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The metabolic syndrome and the risk of cerebral venous and sinus thrombosis: A case–control study

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Abstract

Background & Objective: There is no data about the significance of the metabolic syndrome (MeS) for the development of cerebral venous and sinus thrombosis (CVST). We investigated the association of metabolic syndrome in a consecutive series of patients with CVST. *Methods:* This is a case–control study, where consecutive patients of CVST and control subjects were assessed for MeS according to the National Cholesterol Education Program criteria. The prevalence of the MeS was compared between patients with CVST and controls. *Results:* We enrolled 58 patients with a first episode of CVST and 129 controls. In univariate analysis, MeS was significantly more common in CVST patients than in controls [Patients 28 (48.3%), control 28 (21.7%); odds ratio (OR) 3.36; 95% confidence interval (CI) 1.77, 6.53, p<0.001]. After adjustment for age and sex, we found OCP usage (OR 22.7; 95% CI 7.75, 66.66, p<0.001) and the MeS (OR 3.26; 95% CI 1.15, 9.25, p=0.02) to be independently associated with CVST. When coexistence of OCP usage and MeS was considered as a variant in univariate analysis comparing CVST patients and controls, we found association with CVST to be even higher (OR 47.6; 95% CI 5.91, 333.3, P< 0.001). *Conclusion:* CVST is a disease with multiple risk factors and coexistence of MeS and OCP usage can potentiate the risk of CVST occurrence.

Keyword: Metabolic syndrome, cerebral venous and sinus thrombosis

INTRODUCTION

The metabolic syndrome (MeS) is a cluster of risk factors for atherosclerosis, including abdominal obesity, hypertension, insulin resistance, dyslipidemia with high triglycerides, and low high-density lipoprotein (HDL) cholesterol.[1,2] On the other hand, venous thromboembolism (VTE) and atherosclerosis may share common risk factors such as general and abdominal obesity.[3-5] There is growing data for an association between venous thromboembolism (VTE) and atherosclerosis.[6-9] The MeS affects approximately 21 % of the population in central area of Iran.[10] Its significance in development of cerebral venous sinus thrombosis (CVST) has not been previously studied.

Individuals with MeS have a significantly increased risk of developing cardiovascular disorders[11], probably because of a blood hypercoagulability that may occur as a result of increased plasma levels of plasminogen activator inhibitor-1, fibrinogen, factor (F) VII and FVIII, and von Willebrand factor, and as a results of endothelial activation as expressed by increased circulating adhesion molecules ICAM1 and VCAM1.[12-18] Whether this hypercoagulable factors predisposes patients to VTE is unknown.

Data from two studies on the association of the MeS with VTE are currently available.[19,20] In these studies, patients with a history of deep vein thrombosis (DVT) had a higher prevalence of the MeS than control subjects. Although in several studies MeS was also recognized as an independent risk factor for arterial stroke[21-23], only one recent study showed that obesity is associated with a substantially increased risk of cerebral vein thrombosis in women who use oral contraceptives[24] there is no data about the significance of the MeS for the development of CVST. Therefore the aim of this study was the

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association of the MeS in a consecutive series of patients with CVST in comparison to control subjects.

METHODS

Patients of more than 14 years with a diagnosis of CVST confirmed by digital angiography or magnetic resonance imaging (MRI) with and without contrast, MR venography (MRV), or plain and contrast CT scan magnetic resonance angiography in Al-Zahra and Kashani Hospital of Isfahan University of medical sciences from Jan 2011 till Jan 2014 were included. The study was approved by the research ethics committee of Isfahan University of Medical Sciences and all subjects and controls had signed the informed consents. All patients and controls were Iranian Caucasians. We excluded CVST patients who had surgically modified their waist circumference; pregnancy, puerperium, severe weight loss; cancer, chronic infection or inflammation.

All patients were asked to bring at least one healthy control of the same age, and racial background, and with no clinical sign and symptom and history of thrombosis or be of first degree relatives. Female control must not to be pregnant or have had a recent delivery (up to 6 weeks). These constitute 89.1% of the control group. Physicians and health care workers from the hospital who volunteered served as 10.8% of the controls.

