Med Med J 2019;34(1):1-6
doi:10.5222/MMJ.2019.08870

Original Article/Orijinal Makale
Neurology / Nöroloji

Prognostic Importance of Endocan Level in Patients with Ischemic Cerebrovascular Disease

İskemik Serebrovasküler Olaylarda Endokan Seviyesinin Prognostik Önemi

Dilek Ağırcan, Asuman Orhan Varoğlu

Ethics Committee Approval: Recelved from Istanbul Medeniyet University, 2014/0152, Date: November 18, 2014
Conflict of interest: The authors declare that they have no conflict of interest.
Funding: We do not have any financial relationship whatsoever for this research.
Informed Consent: Informed consent was obtained from all individual participants included in the study.

Cite as: Ağırcan D., Orhan Varoğlu A. Prognostic Importance of Endocan Level in Patients with Ischemic Cerebrovascular Disease. Med Med J. 2019;34(1):1-6

ABSTRACT

Aim: *Endothelial dysfunction and the level of endocan may be related to the development of thrombotic atherosclerotic complications. We aimed to investigate the relationship between ischemic cerebrovascular disease (ICD) and serum level of endocan and prognosis in ICD.*
Method: *We compared the serum level of endocan of 80 patients and of 60 healthy controls. Blood samples were obtained from the patient group within the first 24 hours, by the end of the first week and by the end of the third month. The prognosis of stroke was interpreted with the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) scores at the same intervals.*
Results: *No significant difference was found in regard to serum levels of endocan between the patient and the control groups. Also, there was not any statistically significant difference seen between the two groups for serum levels of endocan within the first 24 hours, first week, and 3rd month. A positive correlation was observed between the 1st week endocan levels and total cholesterol and LDL levels (r=0.329, p=0.021; r=0.317, p=0.032 respectively).*
Conclusion: *We found no relationship between levels of endocan and ICD and its prognosis. It was demonstrated that levels of endocan may be influenced by vascular risk factors and medications.*

Keywords: *Stroke, endocan, atherosclerosis, ischemic cerebrovascular disease*

ÖZ

Amaç: *Endotel disfonksiyonu ve endokan düzeyi trombotik aterosklerotik komplikasyonların gelişmesi ile ilişkili olabilir. İskemik serebrovasküler hastalıkta (ICD) ile serum endokan düzeyi ve prognoz arasındaki ilişkiyi araştırmayı amaçladık.*
Yöntem: *Seksen hastanın endokan serum düzeyi ve 60 sağlıklı kontrol karşılaştırıldı. Hasta grubundan ilk 24 saat içinde, ilk hafta sonuna kadar ve üçüncü ayın sonuna kadar kan örnekleri alındı. İnme prognozu, Ulusal Sağlık İnme Ölçeği (NIHSS) ve değiştirilmiş Rankin Ölçeği (mRS) skorları ile aynı aralıklarla yorumlanmıştır.*
Bulgular: *Hasta ve kontrol grubu arasında serum endokan düzeyleri açısından anlamlı fark bulunmadı. Ayrıca, ilk 24 saat, birinci hafta ve 3. ayda iki grup arasında endokan serum seviyeleri açısından istatistiksel olarak anlamlı bir fark yoktu. Birinci hafta endokan düzeyleri ile total kolesterol ve LDL düzeyleri arasında pozitif korelasyon saptandı (sırasıyla r = 0.329, p = 0.021; r = 0.317, p = 0.032).*
Sonuç: *ICD ve endokan düzeyleri ile prognozu arasında ilişki bulunamadı. Endokan düzeylerinin vasküler risk faktörleri ve ilaçlardan etkilenebileceği gösterilmiştir.*

Anahtar kelimeler: *İnme, endokan, aterosklerosis, iskemik serebreovasküler olay*

Received: 03.08.2018
Accepted: 11.11.2018
Publication date: 30.03.2019

Asuman Orhan Varoğlu
Istanbul Medeniyet University
Medical School,
Department of Neurology,
Istanbul, Turkey
asumanorhan69@gmail.com
ORCİD: 0000-0002-4172-1299

