ORIGINAL ARTICLE

UDC: 613.73:616.379-008.64-074/-078
https://doi.org/10.2298/VSP170319083T

Correlation between coagulation and inflammation state in patients with diabetes mellitus type 2 in relation to gender differences: is there any impact of eight-week exercise training?

Korelacija između koagulacionog i inflamatornog statusa kod bolesnika sa dijabetesom melitusom tip 2 u odnosu na polne razlike: da li postoji uticaj 8-nedeljnog vežbanja?

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Abstract

Background/Aim. The hypercoagulable state and inflammation state in diabetics has been widely studied by previous researchers, but there is a lack of research about a possible impact of exercise training on this relationship. The aim of this study was to assess and compare correlation between the coagulation and inflammation status in patients with type 2 diabetes mellitus taking into account the gender differences as well as an impact of the 8-week exercise training on the correlation coefficient and parameters of the inflammation and coagulation state. **Methods.** A total of 60 patients in stable clinical condition and well-regulated diabetic status passed through all phases of the study. The exercise training included the exercise program as interval training with estimated intensity uphill to 75% of a maximal heart rate in particular individual, 5 times a week for 8 weeks, and walking for 30 minutes with a speed of 5 km/h, 5 times a week for 8 weeks. Further fibrinolytic, coagulation and inflammatory parameters were analyzed before and after the study: D-dimer, von Willebrand factor (vWF), fibrinogen, high sensitivity CRP (hs-CRP), leukocytes, thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT) and coagulation factors: FII, FV, FVII and FX. **Results.** Our research showed a statistically significant reduction in the mean vWF levels after intervention both at the males ($p < 0.001$) and females ($p < 0.001$). According to a correlation analysis between hs-CRP and fibrinogen, there was a positive correlation as baseline both at the males ($p < 0.05$, $r = 0.492$) and females ($p < 0.01$, $r = 0.516$) which became weaker in the males ($p < 0.01$, $r = 0.449$) and disappeared in the females ($p < 0.05$, $r = 0.059$) after intervention. The correlation which existed as baseline in the males between D-dimer and either hs-CRP ($p < 0.01$, $r = 0.633$) or fibrinogen ($p < 0.01$, $r = 0.673$) as well as the correlation between hs-CRP and FII ($p < 0.01$, $r = 0.728$), FV ($p < 0.05$, $r = 0.366$), FVII ($p < 0.05$, $r = 0.373$) coagulation as well as between D-dimer and FII ($p < 0.01$, $r = 0.851$), FVII ($p < 0.05$, $r = 0.367$)was absent in the females. Our research demonstrated a weakening correlations in the males after intervention between D-dimer and hs-CRP ($p < 0.05$, $r = 0.378$), between hs-CRP and FII ($p < 0.01$, $r = 0.501$), FV ($p < 0.05$, $r = 0.298$), FVII ($p < 0.05$, $r = 0.351$) as well as between D-dimer and FII ($p < 0.01$, $r = 0.759$), and FVII ($p < 0.05$, $r = 0.296$). The increase of the FX values ($p < 0.05$) in the females after intervention suggested the possible antiinflammatory effect of exercise training. **Conclusion.** According to previous research, the higher levels of vWF was associated with a risk of cardiovascular disease in people with type 2 diabetes mellitus and vWF may be a risk factor unique to these populations. We demonstrated that the 8-week exercise training can significantly reduce the value of vWF in the males and females, suggesting a potential beneficial effect on the endothelial function parameters. Our research demonstrated a stronger correlation between the coagulation and inflammation parameters as baseline in the males than in the females with type 2 diabetes mellitus. According to our results, the 8-week exercise training lead to a weakening of the strength of correlation between the coagulation and inflammation parameters in the males and complete disappearance of this correlation in the females, suggesting a unique effect of exercise training that should be explored in future research.

Key words:
diabetes mellitus, type 2; blood coagulation; inflammation; exercise; sex.

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Apstrakt

Uvod/Cilj. Hiperkoagulacioni i inflamatorni status kod dijabetičara je opsežno proučavan u dosadašnjim istraživanjima, ali je mogući uticaj fizičkog treninga na međusobnu povezanost između koagulacionog i inflamatornog statusa nedovoljno istražen. Cilj našeg istraživanja bio je ispitivanje korelacija između inflamatornog i koagulacionog statusa kod bolesnika sa dijabetesom melitusom tip 2 u odnosu na pol, kao i uticaj fizičkog treninga na jačinu ovih korelacija i parametre koagulacionog i inflamatornog statusa. **Metode.** U istraživanje je bilo uključeno 60 bolesnika u stabilnom kliničkom stanju sa dobro regulisanim dijabetesom melitusom tip 2. Trening je primenjen u vidu intervalnog treninga sa maksimalnim intenzitetom od 75% maksimalne srčane frekvence, pet puta nedeljno u toku osam nedelja i treninga u vidu hoda brzinom od 5 km/h u trajanju od trideset minuta, pet puta nedeljno u toku osam nedelja. Sledeći fibinolitički, koagulacioni i inflamatorni parametri su analizirani pre i posle sprovedenog programa treninga: D-dimer, von Willebrand factor (vWF), fibrinogen, visokosenzitivni C-reaktivni protein (hs-CRP), leukociti, trombinsko vreme (TT), protrombinsko vreme (PT), aktivirano parcijalno tromboplastinsko vreme (APTT) i faktori koagulacije – FII, FV, FVII i FX. **Rezultati.** Naše istraživanje je pokazalo statistički značajno smanjenje nivoa vWF posle studije kod ispitanika muškog ($p < 0,001$) i ženskog pola ($p < 0,001$). Pozitivna korelacija između hs-CRP i fibrinogena, pokazana bazalno kod ispitanika muškog ($p < 0,05$, $r = 0,492$) i ženskog pola ($p < 0,01$, $r = 0,516$) koja bila je slabija kod ispitanika muškog pola ($p < 0,01$, $r = 0,449$), odnosno, gubila se kod ispitanica ženskog pola ($p < 0,05$, $r = 0,059$) nakon sprovedenog treninga. Pokazane su pozitivne bazalne korelacije kod ispitanika muškog pola između D-dimera sa jedne strane i hs-CRP ($p < 0,01$, $r = 0,633$) i fibrinogena ($p < 0,01$, $r = 0,673$) sa druge strane, kao i između hs-CRP i FII ($p < 0,01$, $r = 0,728$), FV ($p < 0,05$, $r = 0,366$), FVII ($p < 0,05$, $r = 0,373$, kao i između D-dimera i FII ($p < 0,01$, $r = 0,851$) i FVII ($p < 0,05$, $r = 0,367$), dok te korelacije nisu pokazane kod ispitanica ženskog pola. Naše istraživanje je kod ispitanika muškog pola pokazalo slabljenje jačine korelacija nakon sprovedenog treninga između D-dimera i hs-CRP ($p < 0,05$, $r = 0,378$), hs-CRP i FII ($p < 0,01$, $r = 0,501$), FV ($p < 0,05$, $r = 0,298$), FVII ($p < 0,05$, $r = 0,351$), kao i između D-dimera i FII ($p < 0,01$, $r = 0,759$), i FVII ($p < 0,05$, $r = 0,296$). Smanjenje nivoa FX kod ispitanica ženskog pola ($p < 0,05$) nakon sprovedenog treninga ukazuje na mogući antiinflamatorni efekat fizičkog treninga. **Zaključak.** Prema predhodnim istraživanjima, vWF može biti faktor rizika u populaciji dijabetičara i njegov povišeni nivo je povezan sa rizikom od nastanka kardiovaskularnog oboljenja. Mi smo pokazali da fizički trening u trajanju od osam nedelja može znacajno smanjiti nivo vWF kod oba pola, ukazujući na potencijalni povoljni efekat na parametre endotelne funkcije. Naše istraživanje je pokazalo veću jačinu korelacija između koagulacionih i inflamatornih parametara kod ispitanika muškog pola u odnosu na ispitanice ženskog pola. Prema našim rezultatima, osmonedeljni fizički trening dovodi do slabljenja jačine korelacija između koagulacionih i inflamatornih parametara kod ispitanika muškog pola i slabljenje ovih korelacija do potpunog gubitka kod ispitanica ženskog pola, ukazujući na jedinstveni efekat fizičkog treninga koji bi trebalo da bude ispitan u budućim istraživanjima.