The following data was collected from both patients and controls: age, sex, weight, height, body mass index (BMI), waist circumference, history of symptomatic atherosclerosis (i.e. ischemic stroke, transient ischemic attack, acute myocardial infarction, angina, or intermittent claudication), known hypertension, known diabetes mellitus, known hyperlipidemia, smoking status, current use of heparin, oral anticoagulant drugs or antiplatelet agents, current or previous use of antihypertensive drugs, antidiabetic diet or drugs, and lipid lowering drugs. Subsequently, all patients underwent the measurement of blood pressure, fasting glucose, HDL cholesterol, triglycerides levels. Body weight was measured in light underwear by a precision scale to the nearest 0.5 kg and body height was measured by a precision meter to the nearest 0.01 meters. BMI were calculated as body weight (kg) divided by the square of the height (m). A normal BMI is between 20.0 and 25.0 kg/m^2, overweight is defined as a BMI of 25.1–29.9 kg/m^2 and obesity was considered as a BMI of 30 kg/m^{2}or greater.[25] The circumference of the waist was measured with a retractable steel tape, with the subject in the standing position, as described by Ashwell *et al*. (26). The waist was measurement to be recorded was the smallest girth between the rib cage and the iliac crest. Blood pressure was measured in the right arm, with subject in the supine position after 10 min rest by using a mercury sphygmomanometer of appropriate cuff size. Two measurements were repeated subsequently repeated after 5 min and after 10 min from the first measurement. The mean of the three measurements were considered. Venous bloods drown from an antecubital vein with plastic syringes after an overnight fast and will be collected in polystyrene tubes. Glucose, HDL cholesterol, and triglycerides were determined in fresh plasma. The time interval between CVST event and physical measurement and blood collection was at least 6 weeks.

The MeS was based by the presence of three or more of the following risk factors according to the National Cholesterol Education Program (NCEP) guidelines[1]: abdominal obesity (i.e. waist circumference of greater than 102 cm for men and of greater than 88 cm for women), triglycerides levels equal to or greater than 150 mg/dL, HDL cholesterol of lower than 40 mg/dL for men and of lower than 50 mg/dL for women, blood pressure of equal to or greater than 130 and/or 85 mmHg, and fasting glucose levels equal to or greater than 110 mg/dL. Patients currently receiving drug therapy for hypertension, diabetes, or dyslipidemia (only statins) were defined as having those components of the metabolic syndrome. All patients were work up for etiologic factors of CVST.

Statistical analysis

Patients were classified into two groups for the purposes of primary analysis (CVST and controls). The clinical characteristics of patients were compared with Student's t-test (for continuous variables) and the chi-squared test (for dichotomous variables) and Odds ratios and 95% confidence intervals. The influence of individual variables (age, sex, OCP usage) and the MeS on the likelihood of CVST were compared using logistic regression analysis. Multivariable analysis was subsequently performed with age and sex, each of the components of the MeS in the place of the MeS and OCP for female groups. By considering alpha=0.05 and a power level of 0.8, according the data in previous study in VTE[19], the sample size was calculated as 170.

The multivariate analysis was performed using SPSS 13 (SPSS Inc., Chicago, IL, USA). Finally, information on patients with CVST was reported by means of descriptive analysis.

RESULTS

A total of 58 patients with a first episode of CVST admitted to the Al Zahra hospital, Isfahan, Iran and 129 controls were enrolled in the study. Baseline characteristics of patients with CVST and controls are summarized in Table 1. Presenting symptom in CVST cases were 56 (96.5%) headache, 25 (43.1%) papilledema, 22 (37.9%) focal weakness, and 16 (27.5%) seizure. All of the patients were treated with heparin or enoxaparin followed by oral anticoagulant. Forty seven patients (81.03%) were able to achieve independence (MRS<3) and mortality was seen in 5 patients (8.6%). Multiple sinus involvement was found in 25 patients (43.1%), lateral sinus in 10 patients (17.2%), sagittal sinus in 7 patients (12.06%), and deep cerebral venous system in 2 patients (3.4%). OCP was the most common thrombophilic risk factor (62.8%) in our female patients, follow by polycythemia in 4 (6.8%), Hyperhomocysteinemia 4 (6.8%) and antiphospholipid syndrome in 1 (1.7%).

Metabolic syndrome

In univariate analysis, the MeS was significantly more common in CVST patients than in controls [28 (48.3%), 28 (21.7%); odds ratio (OR) 3.36; 95% confidence interval (CI)1.77, 6.53, p<0.001]. Among individual components of the MeS, waist circumference of greater than 102 cm in males and 88 cm in females, glucose level more than 110 mg/dL and HDL levels less than 40 mg/dL in male and 50 in female were significantly more common in CVST patients than in controls (Table 2).