D. Ağırcan 0000-0001-5055-1933
Istanbul Medeniyet University
Medical School,
Department of Neurology,
Istanbul, Turkey

INTRODUCTION

The second most common cause of death is stroke worldwide[1-3]. Ischemic stroke was seen in 80%-90% of all stroke cases[4]. Atherosclerosis is the result of chronic inflammatory events that impair large and small arterioles and arteries[5]. Endothelial dysfunction predisposes to atherosclerosis and thrombosis[6]. Endothelial-specific molecule-1 (endocan) is a dermatan sulfate proteoglycan that is expressed in en-

dothelial cells and can be measured from serum[7]. Endothelial-dependent pathologic events play an important role in inflammatory diseases[7]. Endocan is acknowledged as a mandatory endothelial cell marker[8]. Endocan has an important contribution to the formation of endothelium-dependent diseases such as vascular disease, and cancer including hepatocellular[9], bladder[10], colorectal[11], and lung carcinomas[12], therefore it may be a mandatory marker of endothelial dysfunction[13-15]. In the formation of atherosclerosis, the first triggering factor is endothelial dysfunction[16,17]. The relationship between endothelial dysfunction and ischemic cerebrovascular disease (ICD) might be related to the critical involvement of endothelial dysfunction in the formation of atherothrombotic events[1]. Although there were some studies concerning the importance of endocan in coronary artery disease, there is only one published paper that investigated the role of endocan in patients with ICD[18]. We intended to evaluate the relationship between ICD and endocan levels and whether the prognosis of ICD could be used as a marker.

MATERIAL and METHOD

This prospective study was performed at Istanbul Medeniyet University University, Neurology Department, between January and June 2015, and contained 80 patients with a diagnosis of cerebrovascular disease. Moreover, 60 age-, and sex-matched individuals who had no neurologic disorder served as the control group. The investigation protocol was confirmed by the institutional ethics committee. A written consent form was received from every participant.

The risk factors of ICD and also sociodemographic characteristics were recorded. Systemic and neurologic examinations were performed on all participants. The following tests and examinations were performed on all patients included in the study group: Cranial imaging (at first presentation and follow-up), laboratory tests (blood count, electrolytes, fasting and postprandial blood glucose, HbA1C, insulin, all types of cholesterols, urea, creatinine, AST, ALT, TSH, fibrinogen), urinalysis, electrocardiography (ECG), chest X-ray, echocardiography, and carotid-vertebral artery Doppler ultrasonography were performed. While the patients were positioned supine, 7 mLs of blood samples from the antecubital vein was drawn into serum separator tubes (BD Vacutainer; Becton Dickinson, Meylan, France) involving clot activator and EDTA to be used for biochemical analysis and complete blood counts within the first 24 hours of hospitalization. To avoid hemolysis and hemoconcentration, the tourniquet was taken off immediately by the phlebotomist. We centrifuged all samples at 2000 rpm for approximately 10 minutes and the serums of the patients and controls were maintained at -80°C till analysis. The levels of endocan were evaluated with the enzyme-linked immunosorbent assay (ELISA) method using commercial kits (Aviscera Bioscience, USA). The samples were examined in accordance with the instructions in the package insert of the kit. The intra-assay coefficient of variation (CV) ranged from 6% to 8%, while the interassay CV ranged from 10% to 12% for endocan assay. We found diagnostic sensitivity of our study at 98 pg/mL and the upper limit of the standard was 25 ng/mL. Plate reader of ELISA (MultiscanGo, Thermo Fisher Scientific Inc) and plate washer (Thermo Fisher Scientific Inc) were used to measure the samples. We detected well absorbance at 450 nm. In logarithmic scale, plotting the mean standards of absorbance (Y) against the known standards of concentration (X) to draw the standart curve, by using the four-parameter algorithm. We enrolled outcomes of the endocan concentration (ng/mL). In all of patients, standard laboratory techniques were used to measure other blood parameters.

Exclusion criteria were the presence of intracerebral or a subarachnoid bleeding as a cause of stroke, brain tumor or systemic malignancy, recent or simultaneous symptomatic peripheral artery disease, heart failure and myocardial infarction, sepsis or renal dysfunction . Also, we excluded patients younger than 18 and older than 80 years and those presenting after the initial 24 hours. As a control group, we selected 60 age-matched participants who had vascular risk factors without any history of stroke, systemic or central nervous system malignancy, recent heart fai-

lure and myocardial infarction, and diagnosis of sepsis at the time of the study. All laboratory analyses, including serum endocan levels of the controls were evaluated and the sociodemographic characteristics were recorded.

The OCSP (Oxfordshire Community Stroke Project) and TOAST (Trial of Org. 10172 in Acute Stroke Treatment) classification were used to categorize patients according to subtypes and etiology of stroke. The patients were assessed by NIHSS and mRS score within the first 24 hours of the hospitalization, and at the 1st week and 3rd month of the stroke to determine their clinical and functional status.

