2,51 ± 0,32^{a}	4,78 ± 0,36^{b}	4,73 ± 0,53^{b}	3,98 ± 0,57^{ab}
ATIII (pg/ml)	27,23 ± 3,33	23,84 ± 2,80	23,92 ± 2,71	27,60 ± 3,72
aPTT (sec)	27,90 ± 9,02^{ab}	21,24 ± 1,70^{a}	44,70 ± 6,53^{b}	36,53 ± 2,94^{ab}
PT (sec)	13,08 ± 1,93^{b}	9,63 ± 0,37^{a}	11,30 ± 1,34^{b}	9,78 ± 0,27^{a}

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

that regular physical exercise alleviates the hypercoagulable state by preventing the release of coagulation and thrombosis biomarkers into the bloodstream. Again, in group D, ATIII levels decreased significantly, while TAT levels increased significantly (Table 1). Current evidence indicates that decreased ATIII levels can cause hypercoagulation by causing the procoagulant state, the development of vascular degenerative complications due to increased oxidative stress, and an increase in glycosylation end products (AGE) since they cannot suppress the overproduction of thrombin in a hyperglycemic environment (Karim et al. 2015; Ló Pez et al. 1999). In the diabetic group (ED) performing regular aerobic exercise, the tendency of ATIII and TAT levels to approach those of the control group (Table 1) is a reflection of coagulation activation.

Hemostatic dysfunction such as hyperfibrinogenemia and hypofibrinolysis in T2DM is attributed to increased platelet activation and endothelial dysfunction (Bryk-Wiązania & Undas 2021). Consistent with other studies (Bembde 2012; Gürkan & Kavaklı, 2018), we found that serum fibrinogen levels in diabetic rats (group D) showed a significant increase compared to the control group (Table 1). This increase, associated with poor glycemic control, resists the formation of fibrinolysis, leading to excessive clot production (Neergaard-Petersen et al. 2014). Again, fibrinogen levels tended to decrease in the ED group compared to the D group (Table 1), suggesting that the activation of the fibrinolytic system increased due to improved insulin sensitivity. In addition, the increase in factor VIII and D-dimer markers in group D compared to control (Table 1) may be an indicator of both excessive fibrin clot formation and systemic inflammation. In the ED group, these values decreased compared to the D group (Table 1). The anti-inflammatory effect of regular exercise has a positive effect on both the coagulation profile and thrombotic status (Meirelles et al. 2014).

An important pathophysiologic feature of T2DM is insulin resistance. There is a strong correlation between insulin resistance and T2DM and increased t-PA and PAI-1 levels (Kitagawa et al. 2006). The Insulin Resistance Atherosclerosis Study (IRAS) emphasizes that increased PAI-1 levels are an independent risk factor for the development of metabolic syndrome and T2DM in healthy subjects and that this increase persists when baseline and follow-up periods are considered (Festa et al. 2002, 2006). In the present study, in line with other studies (Ågren et al. 2014; Cavallero et al. 2003), t-PA and PAI-1 levels were significantly increased in diabetic rats compared to the control group (Table 1). Thus, the inactive form of t-PA in the blood and its inability to compensate for this situation results in the development of hypofibrinolysis and hypercoagulability (Karim et al. 2015; Kearney et al. 2017). In the ED group, t-PA and PAI-1 levels showed a tendency to decrease compared to the D group (Table 1). The reduction of these parameters may be related to the fact that improved insulin sensitivity increases fibrinolytic system activation.

Conclusion

There are very few studies on the effects of exercise, an alternative treatment method for STZ-related disabilities, on insulin and some hemostatic drugs (D-dimer, PAI-1, factor VIII, t-PA, TAT, ATIII, aPTT, PT, and fibrinogen), and this study is one of the first explosions in timed metabolism studies of moderate intensity regular aerobic exercise on blood coagulation and fibrinolytic indices in diabetic subjects. Insulin resistance and hyperglycemia in T2DM is a metabolic disease that leads to a state of hypercoagulability and hypofibrinolysis, increasing the risk of thrombotic complications. However, a 4-week aerobic exercise program can be considered a complementary treatment strategy, as it improves insulin sensitivity and glycemic control, thereby regulating coagulation factors to exert an anticoagulant effect and activating the fibrinolytic system to suppress excessive clot formation. In this context, exercise is not only a protocol for maintaining metabolic homeostasis in diabetes but also a non-pharmacological intervention option for promoting vascular health and managing thrombotic risk.

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Data availability No datasets were generated or analysed during the current study.

Ethical approval This study was approved by the Selcuk University Experimental Medicine Research and Application Center Ethics Committee (2021–38).

Informed consent For this type of study informed consent is not required.

Consent for publication For this type of study consent for publication is not required.

Competing interests The authors declare no competing interests.

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