Ključne reči:
dijabetes melitus, insulin-nezavisni; krv, koagulacija; zapaljenje; vežbanje; pol.

Introduction

It is estimated that by 2025 the number of diabetics worldwide will have affected 324 million people and will have an epidemic character [1]. Diabetes mellitus alters blood coagulation and platelet function which supports the suggestion that diabetes mellitus is a hypercoagulable state with changes in fibrinolysis, decreased fibrinolytic activity and increased thrombotic risk [2, 3]. Correlation between the coagulation factors in diabetics is more evident than in health subjects and this may be the reason for the more hypercoagulable conditions stated in diabetics. Dayer et al. [4] (2014) found that a path model or diagram for the coagulation factors were more complicated in diabetic patients than in normal individuals and conveyed that a sudden increase in the synthesis of each coagulation factors or their activation may trigger the initiation of coagulation cascade, leading to vascular clot formation with myocardial consequences.

Adipose tissue releases mediators that induce a chronic inflammation state and alterations in coagulation [5]. The metabolic syndrome is frequently accompanied by a prothrombotic state. This includes the elevated plasma levels of von Willebrand factor (vWF), and coagulation factors: FVIII, FVII and fibrinogen [6]. D-dimer and fibrinogen are known to be the thrombosis risk factors [7, 8]. Elevation of D-dimer may increase a risk of future myocardial infarction, stroke, and peripheral vascular disease [9]. D-dimer indicate a low grade of the prothrombotic risk in patients with diabetes mellitus type 2, but a higher risk of vascular complications [10]. In type 2 diabetic patients with or without vascular complications fibrinogen concentrations do not indicate remarkable difference and may not be an important causal factor for vascular complications [11], and it was found that diabetics had more fibrinogen in blood than healthy subjects [12]. vWF is an acute phase protein and its plasma level increases in systemic inflammation. Hemostatic imbalance may contribute to the development of cardiovascular disease in patients with type 2 diabetes mellitus. In patients with diabetes mellitus there is a state of hypofibrinolysis and increased levels of vWF [13]. The elevated levels of vWF are correlated with atherosclerosis and are associated with endothelial dysfunction in type 2 diabetes, as well as the development of diabetes in post-infarction patients [14, 15]. A recent research has shown that the increased vWF and D-dimer levels were associated with renal dysfunction in patients with type 1 diabetes, suggesting that endothelial dysfunction and hypercoagulability were associated with nephropathy in type 1 diabetes [16]. Regular exercise training has anti-inflammatory effects and can reduce the risk

of future thrombotic events [17]. The coagulation cascade plays a critical role in the development of cardiovascular disease. Exercise training is known to reduce cardiovascular disease risk and through improved coagulation profile may contribute to this reduction [18]. Single physical training has thrombotic effect that results in an increase of the number and activity of platelets, but regular exercise training attenuates these effects and acting suppression of coagulation [19].

The aim of this study was to assess and compare correlation between the coagulation and fibrinolytic state relating to gender differences in diabetics with type 2 diabetes mellitus as well as an impact of exercise training both on the coagulation and fibrinolytic state and correlation between them.

Methods

Study design and study protocol

The study examined the impact of eight-week exercise training (EWET) interval on markers of fibrinolysis, coagulation and inflammation in the patients with well-regulated diabetes mellitus type 2 with regard to gender differences. The study was designed as longitudinal observational study. The study was conducted in accordance with the Declaration of Helsinki. All the procedures were previously approved by the Institutional Review Board and Ethics Committee of the Faculty of Medicine, University of Belgrade (06-17512/62-12, No. 22/XII-4-1 dd 22.03.2012). Sixty patients, 35 males and 25 females were enrolled in the study according to the inclusions criteria. The purpose of the study was clearly explained to the patients. All the subjects were informed about the study protocol and they provided their written consent before the beginning of the study. The investigation was performed in accordance with the ethical standards and according to the national and international guidelines. For the purpose of the fibrinolytic and coagulation states assessment, we analyzed D-dimer, vWF, fibrinogen level, thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT) and coagulation factors: FII, FV, FVII and FX. The inflammation status was assessed by the high sensitivity C-reactive protein (hs-CRP) levels and leukocytes count. Both fibrinolytic and coagulation states were evaluated before and after EWET.

Physical exercise protocols

The training under supervision consisted of the aerobic training with 30 minutes of brisk walking with a speed of 5 km/h and the exercise training program. The exercise training was of an interval mode with intensity that was estimated according to 75% of a maximum heart rate. The rest time between exercise sessions was equivalent of the time spent on exercises. The patients walked and trained 5 times a week for 8 weeks. Each exercise session was completed in 45 minutes and consisted of warm up for 10 minutes at 50% of a maximum heart rate in particular individual, intervals of 25 minutes at 75% of a maximum heart rate in particular individual and 10 minutes cool-down period at 50% of a maximum heart rate in particular individual. The exercise program included flexibility exercise, balance exercise, stretching, circles going forward, circles going backward, hip flexors stretch, hip circles, arm circles, walking on toes and heals, lunge and trunk rotation exercise.

The patients were selected on the basis of their medical history and 60 patients with well-regulated diabetes passed through all phases of the study. The inclusions criteria were the age between 40 and 60 years, a stable clinical condition and well-regulated diabetic status as revealed by glycated haemoglobin (HbA1c) in the range of 6.0–8.0%.

The patients on warfarin or heparin, which might affect APTT and fibrinogen, were excluded from the study. The exclusion criteria were recent surgery or illness, cardiac arrhythmias, abnormal ECG during exercise treadmill testing before the study, diabetic cardiomyopathy, uncontrolled hypertension, uncompensated heart failure, severe valvular heart disease and musculoskeletal conditions that would hinder safe completion of the proposed exercise protocols.