Statistical Evaluation

We used NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) in this study. Quantitative data were expressed as mean ± SD. To compare groups, we used Student's t-test. To determine the relationship among the data, Pearson or Spearman correlation analysis was used. To evaluate the accuracy and respective best cut-off data of endocan level to predict disease prognosis, we used receiver operating characteristic (ROC) curves and their corresponding areas under the curve (AUCs). We accepted p value of <0.05 as statistically significant.

RESULTS

We enrolled 80 patients with acute ischemic cerebrovascular disease with a mean age of 63.85±11.47 years and 60 healthy controls with a mean age of 61.55±12.37 years. We found no difference as for age and gender between patients and control groups (p=1.02). Table 1 shows the patients' and controls' demographic features and laboratory data.

For the evaluation of prognosis, NIHSS (according to neurologic examinations) and mRS (for functional evaluation) scores of the patients were calculated and there were no statistically significant changes between the initial, 1st week and 3rd month NIHSS and mRS scores of group of patients (p<0.01; p=0.049 respectively). Initial NIHSS scores were observed to be significantly higher than the other scores p<0.01). Also, initial mRS scores were statistically significantly higher than the 1st week (p<0.01). However, we found no statistically significant difference among the mRS scores (p>0.05).

Table 1. The baseline demographic and laboratory data in patients with ICD and controls.

		Controls n:60	ICD n:80	P-value
Age		61.55±12.37	63.85±11.47	0.343
Sex	Female	32 / 55.00%	36 / 43.33%	0.253
	Male	28 / 45.00%	44 / 56.67%	
Glucose (mg/dL)		99.71±16.81	124.87±43.7	0.001
Urea (mg/dL)		33.21±9.41	36.03±11.63	0.220
Creatinine (mg/dL)		0.83±0.15	0.86±0.22	0.539
AST (IU/L)		19.57±4.55	18.27±6.69	0.309
ALT (IU/L)		19.29±7.85	16.48±7.56	0.089
Triglycerides (mg/dL)		155.83±85.86	150.4±65.17	0.731
Total cholesterol (mg/dL)		210.28±40.67	197.8±51.73	0.240
HDL cholesterol (mg/dL)		46.92±13.71	43.72±11.35	0.22
LDL cholesterol (mg/dL)		129.78±36.8	126.35±44.03	0.710
WBC (K/uL)		7.24±1.57	8.77±5.19	0.074
RBC (M/uL)		4,75±0.52	4.59±0.59	0.173
HGB (g/dL)		14,23±4,52	13.32±1.73	0.162
Platelet count (K/uL)		243.85±72.95	244±66.61	0.991
TSH (uIU/mL)		1.43±0.89	1.38±1.09	0.846
fT3 (pg/mL)		2.49±0.92	2.79±0.3	0.034
fT4 (ng/dL)		0.96±0.18	0.95±0.13	0.774
HbA1c (%)		5.87±0.64	6.61±1.77	0.116
Insulin		8.11±5.02	13.94±12.36	0.103

*Student's t-test was used to compare groups. Data arepresented as mean ± standard deviation, *Median (min-max); AST: Aspartate Transaminase, ALT: Alanineaminotransferase, TSH:Thyrotrophin-Stimulating Hormone, fT3:free T3, fT4:free T4, HbA1c: Glycated hemoglobin.*

When we compared the patients with controls, there was no significant difference as for for serum endocan levels, (p=0.98) (Table 2) Also, we couldn't find any statistically significantly difference among the

Table 2. Comparison of Endocan levels between the patients and the control groups.

Endocan level (ng/ml)	Controls n:60	ICD n:80	P-value
1st day	1.47±0.48	1.48±0.6	0.092
7th day		1.47±0.43	0.093
3rd month		1.57±0.64	0.361

Student's t-test was used to compare groups.

serum endocan levels in first 24 hours, first week, and 3rd month (p=0.85).

There was no important correlation between the initial, 1st week and 3rd month endocan levels and the groups that were classified according to TOAST and OCSP classification (p=0.78). Moreover, as for the prediction of prognosis, any statistically significant correlation was not observed between the serum endocan levels and NIHSS and mRS scores in the first 24 hours, 1st week, and 3rd month (p=0.96).

We did not see any significant difference as for serum endocan levels between diabetic with and non-diabetic patients (p=0.82). Similarly, there was no substantial difference as for serum endocan levels between hypertensive patients and normotensive patients too (p=0.38).

