European Review for Medical and Pharmacological Sciences 2020; 24: 7131-7137

Endocan and advanced oxidation protein products in adult population with hypertension

A. KLISIC[1], N. KAVARIC[1], S. VUJCIC[2], V. SPASOJEVIC-KALIMANOVSKA[2], A. NINIC[2], J. KOTUR-STEVULJEVIC[2]

[1]Primary Health Care Center, University of Montenegro-Faculty of Medicine, Podgorica, Montenegro
[2]Department for Medical Biochemistry, University of Belgrade - Faculty of Pharmacy, Belgrade, Serbia

Abstract. – OBJECTIVE: Hypertension is closely related to oxidative stress and inflammation. Endocan is a new inflammation marker whose role is not completely elucidated in hypertension. The aim of this study was to explore the association between endocan and several oxidative stress markers [i.e., advanced oxidation protein products (AOPP), total protein sulfhydryl (SH-) groups and prooxidant-antioxidant balance (PAB)] in adult population with hypertension.

PATIENTS AND METHODS: A total of 90 patients with hypertension were compared with 44 controls. Blood pressure, anthropometric and biochemical parameters were measured. Associations of clinical data with hypertension were tested with univariable and multivariable logistic ordinal regression analysis.

RESULTS: Endocan and AOPP were significantly higher in hypertensive patients than in the controls (p=0.006 and p=0.046, respectively). In the multivariable logistic regression analysis, AOPP and endocan kept their independent positive associations with hypertension. As AOPP rose by 1 μmol/L and endocan rose by 1 pg/mL, the probability for hypertension presence rose by 4.2% and 32.2%, respectively and 39.9% of variation in hypertension could be explained with the Model. The area under the Receiver Operating Characteristic curve [(AUC) for AOPP=0.638 (0.550-0.719), p=0.01 and for endocan=0.679 (0.593-0.757), p<0.001] demonstrated sufficient clinical accuracy towards hypertension. On the contrary, the Model showed very good clinical accuracy [AUC= 0.825 (0.749-0.900), p<0.001].

CONCLUSIONS: Endocan and AOPP are independently correlated with hypertension in adult population and these tested markers together could be reliable parameters to discriminate patients with hypertension from normotensive ones.

Key Words:
Advanced oxidation protein products, Endocan, Hypertension, Inflammation, Oxidative stress.

Introduction

Hypertension is regarded as a multifactorial disorder closely related to inflammation and oxidative stress[1,2]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are instigators of vascular inflammation, with the concomitant secretion of the pro-inflammatory cytokines. All these biomarkers lead to the endothelial dysfunction, hypertension occurrence and, if not controlled, to its complications and target organ damages[1,2].

Under physiological circumstances, antioxidant barrier (i.e., enzymatic and non-enzymatic) can prevent the negative side-effects of the free radicals. However, this redox-balance gets disturbed and even exhausted during long-term ROS overproduction, leading to increased oxidative stress and harmful effects on target cells[3]. Endothelial cells, neutrophils, and macrophages are sources of ROS production. However, the major site of ROS production is mitochondria, during adenosine triphosphate (ATP) synthesis through the process of oxidative phosphorylation. Also, myeloperoxidase, monoamine oxidases, cyclooxygenase, and lipoxygenase can contribute to ROS production[3].

Due to a short half-life of ROS and its high reactivity, the estimation of oxidative stress is determined by measuring markers of lipid peroxidation, oxidation of proteins, and oxidative damage of nucleic acids[3].

Endocan is a novel inflammation biomarker related to endothelial dysfunction[4]. It was shown that this proteoglycan, which is mainly secreted by endothelial cells, is included in regulation of different endothelial actions, like cell adhesion, neo-angiogenesis, proliferation, migration, etc[4]. Higher levels of this biomarker are observed in several cardiometabolic disorders[5-7]. Recent studies[8,9] have also shown higher serum endocan levels

Corresponding Author: Aleksandra Klisic, MD, Ph.D; e-mail: aleksandranklisic@gmail.com

in patients with hypertension compared to healthy control. Moreover, patients with higher serum endocan levels also displayed higher arterial pulse wave velocity, which is considered as a marker of arterial stiffness[8]. Endocan was associated with carotid intima-media thickness (cIMT) which is also related with endothelial dysfunction[9].

On the contrary, some investigations reported no difference in endocan levels between hypertensive subjects without and with asymptomatic target organ damage, and reported no significant correlation between serum endocan levels and any of the variables related to asymptomatic target organ damage, like cIMT[10].

Since the role of endocan in endothelial dysfunction is not completely explored, and considering the fact that there are no studies exploring the mutual effect of endocan and variety of oxidative stress markers in hypertensive subjects, in the present study we aimed to explore the association between endocan and several oxidative stress markers [i.e., advanced oxidation protein products (AOPP), total protein sulfhydryl (SH-) groups and prooxidant-antioxidant balance (PAB)] in adult population with hypertension.

Patients and Methods

Patients

A total of 90 patients with hypertension were compared with normotensive 44 participants in this case-control study.

The examinees were recruited in a successive manner when visiting the Primary Health Care Center in a period from May to July 2017. All of them signed an informed consent after the approval of the study protocol by the Institutional Ethics Committee.

A questionnaire consisted of questions regarding demographic data, illnesses, lifestyle habits (cigarette smoking, medications use, alcohol consumption) was given to each examinee with the request to fill it in.