Coagulation tests

The analyzed parameters were evaluated by the samples of drown blood in the patients before meal in the morning period before and after intervention (the first day of the beginning of the study and one day after the last training session). All samples were assayed in duplicate. Venous blood (4.5 mL) for the test of fibrinogen, D-dimer, FII, FV, FVII and FX, APTT, TT and PT was collected in a fasting state into cooled tubes (Vacutainer® system) using 3.2% trisodium citrate as an anticoagulant, after centrifugation at 2,500 g for 15 minutes. All coagulation tests were performed by using the Beckman Coulter ACL Elite Pro, Coagulation Analyzer. APTT and TT were expressed directly in seconds (s), within a normal range of 24.3–35.0 s and 11.0–17.8 s. The PT results were reported in seconds (11.8–15.1s). The coagulation factors were expressed as ratio in %: FII (50.0%–150.0%), FV (62.0%–139.0%), FVII (50.0%–129.0%), FX (77.0%–131.0%). The reference value for D-dimer was 255 ng/mL and for fibrinogen, it was from 2.0 to 4.8 g/L. The determination of vWF Ag was performed by using the automated hemostasis analyzer Siemens BCS-XP (Siemens Healthcare Diagnostics Inc. Marburg/Germany, von Willebrand reagent REF OUBD37. The vWF Ag result was reported in percentage of normality. The reference value for vWF was from 55% to 200%. All plasma samples were stored in the polypropylene tubes at -80°C until used for the measurement. The Le count with the reference value 3.4-9.7 x 10^9/L was determined by using the ADVIA 120 Hematology System, Siemens. The high sensitivity CRP values with the reference value 0–5 mg/L were analyzed by the commercial kits of enzyme immunosorbent assay (ELISA).

Statistical analysis

The evaluated parameters were presented as mean values with standard deviation (SD). The Student's *t*-test was used to assess a statistical difference between the mean values where a

distribution was shown to be normal and the statistical significance was set at $p < 0.05$. The Pearson's correlation coefficient test was done in order to establish correlation between the continuous variables. The Student's *t*-test was used for the paired and unpaired samples to assess a statistical difference between the mean values where distribution was shown to be normal. The significance level of 0.05 was used for the correlation tests. The statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS, USA), version 19.0.

Results

Analysis of the average values of the evaluated parameters before and after EWET in relation to the gender differences (Tables 1 and 2), revealed that there was a significant decrease in the values of vWF in the males (t = 3.488, df = 34, $p < 0.005$) and the females ($t = 3.601$, df = 24, $p < 0.001$) as well as the values of the TT in the males ($t = 4.303$, df = 34, $p < 0.001$) and the females ($t = 3.401$, df = 24, $p < 0.005$) after EWET. There was the significant increase of the values of FVII both in the males within the normal range ($t = -4.354$, df = 34, $p < 0.001$) and the females (t = -4.398, df = 24 p < 0.001), and the FX in the females within the normal range ($t = -2.685$, df = 24, $p < 0.05$) after EWET. Other parameters showed the non-significant changes during the evaluation period (fibrinogen, PT, D-dimer, FII, FV, Le, APTT values) ($p > 0.05$).

The average reduction in the vWF value in the males was 10.32 with 95% confidence interval (CI) of 3.488. The eta-squared value (0.26) showed a large effect of intervention.

The average reduction in the TT value in the males was 0.828 s with 95% CI of 4.303. The eta-squared value (0.35) showed a large effect of intervention.

The average increase in the value of factor FVII coagulation in the males was -11.45 with 95% of the confidence interval -4.364. The eta-squared value(0.35) showed a large effect of intervention.

The average reduction in the vWF value in the females was 15.88% with 95% confidence interval of 3.601%. The eta-squared value (0.35) showed a large effect of intervention.

The average reduction in the value of TT in the females was 0.92 s with confidence interval of 3.401s. The eta-squared value (0.32) showed a large effect of intervention.

The average increase in the value of FVII in the females was 17.924% with 95% CI of -4.398%. The eta-squared value (0.44) showed a large effect of intervention.

The average increase in the value of FX in the females was 6.74% with 95% CI of 2.685%. The eta-squared value (0.23) showed a large effect of intervention.

According to the analysis of the average baseline values of the evaluated parameters in relation to gender differences before EWET (Table 3), there was a significant difference in the mean values for vWF between the males (106.25 ± 32.61%) (t = -1.38, df = 19) and the females (124.28 ± 24.62%) ($t = -1.396$, df = 18.77) ($p < 0.05$) with the values within the normal range. Other parameters showed the non-significant changes as baseline (TT, fibrinogen, PT, D-dimer, F II, FV, FVII, FX, leukocytes, hs-CRP, APTT values) ($p > 0.05$) (Table 1).

According to the analysis of the average values for the evaluated parameters in relation to the gender differences after EWET (Table 4), there were the significant differences in mean values for fibrinogen between the males (4.75 ± 1.06 g/L) (t = -2.02, df = 58) and the females (5.27 ± 0.88 g/L) (t = -2.08, df = 56.57) ($p < 0.05$), FV between the males (113.88 ± 20.37%) (t = -2.12, df = 58) and the females (131.80 ± 22.63%) (t = -2.13, df = 52.24) ($p < 0.05$), FVII between the males (114.05 ± 19.01%) (t = -3.291, df = 58) and the females (131.80 ± 22.63%) (t = -3.196, df = 46.04) ($p < 0.005$), FX between the males (102.21 ± 16.58%) (t = -2.75, df = 58) ($p < 0.01$) and the females (113.08 ± 12.59%) (t = -2.88, df = 57.76) ($p < 0.01$) with all values within the normal range.

According to the analysis of correlation between baseline inflammation and coagulation parameters in the males before EWET (Table 5), there was a very strong positive correlation between D-dimer and FII (t = 0.85, $p < 0.01$). There was a strong positive correlation between hs-CRP and FII (t = 0.78, $p < 0.01$), and hs-CRP and D-dimer (t = 0.63, $p < 0.01$), D-dimer and fibrinogen (t = 0.67, $p < 0.01$), fibrinogen and FII (t = 0.64, $p < 0.01$). There is a week positive correlation between hs-CRP and FV (r = 0.366, $p < 0.05$), hs-CRP and FVII (r = 0.373, $p < 0.05$), hs-CRP and Le (r = 0.355, $p < 0.05$), and FVII and D-dimer (r = 0.37, $p < 0.05$). There were the significant positive moderate correlations between hs-CRP and fibrinogen (r = 0.49, $p < 0.05$), hs-CRP and FX (r = 0.40, $p < 0.05$), fibrinogen and FV coagulation (r = 0.47, $p < 0.01$).

According to the analysis of correlation between baseline inflammation and coagulation parameters in the females before EWET (Table 6), there were the significant moderate positive correlations between hs-CRP and fibrinogen (r = 0.52, $p < 0.05$), and FII (r = 0.52, $p < 0.01$).

According to the analysis of correlation between the inflammation and coagulation parameters in the males after EWET (Table 7), there were strong positive correlations between D-dimer and fibrinogen (r = 0.72, $p < 0.01$), D-dimer and FII (r = 0.76, $p < 0.01$), fibrinogen and FII (r = 0.61, $p < 0.05$). Also, there were the significant moderate positive correlations between CRP and fibrinogen (r = 0.45, $p < 0.01$), Le and fibrinogen (r = 0.52, $p < 0.01$), hs-CRP and FII (r = 0.50, $p < 0.05$). There were the significant weak positive correlations between CRP and FVII (r = 0.35, $p < 0.05$), fibrinogen and FV (r = 0.35, $p < 0.05$), D-dimer and FV (r = 0.39, $p < 0.05$).

According to the analysis of correlation between the inflammation and coagulation parameters in the females after EWET (Table 8), the negative correlation between D-dimer and hs-CRP (r = -0.46, $p < 0.05$) was demonstrated.