Table 3 showed multivariable analysis (age, MeS, OCP usage) performed comparing CVST patients and controls. This analysis found OCP usage and the MeS to be independently associated with CVST. When coexistence of OCP usage and metabolic syndrome was considered as a variant in univariable analysis comparing CVST patients and controls, we found independently association with CVST with higher OR (OR 47.6; 95% CI 5.91, 333.3, P< 0.001). When all previous variables and the individual components of the MeS in the place of MeS were subsequently adjusted for potential confounders, we found no component were independently associated with CVST.

Table 1: Baseline characteristics

	CVST (n=58)	Controls (n=129)	P-values
Mean age, years (SD)	38.01 (12.2)	36.03 (11.3)	P=0.28
Sex, n (%)			
Female	43 (74.1)	95 (73.6)	P=0.54
Male	15 (25.9)	34 (26.4)	
BMI (SD) kg/ m2,	27.1 (5.4)	25.6 (5.2)	P=0.22
Smokers, n (%)	5.2 (3)	6 (4.7)	P=0.56
History of symptomatic atherosclerosis, n (%)	2 (3.4)	2 (1.6)	p=036
Mean HDL, mg/ dl (SD)	41.4 (8.5)	49.3 (9.5)	P<0.001*
Mean triglycerides, mg/ dl (SD)	136.7 (58.2)	128.7 (54.4)	P=0.36
Mean glycemia, mg/dl (SD)	94.0 (18.5)	90.4 (19.2)	P=0.23
Mean systolic blood pressure, mmHg (SD)	116 (13.1)	113 (14.1)	P=0.18
Mean diastolic blood pressure, mmHg (SD)	70.6 (10.6)	71.4 (11.9)	P=0.65
Ongoing antihypertensive therapy (%)	5 (8.6)	9 (7.0)	P=0.44
Ongoing therapy for diabetes (%)	8 (13.8)	8 (6.2)	P=0.07
Oral contraceptive usage (%)	27 (62.8)	6 (6.3)	P<0.001*
Past history of anticoagulant drugs	0 (0%)	0 (0%)	-
Past history of antiplatelet drugs	0 (0%)	2 (1.5%)	P=0.47

BMI, body mass index; CVST, cerebral vein and sinus thrombosis; HDL, high-density lipoprotein; * significant; SD, standard deviation.

Table 2: Univariate analysis examining the components of the metabolic syndrome

	CVST	Control	OR (95% CI)	P value
Waist circumference > 102/88 cm n (%)	34(58.6)	50(38.8)	2.23(1.19, 3.53)	0.009*
Blood pressure > 130/85 mm/ Hg, n (%)	6(14.0)	6(6.3)	2.40(0.72,7.93)	0.12
Triglycerides > 150 mg /dL, n (%)	31(18)	36(27.9)	1.16(0.59, 2.88)	0.39
HDL cholesterol < 40/50 mg/ dL n (%)	31(53.4)	45(34.9)	2.14(1.14, 4.03)	0.01*
Glucose > 110 mg /dL n (%)	14(24.1)	12(9.4)	3.07(1.32, 7.14)	0.007*

CVST, cerebral vein and sinus thrombosis; OR, odds ratio; CI, confidence interval; HDL, high-density lipoprotein, *significant.

When stratify the result by sex, in female the analysis remained significant [22 (51.2 %), 20(21.1%); OR 4.4; 95%, CI 1.8, 8.54, p<0.001], however in male the result was not significant [6(40.0%), 8(23.5%); OR 2.16; 95%, CI 0.58, 7.93, p=0.20].

DISCUSSION

To our knowledge this is the first study that explores the relationship between CVST and the MeS. We found that patients with CVST have a significantly higher prevalence of the MeS than control subjects. The presence of the MeS was independently associated with a three-fold higher risk of CVST. In particular, despite a similar mean BMI, univariate analysis found that patients with CVST had a greater waist circumference, more adverse lipid profile and higher serum glucose level than controls. With stratification of the result by gender, only in female did the analysis remain significant with four-fold higher risk. Multivariable analysis revealed that the MeS is an independent predictor of CVST after adjustment for age, sex, and OCP. Coexistence of OCP and MeS was independently associated with 40-fold higher risk of CVST.