There was no significantly difference in the initial, 1st week and 3rd month endocan levels between male and female patients (p=0.82). We found a positive correlation between the first week endocan levels and both total cholesterol and LDL levels (r=0.329 p=0.021, r=0.317 p=0.032 respectively) and between 3rd month levels of endocan and sedimentation rates (ESR) (r=0.467 p=0.018).

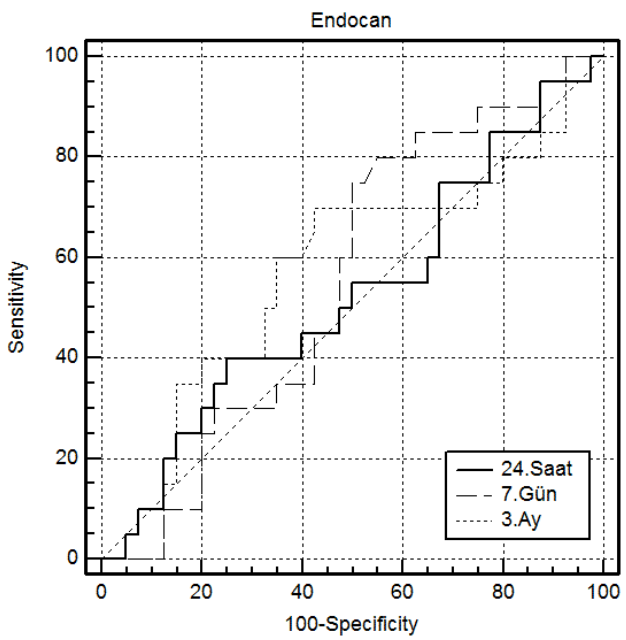

Figure 1. Receiver-operating characteristic (ROC) curve of endocan for predicting ICD.

The areas under the ROC curve, which were insufficient for differential diagnosis or follow-up of endocan levels, were as follows: the initial 0.524 (0.391-0.654), 1st week 0.554 (0.420-0.683), 3rd month 0.572 (0.438-0.699) (Figure 1).

DISCUSSION

Following deterioration in the blood-brain barrier, endothelial activation and damage have important roles in the development of ICD[19]. Endocan is an important predictor for all of vascular diseases, organ-specific inflammation events and endothelium-dependent disorders[8]. Its concentrations may provide projection against endothelial cell dysfunction[20].

Although ICD may develop secondary to underlying diseases, the most prominent pathological factor is atherosclerosis, particularly in patients over 50 years of age[21]. Endothelial dysfunction is thought as an early marker for atherosclerosis[22]. In the studies concerning the role of endocan in the formation of atherosclerotic lesions, immunohistochemical studies have demonstrated that endocan is highly concentrated in the atherosclerotic plaque[7]. Hyperlipidemia, and atherosclerosis leads to an increased risk of secondary stroke[23] and it has been revealed that high level of blood cholesterol deteriorates endothelial function[24]. In the literature, we did not encounter a study which investigated the relationship between levels of endocan and total cholesterol and LDL. In accordance with the literature, we found a positive correlation between the 1st week levels of endocan and total cholesterol as well as LDL which supports the relationship between atherosclerosis and endothelial dysfunction.

The most important role in the pathogenesis of ischemic cerebrovascular disease is inflammation and the underlying complex. pathophysiological process. Pro-inflammatory and anti-inflammatory indicators are very important in the pathogenesis of ischemic

cerebrovascular disease, but inflammatory indicators are dominant[25]. Higher endocan levels in patients with Behçet's disease (BD) and its classical conventional inflammatory markers which are indicating disease activity were shown to be positively correlated[14]. It was shown that psoriasis vulgaris (PV) patients had significantly higher serum endocan levels than controls. Also, high serum endocan level correlated with hsCRP and cIMT which are indicating disease activity in these patients[13]. However, no correlation between serum endocan levels and inflammatory markers in patients with acute coronary syndrome (ACS) patients was found[26]. In this study, there was no statistically significant relationship between CRP levels and serum endocan levels. Presumably, the mechanisms of inflammation in PV and BD which are the diseases of collagen tissue are different from the mechanism of inflammation in ischemic vascular diseases such as ICD and ACS. Also, the inflammation in PV and BD may be more severe than the inflammation of ICD and ACS.