Table 1
Average values of evaluated parameters before and after the 8-week exercise training (EWET) in the males with diabetes mellitus type 2

Parameters relative to EWET	Mean ± SD	*p*
vWF (%) (55–200) #		
before	106.26 ± 32.618	< 0.001*
after	95.94 ± 32.685	
Thrombin time (s) (11.0–17.8)#		
before	14.63 ± 1.34	< 0.001*
after	13.84 ± 1.07	
Fibrinogen (g/L) (2.0–4.8) #		
before	4.65 ± 1.09	> 0.05
after	4.75 ± 1.06	
Prothrombin time (s) (11.8–15.1) #		
before	13.86 ± 0.99	> 0.05
after	13.69 ± 0.95	
D-dimer (ng/mL) (255)#		
before	206.52 ± 141.47	> 0.05
after	206.58 ± 137.85	
Factor II (%) (50–150) #		
before	130.20 ± 136.32	> 0.05
after	134.02 ± 119.07	
Factor V (%) (62–139) #		
before	112.76 ± 19.03	> 0.05
after	113.88 ± 20.37	
Factor VII (%) (50–129)		
before	102.60 ± 22.84	< 0.001*
after	114.05 ± 19.01	
Factor X (%) (77–131)#		
before	97.71 ± 19.70	> 0.05
after	102.21 ± 16.58	
Hs-CRP (mg/L) (0–5)#		
before	1.80 ± 2.55	> 0.05
after	2.20 ± 3.25	
APTT (s) (24.3–35.0)#		
before	26.50 ± 2.19	> 0.05
after	26.34 ± 2.35	
Leukocytes (10^9/L) (3.4–9.7)#		
before	6.85 ± 2.14	> 0.05
after	7.13 ± 1.79	

#normal value; *significant correlation at $p < 0.05$;
vWF – won Willebrand factor; CRP – C-reactive protein; Hs-CRP – high sensitivity CRP; APTT – activated partial thromboplastin time; SD – standard devations.

Table 2
Average values of the evaluated parameters before and after the 8-week exercise training (EWET) in the females with diabetes mellitus type 2

Parameters relative to EWET	Mean ± SD	*p*
vWF (%) (55–200) #		
before	124.28 ± 24.62	< 0.001*
after	108.40 ± 23.65	
Thrombin time (s) (11.0–17.8) #		
before	14.94 ± 1.32	< 0.005*
after	14.02 ± 1.05	
Fibrinogen (g/L) (2.0–4.8) #		
before	5.21 ± 1.20	> 0.05
after	5.27 ± 0.88	
Prothrombin time (s) (11.8–15.1) #		
before	13.56 ± 0.72	> 0.05
after	13.64 ± 0.74	
D-dimer (ng/L) (255) #		
before	208.16 ± 55.30	> 0.05
after	211.64 ± 94.86	
Factor II (%) (50–150) #		
before	118.71 ± 29.88	> 0.05
after	121.80 ± 15.79	
Factor V (%) (62–139) #		
before	118.69 ± 21.95	> 0.05
after	125.15 ± 20.12	
Factor VII (%) (50–129) #		
before	113.87 ± 23.10	< 0.001*
after	131.80 ± 22.63	
Factor X (%) (77–131) #		
before	106.34 ± 12.74	< 0.05*
after	113.08 ± 12.59	
Hs-CRP(mg/L) (0–5) #		
before	2.55 ± 2.57	> 0.05
after	2.49 ± 2.04	
APTT (s) (24.3–35.0) #		
before	25.62 ± 2.55	> 0.05
after	25.48 ± 2.49	
Leukocytes(10^9/L) (3.4–9.7) #		
before	7.44 ± 1.60	> 0.05
after	6.91 ± 1.45	

#normal value; *significant correlation at $p < 0.05$;
vWF – won Willebrand factor; CRP – C-reactive protein; Hs-CRP – high sensitivity CRP; APTT – activated partial thromboplastin time; SD – standard devations.

Table 3

Average values of the evaluated parameters before the 8-week exercise training (EWET) in the males and females with diabetes mellitus type 2

Parameters	Sex	Mean ± SD	*p*
vWF (%)	m	106.26 ± 32.61	< 0.05*
(55–200) #	f	124.28 ± 24.62	
Thrombin time (s)	m	14.63 ± 1.34	> 0.05
(11.0–17.8)	f	14.94 ± 1.32	
Fibrinogen (g/L)	m	4.65 ± 1.09	> 0.05
(2.0–4.8) #	f	5.21 ± 1.20	
Prothrombin time(s)	m	13.86 ± 0.99	> 0.05
(11.8–15.1) #	f	13.56 ± 0.72	
D-dimer (ng/L)	m	206.52 ± 141.47	> 0.05
(255)	f	208.16 ± 55.30	
Factor II (%)	m	130.20 ± 136.32	> 0.05
(50–150) #	f	118.71 ± 29.88	
Factor V (%)	m	112.76 ± 19.03	> 0.05
(62–139) #	f	118.69 ± 21.95	
Factor VII (%)	m	102.60 ± 22.84	> 0.05
(50–129) #	f	113.87 ± 23.10	
Factor X (%)	m	97.71 ± 19.70	> 0.05
(77–131) #	f	106.34 ± 12.74	
Hs-CRP (mg/L)	m	1.80 ± 2.55	> 0.05
(0–5) #	f	2.55 ± 2.57	
APTT (s)	m	26.50 ± 2.19	> 0.05
(24.3–35.0) #	f	25.63 ± 2.55	
Leukocytes (10^9/L)	m	6.85 ± 2.14	> 0.05
(3.4–9.7) #	f	7.44 ± 1.60	

***Significant correlation at $p < 0.05$; m – males; f – females.**
For other abbreviations see under Tables 1 and 2.

Table 4

Average values of the evaluated parameters after the 8-week exercise training (EWET) in the males and females with diabetes mellitus type 2

Parameters	Sex	Mean ± SD	*p*
vWF (%)	m	95.94 ± 32.685	> 0.05
(55–200) #	f	108.40 ± 23.656	
Thrombin time (s)	m	13.84 ± 1.07	> 0.05
(11.0–17.8)	f	14.02 ± 1.05	
Fibrinogen (g/L)	m	4.75 ± 1.06	< 0.05*
(2.0–4.8) #	f	5.27 ± 0.88	
Prothrombin time(s)	m	13.69 ± 0.95	> 0.05
(11.8–15.1) #	f	13.64 ± 0.74	
D-dimer (ng/L)	m	211.42 ± 138.79	> 0.05
(255)	f	211.64 ± 94.86	
Factor II (%)	m	134.02 ± 119.07	> 0.05
(50–150) #	f	121.80 ± 15.79	
Factor V (%)	m	113.88 ± 20.37	< 0.05*
(62–139) #	f	125.15 ± 20.12	
Factor VII (%)	m	114.05 ± 19.01	< 0.005*
(50–129) #	f	131.80 ± 22.63	
Factor X (%)	m	102.21 ± 16.58	< 0.01*
(77–131) #	f	113.08 ± 12.59	
Hs-CRP (mg/L)	m	2.20 ± 3.25	> 0.05
(0–5) #	f	2.55 ± 1.97	
APTT (s)	m	26.34 ± 2.35	> 0.05
(24.3–35.0) #	f	25.48 ± 2.49	
Leukocytes (10^9/L)	m	7.13 ± 1.79	> 0.05
(3.4–9.7) #	f	6.91 ± 1.45	