Our results is consistent with the findings from two previous case-control study, which suggest the MeS associated with two-fold higher risk for VTE.[19,20] Our study further discloses that patients with CVST were more likely to display risk factors for atherosclerosis than control subjects.

The MeS is a well-known risk factor for the development of atherosclerotic cardiovascular disease. Abdominal obesity, defined by a waist circumference of greater than 102 cm for men and of greater than 88 cm for women, dyslipidemia, arterial hypertension and diabetes is an independent risk factor for coronary heart disease[27], and has been previously found to predict VTE.[28-31]

In our study, only three individual components (HDL cholesterol, glucose level, waist circumference) of the MeS were consistently associated with CVST, and yet the MeS was shown to be an independent predictor of CVST, which would argue in favor of the hypothesis that it is not the presence of a single component, but rather the collection of multiple components

Table 3: Multivariable logistic regression model of age, oral contraceptive and metabolic syndrome in case and control group

Variables	Multivariate logistic regression		
	* OR	** CI	*P*
OCP usage	22.7	7.75-66.66	<0.001
Metabolic syndrome	3.26	1.15-9.25	p=0.02
Age	1.01	1.05-0.73	P=0.644

*Odd Ratio, ** Confidence Interval

of the MeS that is essential. These findings are similar to case-control studies about VTE and MeS.[19,20]

Some previous studies showed the fibrinogen and factor VIII can be as a risk factor for CVST.[32-34] Therefore, the important underlying pathophysiological mechanism for occurrence of CVST in MeS and obese could be mediated through hypercoagulability due to increased levels of fibrinogen, PAI-1, factor VIII and decreased fibrinolytic potential in MeS and obese patients.[2,15,16,33]

We showed that with stratification of the result by gender, only in female did the analysis remain significant with four-fold higher risk. Rudnicka *et al.'s* study indicated that associations between C reactive protein, fibrinogen and tissue plasminogen activator antigen and MeS and its components were stronger in female than in male. These findings can be important in understanding the female predominance of MeS in CVST patients.[35]

In multivariate analysis, we found that OCP and metabolic syndrome was independently associated with a 22 and 3 -fold higher risk of CVST respectively. However, coexistence of these factors increased the risk of developing CVST, more than 47-fold. This suggests that CVST is a disease with multiple risk factors and if the coexistence of these factors such as MeS and OCP appear, the chance of CVST occurrence will progressively increase. This is similar to previous study which that showed that in women who used oral contraceptives, was overweight and obese; were associated with an increased risk of CSVT.[24]

Our study has several limitations. First, thrombophilia was only investigated in CVST patients, not in control group. However, its impact on the results of our analysis is likely to be low, because OCP as the most common thrombophilic factor in both groups was investigated, and the frequency of the other thrombophilic factor in CVST group was low. Second, 10 % of control group were volunteer physicians and health care workers from the hospital. These controls introduced a bias, because they maybe more likely to be aware of the importance of weight control for health and may not accurately the general population. However, the observed prevalence of MeS in our control group is almost the same as that reported previously in the general Iranian population[10], thus suggesting that our control group is rather reflective of the general population. Third, we included CVST patients from two university hospitals . There were another three hospitals with neurology ward in Isfahan that were not included. It can lead to selection bias. However, the hospital information system (HIS) of the two hospitals included was more comprehensive, with better patient information such as medication and history of thrombosis. Fourth, we used NCEP criteria for the diagnosis of MeS, but there is also modified version with Asia–Pacific criteria for obesity based on BMI (>25 kg/m2) or waist circumference (>90 cm for men, >80 cm for women). However, although modified criteria is more appropriate for East Asia, the Middle East and Iran are racially Caucasian. Thus, the original criteria may be more suitable for our study.

In conclusion, the results of our study suggest that the MeS, beside its well-recognized impact on atherosclerotic cerebrovascular disease, is also a considerable risk factor for CVST especially for female and may contribute to the multifactorial pathogenesis of CVST. Thus, identification, treatment and prevention of the MeS including lifestyle changes and management to control components of the syndrome; and avoidance of OCP in patients with MeS may help to prevent the occurrence of CVST. However, further multi centric prospective case-control study with larger sample with analysis that include all CVST risk factors is needed to confirm MeS as an independent risk factor for CVST.