We found that there was no significant difference in the serum endocan levels between the patient and the control groups. Serum endocan levels may be affected by other vascular occlusion risk factors (smoking, alcohol use, the presence of hypercholesterolemia, and hypothyroidism, etc) and medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, statins, etc)[15,27-29]. However, Heet al.[18] reported that endocan levels are higher than normal and correlated with pooor prognosis in ischemic cerebrovascular disease patients at the earlier stage of the disease. It is thought that in the pathogenesis of ischemic cerebrovascular disease, inflammatory mechanisms may be different from the other systemic collagen tissue diseases. It is also thought that there are some situations and drugs affecting endocan blood levels which have not been identified till now. Therefore, determination of the role of endocan level in the events of cerebrovascular disease requires further studies.

No important difference in levels of serum endocan was found between hypertensive patients with ICD and normotensive patients with ICD. It was shown that endocan levels decreases under antihypertensive therapy; such as valsartan and amlodipine in newly diagnosed HT patients[30]. Using antihypertensive therapy may be the cause of this finding in our patients.

We thought that maybe there are some different unknown medications and situations to affect endocan levels. In our study, there was no statistically important difference in serum endocan levels between diabetic, and nondiabetic ICD patients. Maybe insulin and oral antidiabetics used in our patients can affect endocan levels.

CONCLUSION

No significant difference in serum levels of endocan is found between the patients and the control groups in our study. Referring to the literature, it was demonstrated that levels of endocan may be influenced by vascular risk factors and medications. Perhaps unknown medications and conditions so far may influence endocan levels. Further investigations are needed to determine the effect of medications and conditions on endocan levels. Also, because of the limited number of our patients, there is a need for studies with more patients to determine the role of endocan levels in ICD patients.

REFERENCES

1. Schächinger V, ZeiherAM. Prognostic implications of endothelial dysfunction: does it mean anything? Coron Artery Dis. 2001;12:435-43. PMID: 11696682. https://doi.org/10.1097/00019501-200109000-00002
2. WHO. The Top 10 Causes of Death. Available online: http://www.who.int/mediacentre/factsheets/ (accessed on 8 June 2014).
3. Lozano R, Naghavi M, Foreman K. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the global burden of disease study 2010. Lancet. 2012;380(9859):2095-128. https://doi.org/10.1016/S0140-6736(12)61728-0
4. Go AS, Mozaffarian D, Roger VL. Heart disease and stroke statistics-2013 update: A report from the American heart association. Circulation. 2013;127:e6-e245. https://doi.org/10.1161/CIR.0b013e31828124ad
5. Ross R. Atherosclerosis-An inflammatory disease. N Engl J Med. 1999;340(2):115-26.