***Significant correlation at $p < 0.05$.**
For other abbreviations see under Tables 1 and 2.

Table 5

Correlation between the baseline inflammation and coagulation parameters before the 8-week exercise training (EWET) in the males with diabetes mellitus type 2

Parameters before	CRP		D-dimer		Fibrinogen		vWF	
EWET	test values	*p*	test values	*p*	test values	*p*	test values	*p*
Fibrinogen	0.492*	< 0.05	0.673**	< 0.01	1		-0.044	> 0.05
Factor II	0.728**	< 0.01	0.851**	< 0.01	0.637**	< 0.01	-0.211	> 0.05
Factor V	0.366**	< 0.05	0.327	> 0.05	0.467**	< 0.01	-0.185	> 0.05
Factor VII	0.373*	< 0.05	0.367*	< 0.05	0.174	> 0.05	-0.021	> 0.05
Factor X	0.400*	< 0.05	0.232	> 0.05	0.152	> 0.05	0.093	> 0.05
vWF	-0.144	> 0.05	-0.220	> 0.05	-0.044	> 0.05	1	
APTT	0.118	> 0.05	0.043	> 0.05	0.182	> 0.05	-0.007	> 0.05
Thrombin time	-0.070	> 0.05	-0.130	> 0.05	-0.542**	< 0.01	0.022	> 0.05
Prothrombin time	-165	> 0.05	-0.242	> 0.05	-0.385	> 0.05	-0.012	> 0.05
Leukocytes	0.355*	< 0.05	0.203	> 0.05	0.298	> 0.05	-0.292	> 0.05
Hs-CRP	1		0.633**	< 0.01	0.492*	> 0.05	-0.144	> 0.05
D-dimer	0.633**	< 0.01	1		0.673**	< 0.01	-0.220	> 0.05

***Correlation is significant at the 0.05 level (2-tailed);**Correlation is significant at the 0.01 level (2-tailed).**
For other abbreviations see under Table 1.

Table 6

Correlation between the inflammation and coagulation parameters before the 8-week exercise training (EWET) in the females with diabetes mellitus type 2

Parameters before EWET	CRP		D-dimer		Fibrinogen		vWF	
	test values	*p*	test values	*p*	test values	*p*	test values	*p*
Fibrinogen	0.516*	< 0.01	-0.172	> 0.05	1		-0.224	> 0.05
Factor II	0.069	> 0.05	-0.294	> 0.05	0.518**	< 0.01	-0.206	> 0.05
Factor V	0.025	> 0.05	-0.083	> 0.05	0.158	> 0.05	0.370*	< 0.05
Factor VII	0.021	> 0.05	0.140	> 0.05	0.174	> 0.05	0.383*	< 0.05
Factor X	0.050	> 0.05	-0.092	> 0.05	0.052	> 0.05	0.384*	< 0.05
vWF	0.100	> 0.05	0.127	> 0.05	-0.224	> 0.05	1	
APTT	-0.213	> 0.05	-0.238	> 0.05	-0.214	> 0.05	-0.139	> 0.05
Thrombin time	-0.435*	< 0.05	-0.065	> 0.05	-0.752**	< 0.01	0.107	> 0.05
Prothrombin time	-0.318	> 0.05	-0.141	> 0.05	-0.074	> 0.05	-0.297	> 0.05
Leukocytes	-0.045	> 0.05	0.128	> 0.05	0.308*	< 0.05	-0.286	> 0.05
Hs-CRP	1		-0.372	> 0.05	0.516*	< 0.05	0.100	> 0.05
D-dimer	-0.372	> 0.05	1		-0.172	> 0.05	0.127	0.05

***Correlation is significant at the 0.05 level (2-tailed);**Correlation is significant at the 0.01 level (2-tailed).**
For other abbreviations see under Tables 1 and 2.

Table 7

Correlation between the inflammation and coagulation parameters after the 8-week exercise training (EWET) in the males with diabetes mellitus type 2

Parameters after EWET	CRP		D-dimer		Fibrinogen		vWF	
	test values	*p*	test values	*p*	test values	*p*	test values	*p*
Fibrinogen	0.449**	< 0.01	0.722**	< 0.01	1		-0.039	> 0.05
Factor II	0.501**	< 0.01	0.759**	< 0.01	0.607**	< 0.01	-0.114	> 0.05
Factor V	0.297	> 0.05	0.389*	< 0.05	0.348*	< 0.05	-0.052	> 0.05
Factor VII	0.351*	< 0.05	0.296	> 0.05	0.232	> 0.05	-0.144	> 0.05
Factor X	0.267	> 0.05	0.430**	< 0.01	0.336*	< 0.05	-0.170	> 0.05
vWF	-0.101	> 0.05	0.055	> 0.05	-0.039	> 0.05	1	
APTT	0.220	> 0.05	-0.120	> 0.05	0.198	> 0.05	-146	> 0.05
Thrombin time	-0.083	> 0.05	-0.034	> 0.05	-0.340	> 0.05	-0.033	> 0.05
Prothrombin time	-0.195	> 0.05	-0.174	> 0.05	-0.262	> 0.05	-0.296	> 0.05
Leukocytes	0.252	> 0.05	0.363*	< 0.05	0.523**	< 0.01	0.236	> 0.05
Hs-CRP	1		0.378*	< 0.05	0.449*	< 0.05	-0.101	> 0.05
D-dimer	0.378*	< 0.05	1		0.722**	< 0.01	-0.041	> 0.05

***Correlation is significant at the 0.05 level (2-tailed);**Correlation is significant at the 0.01 level (2-tailed).**
For other abbreviations see under Tables 1 and 2.

Table 8

Correlation between the inflammation and coagulation parameters after the 8-week exercise training (EWET) in the females with diabetes mellitus type 2

Parameters after EWET	CRP		D-dimer		Fibrinogen		vWF	
	test values	*p*	test values	*p*	test values	*p*	test values	*p*
Fibrinogen	0.059	> 0.05	0.006	> 0.05	1		-0.115	> 0.05
Factor II	-0.068	> 0.05	-0.413*	< 0.05	0.432*	< 0.05	-0.171	> 0.05
Factor V	-0.123	> 0.05	-0.224	> 0.05	0.031	> 0.05	-0.042	> 0.05
Factor VII	0.011	> 0.05	-0.116	> 0.05	-0.136	> 0.05	0.105	> 0.05
Factor X	-0.053	> 0.05	-0.126	> 0.05	0.082	> 0.05	-0.138	> 0.05
vWF	0.059	> 0.05	-0.018	> 0.05	0.102	> 0.05	1	
APTT	-0.086	> 0.05	0.272	> 0.05	0.031	> 0.05	-0.173	> 0.05
Thrombin time	-0.010	> 0.05	0.104	> 0.05	-0.144	> 0.05	-0.108	> 0.05
Prothrombin time	-0.208	> 0.05	0.400	> 0.05	0.109	> 0.05	-0.308	> 0.05
Leukocytes	-0.327	> 0.05	0.058	> 0.05	0.180	> 0.05	0.013	> 0.05
Hs-CRP	1		-0.465*	< 0.05	0.059	> 0.05	0.059	> 0.05
D-dimer	-0.465*	< 0.05	1		0.006	> 0.05	-0.018	> 0.05

***Correlation is significant at the 0.05 level (2-tailed);**Correlation is significant at the 0.01 level (2-tailed).**
For other abbreviations see under Tables 1 and 2.