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DISCLOSURE

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REFERENCES

1. Executive summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001; 285:2486-97. doi: 10.1001/jama.285.19.2486.
2. Grundy SM, Cleeman JI, Daniels SR, *et al*. Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute Scientific Statement.

Circulation 2005;112:2735-52. doi: 10.1161/CIRCULATIONAHA.105.169404.
3. Hansson PO, Eriksson H, Welin L, Svardsudd K, WilhelmsenL. Smoking and abdominal obesity: risk factors for venous thromboembolism among middle-aged men: "the study of men born in 1913". *Arch Intern Med* 1999;159:1886-90. doi: 10.1001/archinte.159.16.1886.
4. Fujii S, Goto D, Zaman T, *et al*. Diminished fibrinolysis and thrombosis: clinical implications for accelerated atherosclerosis. *J AtherosclerThromb* 1998;5:76-81. doi: 10.5551/jat1994.5.76.
5. Fendri S, Roussel B, Lormeau B, Tribout B, Lalau JD. Insulin sensitivity, insulin action, and fibrinolysis activity in nondiabetic and diabetic obese subjects. *Metabolism* 1998; 47:1372-5 doi: 10.1016/s0026-0495(98)90307-9.
6. Prandoni P, Bilora F, Marchiori A, *et al*. An association between atherosclerosis and venous thrombosis. *N Engl J Med* 2003;348:1435-41. doi: 10.1056/NEJMoa022157
7. Hong C, Zhu F, Du D, Pilgram TK, Sicard GA, Bae KT. Coronary artery calcification and risk factors for atherosclerosis in patients with venous thromboembolism. *Atherosclerosis* 2005;183:169-74. doi: 10.1016/j.atherosclerosis.2005.03.047.
8. Becattini C, Agnelli G, Prandoni P, *et al*. A prospective study on cardiovascular events after acute pulmonary embolism. *Eur Heart J* 2005;26:77-83. doi: 10.1093/eurheartj/ehi018.
9. Prandoni P, Ghirarduzzi A, Prins MH, *et al*. Venous thromboembolism and the risk of subsequent symptomatic atherosclerosis. *J ThrombHaemost* 2006;4:1891-6. doi: 10.1111/j.1538-7836.2006.02058.x.
10. Sarrafzadegan N, Gharipour M, Ramezani MA, *et al*. Metabolic syndrome and health-related quality of life in Iranian population. *J Res Med Sci* 2011;16(3):254-61.
11. Reusch JEB. Current concepts in insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome. *Am J Cardiol* 2002; 90 (Suppl.): 19G–26G. doi: 10.1016/s0002-9149(02)02555-9.
12. Festa A, D'Agostino R, Mykkanen L, *et al*. Relative contribution of insulin and its precursor to fibrinogen and PAI-1 in a large population with different states of glucose tolerance. The Insulin Resistance Atherosclerosis Study (IRAS). *ArteriosclerThrombVascBiol* 1999; 19: 562–8. doi: 10.1161/01.atv.19.3.562.
13. Kohler HP, Grant PJ. Plasminogen-activator inhibitor type 1 and coronary artery disease. *N Engl J Med* 2000; 342: 1792–801. doi: 10.1056/NEJM200006153422406.
14. Agewall S, BokemarkL,Wikstrand J, LindahlA, Fagerberg B. Insulin sensitivity and hemostatic factors in clinically healthy 58-year-oldmen. *ThrombHaemost* 2000; 84: 571-5.
15. Juhan-Vague I, Alessi MC, Morange PE. Hypofibrinolysis and increased PAI-1 are linked to atherothrombosis via insulin resistance and obesity. *Ann Med* 2000; 32: 78–84.
16. Juhan-Vague I,Morange P, Christine Alessi M. Fibrinolytic function and coronary risk. *CurrCardiol Rep* 1999; 1: 119–24. doi: 10.1007/s11886-999-0069-x.
17. Yudkin JS. Abnormalities of coagulation and fibrinolysis in insulin resistance. Evidence for a common antecedent? *Diabetes Care* 1999; 22:C25-30.
18. Imperatore G, RiccardiG, Iovine C, Rivellese AA, Vaccaro O. Plasma fibrinogen: a new factor of the metabolic syndrome. *Diabetes Care* 1998; 21: 649-54. doi: 10.2337/diacare.21.4.649.
19. Ageno W, Prandoni P, Romualdi E, *et al*. The metabolic syndrome and the risk of venous thrombosis: a case-control study. *J Thromb Haemost* 2006;4:1914-8. doi: 10.1111/j.1538-7836.2006.02132.x.
20. Ay C, Tengler T, Vormittag R, *et al*. Venous thromboembolism--a manifestation of the metabolic syndrome. *Haematologica* 2007;92(3):374-8. doi: 10.3324/haematol.10828.
21. Kurl S, Laukkanen JA, Niskanen L, *et al*. Metabolic syndrome and the risk of stroke in middle-aged men. *Stroke* 2006;37:806-11. doi: 10.1161/01.STR.0000204354.06965.44.
22. Milionis HJ, Rizos E, Goudevenos J, Seferiadis K, Mikhailidis DP, Elisaf MS. Components of the metabolic syndrome and risk for first-ever acute ischemic nonembolic stroke in elderly subjects. *Stroke* 2005;36: 1372-6. doi: 10.1161/01.STR.0000169935.35394.38.
23. Koren-Morag N, Goldbourt U, Tanne D. Relation between the metabolic syndrome and ischemic stroke or transient ischemic attack: a prospective cohort study in patients with atherosclerotic cardiovascular disease. *Stroke* 2005;36:1366-71. doi: 10.1161/01.STR.0000169945.75911.33.
24. Zuurbier SM, Arnold M, Middeldorp S, *et al*. Risk of cerebral venous thrombosis in obese women. *JAMA Neurol* 2016;73(5):579-84. doi: 10.1001/jamaneurol.2016.0001.
25. Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Executive summary of the clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults. *Arch Intern Med* 1998; 158: 1855-68. doi: 10.1001/archinte.158.17.1855.
26. Ashwell M, Chinn S, Stalley S, Garrow JS. Female fat distribution – a simple classification based on two circumference measurements. *IntObes* 1982; 6: 143-52.
27. Lakka HM, Lakka TA, Tuomilehto J, Salonen JT. Abdominal obesity is associated with increased risk of acute coronary events in men. *Eur Heart J* 2002; 23: 706-13. doi: 10.1053/euhj.2001.2889.
28. Ray JG. Dyslipidemia, statins, and venous thromboembolism: a potential risk factor and a potential treatment. *CurrOpinPulm Med* 2003; 9: 378-84. doi: 10.1097/00063198-200309000-00007.
29. Deguchi H, Pecheniuk NM, Elias DJ, Averell PM, Griffin JH. High density lipoprotein deficiency and dyslipoproteinemia associated with venous thrombosis in men. *Circulation* 2005; 112: 893-9. doi: 10.1161/CIRCULATIONAHA.104.521344.
30. Goldhaber SZ, Grodstein F, Stampfer MJ, *et al*.