https://doi.org/10.1056/NEJM199901143400207
6. Probstfield JL, Byington RP, Egan DA. Methodological issues facing studies of atherosclerotic change. Circulation. 1993;87(3):1174-81. PMID:8443927.
7. Menon P, Kocher ON, Aird WC. Endothelial cell specific molecule-1 (ESM-1), a novel secreted proteoglycan stimulates vascular smooth muscle cell proliferation and migration. Circulation. 2011;124(21):A15455.
8. Bechard D, Scherpereel A, Hammad H, et al. Human endothelial cell specific molecule-1 binds directly to the integrin CD11a/ CD18 (LFA-1) and blocks binding to intercellular adhesion molecule-1.J Immunol. 2001;167(6):3099-106. https://doi.org/10.4049/jimmunol.167.6.3099
9. Ozaki K, Toshikuni N, George J, et al. Serum endocan as a novel prognostic biomarker in patients with hepatocellular carcinoma. J Cancer. 2014;5:221-30. https://doi.org/10.7150/jca.7691
10. Laloglu E, Aksoy H, Aksoy Y, et al. Determination of serum and urinary endocan concentrations in patients with bladder cancer. Ann Clin Biochem. 2016;53:647-53. https://doi.org/10.1177/0004563216629169
11. Jiang H, Fu XG, Chen YT. Serum level of endothelialcell-specific molecule-1 and prognosis of colorectal cancer. Genet Mol Res. 2015;14: 5519-26. https://doi.org/10.4238/2015.May.25.3
12. Lassalle P, Molet S, Janin A, et al. ESM-1 is a novel human endothelial cell-specific molecule expressed in lung and regulated by cytokines. J Biol Chem. 2005;271:20458-64. https://doi.org/10.1074/jbc.271.34.20458
13. Balta I, Balta S, Demirkol S, et al. Elevated serum levels of endocan in patients with psoriasis vulgaris: correlations with cardiovascular risk and activity of disease. Br J Dermatol. 2013;169(5):1066-70. https://doi.org/10.1111/bjd.12525
14. Balta I, Balta S, Koryurek OM, et al. Serum endocan levels as a marker of disease activity in patients with Behcet disease. J Am Acad Dermatol. 2014;70(2):291-6. https://doi.org/10.1016/j.jaad.2013.09.013
15. Balta S, Mikhailidis DP, Demirkol S, et al. Endocan-a novel inflammatory indicator in newly diagnosed patients with hypertension: a pilot Angiology. 2014;65(9):773-7. https://doi.org/10.1177/0003319713513492
16. Balta S, Demirkol S, Celik T, et al. Association between coronary artery ectasia and neutrophil-lymphocyteratio. Angiology. 2013; 64(8):627-32. https://doi.org/10.1177/0003319713480424
17. Keles N, Aksu F, Aciksari G, Yilmaz Y, Demircioglu K, Kostek O, Cekin ME, Kalcik M, Caliskan M. Is triglyceride/HDL ratio a reliable screening test for assessment of atherosclerotic risk in patients with chronic inflammatory disease? North Clin Istanb. 2016 25;3(1):39-45. https://doi.org/10.14744/nci.2016.52824
18. He XW, Ke SF, Bao YY, Hong WJ, Shen YG, Li C, Zhu F, Wang E Jin XP. Serum levels of endocan and endoglin areassociated with large-artery atherosclerotic stroke. Clin Chim Acta. 2018;478:157-61. https://doi.org/10.1016/j.cca.2017.12.040
19. Stanimirovic D, Satoh K. Inflammatory mediators of cerebral endothelium: a role in ischemic brain inflammation. Brain Pathol. 2000;10:113-26. https://doi.org/10.1111/j.1750-3639.2000.tb00248.x
20. Yilmaz MI, Siriopol D, Saglam M, et al. Plasma endocan levels associate with inflammation, vascular abnormalities, cardiovascular events, and survival in chronic kidney disease. Kidney Int. 2014;86(6):1213-20. https://doi.org/10.1038/ki.2014.227
21. Albers GW, Easton JD, Sacco RL, Teal P.Antithrombotic and thrombolytic therapy for ischemic stroke. Chest. 1998;114(5):683S-8S. https://doi.org/10.1378/chest.114.5_Supplement.683S
22. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol. 2003;23:168-75. https://doi.org/10.1161/01.ATV.0000051384.43104.FC
23. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for health care professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention. Stroke. 2006;37(2):577-617. https://doi.org/10.1161/01.STR.0000199147.30016.74
24. Kirma C, Akcakoyun M, Esen AM, et al. Relationship Between Endothelial Function and Coronary Risk Factors in Patients With Stable Coronary Artery Disease. Circulation. 2007;71:698-702. https://doi.org/10.1253/circj.71.698
25. Pei J, You X, Fu Q. Inflammation in the pathogenesis of ischemic stroke. Front Biosci (LandmarkEd). 2015;20:772-83. http://dx.doi.org/10.2741/4336
26. Kose M, Emet S, Akpinar TS, et al. Serum Endocan Level and the Severity of Coronary Artery Disease: a pilot study. Angiology. 2015;66(8):727-31. https://doi.org/10.1177/0003319714548870
27. Unlu M, Karaman M, Ay SA, et al. The comparative effects of valsartan and amlodipine on vascular microinflammation in newly diagnosed hypertensive patients. Clin Exp Hypertens. 2013;35(6):418-23. https://doi.org/10.3109/10641963.2012.739237
28. Karaman M, Balta S, Ay SA, et al. The comparative effects of valsartan and amlodipine on vWf levels and N/L ratio in patients with newly diagnosed hypertension. Clin Exp Hypertens. 2013; 35(7):516-22. https://doi.org/10.3109/10641963.2012.758734
29. Ozturk C, Balta S, Balta I, et al. Neutrophil-lymphocyte ratio and carotid-intima media thickness in patients with behcet disease without cardiovascular involvement. Angiology. 2015;66(3):291-6. https://doi.org/10.1177/0003319714527638
30. Fici F, Celik T, Balta S, et al. Comparative effects of nebivolol and metoprolol on red cell distribution width and neutrophil/lymphocyte ratio in patients with newly diagnosed essential hypertension. J Cardiovasc Pharmacol. 2013;62(4):388-93. https://doi.org/10.1097/FJC.0b013e31829f716a