Discussion

The present study was undertaken to explore the correlation between the inflammation and coagulation state as well as an impact of exercise training on this correlation in diabetics. WF is associated with cardiovascular disease, type 2 diabetes mellitus and insulin resistance. The higher levels of vWF are associated with a risk of cardiovascular disease in people with type 2 diabetes mellitus or insulin resistance, which suggests that vWF may be a risk factor unique to these populations. In addition, the elevated levels of vWF are associated with an increased risk of cardiovascular disease in a community-based sample, even after accounting for traditional cardiovascular disease risk factors [20].

Our study showed a significant decrease in the values of vWF both in the males ($p < 0.005$) and females ($p < 0.001$) with diabetes mellitus type 2 after EWET and these results correlated with recent researches. Creighton et al. [21] explored the effects of an acute resistance exercise test on the primary hemostatic system both in resistance-trained and untrained individuals and concluded that reduced vWF in both groups may be attributed to the training status. Androulakis et al. [22] examined whether a high volume of training could lead to the endothelial activation and/or dysfunction in professional soccer players due to exercise-induced oxidative stress and vWF antigen plasma levels were measured 1 day before and after 7 weeks of strenuous exercise. It was showed that the mean vWF Ag plasma levels were significantly decreased from 95.1% ± 26% to 88.3% ± 27.2% at the end of the experimental period ($p = 0.018$), suggesting a potential beneficial effect on the endothelium. According to Jahangard et al. [23], vWF showed a significant reduction after 10 sessions of submaximal aerobic cycling in sedentary healthy postmenopausal women. We found the the significant differences in the mean values for vWF between the males (106.25 ± 32.61%) and the females (124.28 ± 24.62%) ($p < 0.05$) as baseline with a higher value in the females within the reference value.

We showed the significant decreases in the values of TT both in the males ($p < 0.001$) and females ($p < 0.005$) after EWET. Our findings demonstrated no differences in APTT, PT and FII coagulation in diabetics and they were consistent with the results obtained by Lamprechts et al. [24] that showed no statistically significant differences between pre- and post a single bout of walking exercise in APTT, FII coagulation and PT in the obese women. A short-term exercise in healthy subjects is usually associated with a significant shortening of APTT [25, 26], but according to our results there was no differences in APTT after regular eight- week training. According to Lockard et al. [18] plasma prothrombin fragment was found to decrease significantly with exercise training three times a week in six months.

We found that the values of fibrinogen were distinctly above normal in the females both as baseline and after study and similar findings were reported by Kafle and Shrestha [12]. They found a significantly higher fibrinogen in patients with diabetes than in controls and showed that fibrinogen was significantly higher in diabetic patients with coronary artery disease than in those patients who had only diabetes or coronary artery disease. We found no changes in fibrinogen concentration after intervention and these findings correlated with a research of Bizheh and Jaafari al. [27] who examined an effect of a single bout resistance exercise in sedentary middle aged men on fibrinogen. According to a recent investigation, physical training reduced fibrinogen concentration in patients with coronary heart diseases who had long-term physical training. It was determined that fibrinogen concentration significantly increased after physical load in all the treatment stages both in the coronary heart disease and the control group, while fibrinogen concentration gradually decreased in the group of the trained patients after 1 year [28], supporting that physical training lasting for a longer period could effectively reduce fibrinogen concentration.

A recent study showed a correlation between hs-CRP and D-dimer in patients with pulmonary embolism [29]. According to our research, a stronger baseline correlation was found between hs-CRP and D-dimer than between hs-CRP and fibrinogen in the males as baseline. In the females, a strong positive correlation between hs-CRP and fibrinogen as baseline was demonstrated, but there was no correlation between those parameters after the study. In the females, a negative correlation was demonstrated between hs-CRP and D-dimer both as baseline and after the study. According to the Speedwell Study, a positive correlation was shown between hs-CRP and D-dimer and a much stronger association between hs-CRP and fibrinogen in heart disease [30], and these findings correlate with our findings as baseline. Also, according to a recent research, hs-CRP correlated positively with fibrinogen and D-dimer in hemodialysis patients [31]. These findings correlate with our findings which showed a strong positive correlation between hs-CRP and either D-dimer or fibrinogen in the males as baseline. In addition, we demonstrated a weakness of this correlation in the males after EWET.

According to Long et al. [32] , D-dimer did not correlate positively with fibrinogen in diabetics. In our study, there was no correlation found between D-dimer and fibrinogen but only in the females. We demonstrated a strong correlation between D-dimer and fibrinogen in the males both before and after the study.

FII is the main cause for hypercoagulable state and the last target of coagulation cascade either from intrinsic or extrinsic origin and they play a determinant role in initiation of vascular complications in diabetics, while D-dimer indicate a higher risk of vascular complications in patients with diabetes mellitus type 2. According to our study, it was demonstrated that a strong correlation between D-dimer and FII in the males became moderate after the study. In the females, there was a negative correlation between D-dimer and FII either as baseline or after the study.

We demonstrated no change in hs-CRP concentration in our study which correlated with the research done by Levinger et al. [33] on 56 middle-aged men and women. They showed that 10 weeks of resistance training did not alter significantly the hs-CRP expression. In our research, we demonstrated a strong correlation between hs-CRP and FII in the males as baseline, and a moderate correlation after intervention, suggesting a potential benefit of EWET on the rela-

tionship between coagulation and inflammation. In addition, we showed no correlation between hs-CRP and FII in the females either before or after the study, pointing to a weaker association between coagulation and inflammation in the females in comparison with the males.

According to the analysis of correlation between baseline inflammation and coagulation parameters in the males before our study, there was a strong positive correlation between D-dimer and either FII or fibrinogen as baseline that stayed strong after the intervention, while those correlation were negative in the females both before and after the study. We found a weakness in correlation between hs-CRP and either fibrinogen, FII, FV, FVII, FX, Le or D-dimer in the males after the study, supporting effectiveness of the intervention.

In a recent research, Dayer et al. [34] obtained correlation between FV and vWF in diabetics which was absent in a normal mode, and, in addition, FV may bind to vWF [4], and both findings correlated with our findings. We demonstrated a moderate correlation between vWF and either FV, FII or FX but only in the females, which completely disappeared after the study, suggesting potential effect of the 8-week training. We obtained moderate correlation between fibrinogen and FV in the males as baseline, and a weak correlation after 8-week training suggesting both the higher coagulation state and anti-coagulation effects of intervention in the males, while there was no correlation between fibrinogen and FV in the females either before or after the training, suggesting a lower coagulation state in the females.

A recent study which investigated the correlation of the coagulation indicators with the inflammatory markers for sepsis in hematologic malignancy patients demonstrated that the level of procalcitonin positively correlated with the APTT and D-dimer level [35]. Our study showed the significant moderate positive correlation between hs-CRP and fibrinogen both in the males and females as baseline as well as in the males after EWET, but no correlation between hs-CRP and fibrinogen in the females after the 8-week training. Similar results were reported by Thor et al. [36] as a strong positive correlation between hs-CRP and fibrinogen particularly in diabetics which correlated with our findings. In addition, they reported a correlation between hs-CRP and either fibrinogen or vWF in diabetics. According to them, there was no correlation between fibrinogen and other markers of hypercoagulability, thrombin-anti thrombin, prothrombin and D-dimer, although the last three ones correlated with each other. In our study there was no correlation between vFW and hs-CRP. We showed a correlation between hs-CRP and fibrinogen in the males both as baseline and after the training, and, in addition, we showed a positive correlation between hs-CRP and fibrinogen as baseline in the females, which became not significant after the training. This result supports an anti-inflammatory effect of EWET.