A prospective study of risk factors for pulmonary embolism in women. *JAMA* 1997; 277: 642-5.
31. Petrauskiene V, FalkM, WaernbaumI,Norberg M, Eriksson JW. The risk of venous thromboembolism is markedly elevated in patients with diabetes. *Diabetologia* 2005; 48: 1017-21. doi: 10.1007/s00125-005-1715-5.
32. Shahsavarzadeh T, Javanmard SH, Saadatnia M. Impact of factor VIII and von Willebrand factor plasma levels on cerebral venous and sinus thrombosis: are they independent risk factors? *Eur Neurol* 2011;66(4):243-6. doi: 10.1159/000331048.
33. Bugnicourt JM, Roussel B, Tramier B, Lamy C, Godefroy O. Cerebral venous thrombosis and plasma concentrations of factor VIII and von Willebrand factor: a case control study. *J Neurol Neurosurg Psychiatry* 2007;78(7):699-701. doi: 10.1136/jnnp.2006.103465.
34. Imperatore G, Riccardi G, Iovine C,Rivellese AA, Vaccaro O. Plasma fibrinogen: a new factor of the metabolicsyndrome. A population-basedstudy. *Diabetes Care* 1998; 21:649-54. doi: 10.2337/diacare.21.4.649.
35. Rudnicka AR, Rumley A, Whincup PH, Lowe GD, Strachan DP. Sex differences in the relationship between inflammatory and hemostatic biomarkers and metabolic syndrome: British 1958 Birth Cohort. *J Thromb Haemost* 2011; 9(12):2337-44. doi: 10.1111/j.1538-7836.2011.04517.x.