According to Alehagen et al. [37], patients with suspected heart failure and low plasma concentrations of FII, FVII and FXI had significantly higher mortality rate during the follow-up period of 10 years as compared with those with a higher plasma concentrations. Increasing in plasma concentrations of FII and FVII after exercise training may indicate a protective effect of training on mortality and a protective effect of exercise training on hemorrhage. We demonstrated significant increase within the normal range of FVII in the males and little above normal range in the females after EWET, suggesting a protective effect of training on mortality. According to Ruiz-Saez [38] afibrinogenemia, FVII or FXI deficiencies are the ones most commonly associated with venous or arterial thrombosis. FVIIa is significantly higher in the patients with type 2 diabetes mellitus [39]. FVII deficiency is an uncommon coagulation disorder that patient usually presents with bleeding diathesis, but thrombotic event was reported in patients with acute ishemic stroke [40]. Increasing of the FVII levels in our study may indicate possible reduction of a risk for venous or arterial thrombosis after 8-week training.

The function of FXa is unclear. Interesting results were recently reported by Ku and Bae [41]. The expression level of the secretory group IIA phospholipase A2 is elevated in inflammatory diseases and lipopolysaccharide upregulates the expression. FXa suppressed the activation of cytosolic phospholipase A2 and extracellular signal-regulated kinase by lipopolysaccharide [41]. According to a study by Bukowska et al. [42], FXa mediates inflammatory signaling in atrial tissue by inducing an inflammatory signaling by activation of protease-activated receptors. Gleeson et al. [43] pointed out to the novel function concerning the FX as an endogenous, receptor-associated protein-sensitive, protease-activated receptor 2-dependent regulator of myeloid cell proinflammatory cytokine production. Further, exposure to the FX significantly impairs pro-inflammatory cytokine production. The FX inhibits the nuclear factor-kappa B activation in THP-1 reporter cells requires phosphatidylinositol 3-kinase activity for its anti-inflammatory effect [43]. We demonstrated a significant increase of the FX level in the females within the normal range after 8-week training. In addition, we demonstrated moderate positive correlation between hs-CRP and FX in the males as baseline that became weak correlation after the study, and none correlation between hs-CRP and FX in the females. The increase in the plasma concentration of the FX after EWET only in the females could suggest the possible anti-inflammatory effect of exercise training and should be examined in future research.

The main limitation of the present study is the relatively small number of patients, but the study enrolled both men and women in an adequate number to obtain the statistically significant results. The major advantage of the present study is an investigation of correlation between the inflammation and coagulation state in relation to two sexes with diabetes, which was insufficient in the previous researches. This longitudinal study may bring some new findings regarding effects of exercise training on treatment of patients with type 2 diabetes mellitus.

Conclusion

We demonstrated a statistically significant reduction in the mean vWF levels after EWET training both in the males and females with type 2 diabetes mellitus, suggesting a po-

tential beneficial effect on the endothelial function parameters. According to our research, a stronger correlation between the coagulation and inflammation parameters in the males than in the females as baseline was obtained, and, in addition, we obtained the weakening of correlation between the coagulation and inflammation parameters both in males and females after intervention, suggesting an anti-inflammatory and anticoagulant effect of 8-week training. The effect of exercise training on correlation between the coagulation and inflammation state in the patients with both well-controlled and poorly-controlled type 2 diabetes mellitus should be explored in future.

REFERENCES

1. *Cheng D*. Prevalence, predisposition and prevention of type II diabetes. Nutr Metab (Lond) 2005; 2: 29.
2. *Hilberg T, Eichler E, Gläser D, Schmidt V, Gabriel HH*. Platelet activity, reactivity and platelet-leukocyte conjugate formation before and after exhaustive or moderate exercise in patients with IDDM. Platelets 2004; 15(2): 101–8.
3. *Malý J*. Diabetes mellitus and prothrombotic activity. Vnitr Lek 2010; 56(4): 284–8.
4. *Dayer MR, Mard-Soltani M, Dayer MS, Alavi SM*. Interpretation of correlations between coagulation factors FV, FVIII and vWF in normal and type 2 diabetes mellitus patients. Pak J Biol Sci 2011; 14(9): 552–7.
5. *Stoppa-Vaucher S, Dirlewanger MA, Meier CA, de Moerloose P, Reber G,Roux-Lombard P,* et al. Inflammatory and prothrombotic states in obese children of European descent. Obesity (Silver Spring) 2012; 20(8): 1662–8.
6. *Previtali E, Bucciarelli P, Passamonti SM, Martinelli I*. Risk factors for venous and arterial thrombosis. Blood Transfus 2011; 9(2): 120–38.
7. *Prelipcean CC, Fierbinteanu-Braticevici C, Drug VL, Lăcătuşu C, Mihai B, Mihai C*. Liver cirrhosis-procoagulant stasis. Rev Med Chir Soc Med Nat Iasi 2011; 115(3): 678–85. (Romanian)
8. *Lelakowski J, Rydlewska A, Domagała TB, Piekarz J, Karkowski G, Januszek R,* et al. Venous thrombosis as a complication of pacemaker implantation--own observations. Pol Merkur Lekarski 2011; 30(176): 102–10. (Polish)
9. *Coban E, Ozdoğan M, Akçit F*. Levels of plasma fibrinogen and D-dimer in subjects with white-coat hypertension. J Hum Hypertens 2004; 18(4): 291–2.
10. *Ruszkowska-Ciastek B, Sokup A, Wernik T, Rhone P, Góralczyk K, Bielawski K,* et al. Low-grade risk of hypercoagulable state in patients suffering from diabetes mellitus type 2. J Zhejiang Univ Sci B 2015; 16(9): 788–95.
11. *Koh GC, Meijers JC, Maude RR, Limmathurotsakul D, Day NP, Peacock SJ*, et al. Diabetes does not influence activation of coagulation, fibrinolysis or anticoagulant pathways in Gram-negative sepsis (melioidosis). Thromb Haemost 2011; 106(6): 1139–48.
12. *Kafle DR, Shrestha P*. Study of fibrinogen in patients with diabetes mellitus. Nepal Med Coll J 2010; 12(1): 34–7.
13. *Verkleij CJ, Bruijn RE, Meesters EW, Gerdes VE, Meijers JC, Marx PF*. The hemostatic system in patients with type 2 diabetes with and without cardiovascular disease. Clin Appl Thromb Hemost 2011; 17(6): E57–63.
14. *Lim SC, Caballero AE, Smakowski P, LoGerfo FW, Horton ES, Veves A*. Soluble intercellular adhesion molecule, vascular cell adhesion molecule, and impaired microvascular reactivity are early markers of vasculopathy in type 2 diabetic individuals without microalbuminuria. Diabetes Care 1999; 22(11): 1865–70.
15. *Zareba W, Pancio G, Moss AJ, Kalaria VG, Marder VJ, Weiss HJ,* et al. Increased level of von Willebrand factor is significantly and independently associated with diabetes in postinfarction patients. THROMBO Investigators. Thromb Haemost 2001; 86(3): 791–9.
16. *Domingueti CP, Dusse LM, Fóscolo RB, Reis JS, Annichino-Bizzacchi JM, Orsi FL,* et al. Von Willebrand Factor, ADAMTS13 and D-Dimer Are Correlated with Different Levels of Nephropathy in Type 1 Diabetes Mellitus. PLoS One 2015; 10(7): e0132784.
17. *de Meirelles LR, Matsuura C, Resende Ade C, Salgado AA, Pereira NR, Coscarelli PG,* et al. Chronic exercise leads to antiaggregant, antioxidant and anti-inflammatory effects in heart failure patients. Eur J Prev Cardiol 2014; 21(10): 1225–32.
18. *Lockard MM, Gopinathannair R, Paton CM, Phares DA, Hagberg JM*. Exercise training-induced changes in coagulation factors in older adults. Med Sci Sports Exerc 2007; 39(4): 587–92.
19. *Ribeiro J, Almeida-Dias A, Oliveira AR, Mota J, Appell H, Duarte JA*. Exhaustive exercise with high eccentric components induces prothrombotic and hypofibrinolytic responses in boys. Int J Sports Med 2007; 28(3): 193–6.
20. *Frankel DS, Meigs JB, Massaro JM, Wilson PWF, O'Donnell CJ, D'Agostino RB*, et al. Von Willebrand factor, type 2 diabetes mellitus, and risk of cardiovascular disease: The framingham offspring study. Circulation 2008; 118(24): 2533–9.
21. *Creighton BC, Kupchak BR, Aristizabal JC, Flanagan SD, Dunn-Lewis C, Volk BM,* et al. Influence of training on markers of platelet activation in response to a bout of heavy resistance exercise. Eur J Appl Physiol 2013; 113(9): 2203–9.
22. *Androulakis NE, Koundourakis NE, Nioti E, Spatharaki P, Hatzisymeon D, Miminas I,* et al. Preseason preparation training and endothelial function in elite professional soccer players. Vasc Health Risk Manag 2015; 11: 595–9.
23. *Jahangard T, Torkaman G, Ghoosheh B, Hedayati M, Dibaj A*. The effect of short-term aerobic training on coagulation and fibrinolytic factors in sedentary healthy postmenopausal women. Maturitas 2009; 64(4): 223–7.
24. *Lamprecht M, Moussalli H, Ledinski G, Leschnik B, Schlagenhauf A, Koestenberger M,* et al. Effects of a single bout of walking exercise on blood coagulation parameters in obese women. J Appl Physiol 2013; 115(1): 57–63.
25. *Beltan E, Chalabi T, Tripette J, Chout R, Connes P*. Coagulation responses after a submaximal exercise in sickle cell trait carriers. Thromb Res 2011; 127(2): 167–9.
26. *el-Sayed MS*. Effects of exercise on blood coagulation, fibrinolysis and platelet aggregation. Sports Med 1996; 22(5): 282–98.
27. *Bizjeh N, Jaafari M*. The Effect of a Single Bout Circuit Resistance Exercise on Homocysteine, hs-CRP and Fibrinogen in Sedentary Middle Aged Men. Iran J Basic Med Sci 2011; 14(6): 568–73.
28. *Mongirdienė A, Kubilius R*. Effect of physical training on indices of platelet aggregation and fibrinogen concentration in patients with chronic heart failure. Medicina (Kaunas) 2015; 51(6): 343–50.
29. *Crop MJ, Siemes C, Berendes P, van der Straaten F, Willemsen S, Levin M*. Influence of C-reactive protein levels and age on the value of D-dimer in diagnosing pulmonary embolism. Eur J Haematol 2014; 92(2): 147–55.
30. *Lowe GD, Yarnell JW, Rumley A, Bainton D, Sweetnam PM*. C-reactive protein, fibrin D-dimer, and incident ischemic heart disease in the Speedwell study: Are inflammation and fibrin turnover linked in pathogenesis? Arterioscler Thromb Vasc Biol 2001; 21(4): 603–10

31. *Topçiu-Shufta V, Haxhibeqiri V, Begolli L, Baruti-Gafurri Z, Veseli S, Haxhibeqiri S,* et al. Correlation of Inflammation and Lipoprotein (a) with Hypercoagulability in Hemodialysis Patients. Med Arch 2015; 69(4): 232–5.
32. *Long ZF, Qu GY, Xu M.* Relationship between the level of plasma D-dimer and diabetic microangiopathy. Hunan YiKe Da Xue Xue Bao 2001; 26(5): 434–6. (Chinese)
33. *Levinger I, Goodman C, Peake J, Garnham A, Hare DL, Jerums G,* et al. Inflammation, hepatic enzymes and resistance training in individuals with metabolic risk factors. Diabet Med 2009; 26(3): 220–7.
34. *Dayer MR, Mard-Soltani M, Dayer MS, Alavi SM.* Causality relationships between coagulation factors in type 2 diabetes mellitus: Path analysis approach. Med J Islam Repub Iran 2014; 28: 59.
35. *Fu Y, Jiang H, Li LX, Chen J, Niu Q, Li RX.* Correlation of coagulation indicators with inflammatory markers for sepsis in the patients with hematological malignancies. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2014; 22(5): 1381–5. (Chinese)
36. *Thor M, Yu A, Swedenborg J.* Markers of inflammation and hypercoagulability in diabetic and nondiabetic patients with lower extremity ischemia. Thromb Res 2002; 105(5): 379–83.
37. *Alehagen U, Dahlström U, Lindahl TL.* Low plasma concentrations of coagulation factors II, VII and XI indicate increased risk among elderly with symptoms of heart failure. Blood Coagul Fibrinolysis 2010; 21(1): 62–9.
38. *Ruiz-Saez A.* Occurrence of thrombosis in rare bleeding disorders. Semin Thromb Hemost 2013; 39(6): 684–92.
39. *El-Hagracy RS, Kamal GM, Sabry IM, Saad AA, Abou El Ezz NF, Nasr HA.* Tissue Factor, Tissue Factor Pathway Inhibitor and Factor VII Activity in Cardiovascular Complicated Type 2 Diabetes Mellitus. Oman Med J 2010; 25(3): 173–8.
40. Ip H, Chan AY, Ng K, Soo YO, Wong LK. Case report: A 70-year-old man with undiagnosed factor VII deficiency presented with acute ischemic stroke. J Stroke Cerebrovasc Dis 2013; 22(8): e664–6
41. *Ku SK, Bae JS.* Inhibitory Effect of FXa on Secretory Group IIA Phospholipase A2. Inflammation 2015; 38(3): 987–94.
42. *Bukowska A, Zacharias I, Weinert S, Skopp K, Hartmann C, Huth C,* et al. Coagulation factor Xa induces an inflammatory signalling by activation of protease-activated receptors in human atrial tissue. Eur J Pharmacol 2013; 718(1–3): 114–23.
43. *Gleeson EM, O'Donnell JS, Hams E, Ní Áinle F, Kenny BA, Fallon PG,* et al. Activated factor X signaling via protease-activated receptor 2 suppresses pro-inflammatory cytokine production from lipopolysaccharide-stimulated myeloid cells. Haematologica 2014; 99(1): 185–93.

Received on March 19, 2017.
Revised on May 17, 2017.
Accepted on May 22, 2017.
Online First May, 2017.