A sphygmomanometer was used for systolic (SBP) and diastolic blood pressure (DBP) measurement after the participant's rest for 5 minutes and the average of the 3 measurements at 30 seconds intervals taken on the right arm in the seating position was recorded. Hypertension was defined as SBP $\geq$ 140 mmHg and/or diastolic DBP $\geq$ 90 mmHg, or the use of antihypertensive medications[11].

Body weight (kg) and body height (cm) were obtained from each participant, whereas body mass index (BMI) was calculated.

The inclusion criterion for the research was diabetes-free individuals who were willing to enter the study.

Subjects were excluded if reported: acute infection, pregnancy, secondary hypertension (e.g., renal artery stenosis, pheochromocytoma, Cushing's syndrome, hyperaldosteronism), acute myocardial infarction or stroke in the last 6 months, coronary artery disease, type 1 or type 2 diabetes mellitus, thyroid dysfunction, malignant disease, renal disease, hepatic disease, severe anemia, ethanol consumption >20 g/day, use of glucocorticoids, antihyperglycemic medications, antibiotics and non-steroidal anti-inflammatory medications. Additionally, subjects with high sensitivity C-reactive protein (hsCRP), (> 10 mg/L), glycated hemoglobin (HbA1c) level higher than 6.4%, fasting glucose equal to or higher than 7.0 mmol/L and with estimated glomerular filtration rate ($eGFR_{MDRD}$) < 30 mL/min/1.73 m^2 were also excluded from the study. Furthermore, if participants exhibited fasting glucose between $\geq$ 5.6 mmol/L and < 7.0 mmol/L, they underwent oral glucose tolerance test and those with plasma glucose level $\geq$ 11.1 mmol/L were additionally excluded from the study[12].

Hypolipidemics (i.e., statins) and those with plasma glucose level $\geq$ 11.1 mmol/L after 2-hours of the test were used by 16% and 30% examinees in control and hypertensive group, respectively.

Antihypertensive drugs were used by 79% (71/90) of participants in hypertensive group, whereas in control group there were no subjects that used such medications, as it would be expected based on inclusion criteria in this study.

Methods

The two blood samples were collected for each participant in the morning after an over night fast of at least 8 hours. One sample of a whole blood in the tube with K_2EDTA was obtained for determination of HbA1c levels, immunoturbidimetrically on Roche Cobas c501 chemistry analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

The other sample was taken in the tube with serum separator and clot activator for determination of biochemical parameters. After being left to clot within 30 minutes, those samples were then centrifuged at room temperature for 10 minutes at 3000 xg. Thereafter, the obtained sera were used for routine biochemical markers determination [i.e., fasting glucose, urea, creatinine, uric acid, lipid parameters- total cholesterol, triglycerides (TG), high density lipoprotein cholesterol (HDL-c), low den-

sity lipoprotein cholesterol (LDL-c) and hsCRP] on Roche Cobas c501 chemistry analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

The remaining sera were used for serum endocan and oxidative stress markers measurement. Endocan levels were determined by using an enzyme-linked immunosorbent commercial assay (ab213776 – Human ESM1 ELISA Kit, Abcam, Cambridge, UK).

A method of reaction with glacial acetic acid and potassium iodide was applied for AOPP measurement[13]. A spectrophotometric method using 5,5'-dithiobis (2-nitro benzoic acid) was used for total protein sulfhydryl (SH-) groups determination[14], whereas a method using 3,3', 5,5'-tetramethylbenzidine as a chromo gen was applied for PAB measurement[15].

Statistical Analysis

Data distribution was tested by Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally and *log*-transformed normally distributed data were tested by Student's *t*-test and presented as mean ± standard deviation and geometrical mean (95% Confidence interval – CI), respectively. Skewed distributed data were tested by Mann-Whitney test and presented as median (interquartile range). Differences in tested markers which were significant after two group comparisons, were further adjusted for age and BMI and tested by ANCOVA or Quade test, dependent on data distribution. Associations between clinical markers and presence of hypertension were tested by binary logistic regression analysis. All the markers that were significantly associated with hypertension were tested by multivariable logistic regression analysis. Data were given as odds ratio (OR) and 95% CI in order to determine possible independent predictors for hypertension. The explained variation in hypertension was presented by Nagelkerke R^2. Receiver Operating Characteristic (ROC) curve analysis was used to test the diagnostic performance of clinical markers and the Model to distinguish patients with hypertension from those who have not got it. Data from this analysis were given as areas under curve (AUCs) and 95% CI. Significance was set at the probability level less than 0.05.

Results

Patients with hypertension were older and had higher BMI than patients without hypertension. These two tested groups differed in uric acid, AOPP and endocan levels. All these parameters were significantly higher in patients with hypertension than in those without it (Table I).

Univariable binary regression analysis was used to test associations between hypertension and other clinical parameters. Dependent variable was coded as follows: 0 – patients without hypertension and 1 – patients with hypertension. Significant positive associations were determined between hypertension and years of age, glucose, uric acid, hsCRP, AOPP and endocan levels. Only PAB was negatively associated with hypertension (Table II).

Data with significant odds in univariable analysis were tested in the Model. After multivariable logistic regression analysis, AOPP and endocan kept their independent positive associations with hypertension (Table II). As AOPP rose by 1 μmol/L and endocan rose by 1 pg/mL, the probability for hypertension presence rose by 4.2% and 32.2%, respectively. Adjusted R^2 for the Model was 0.399, which meant that 39.9% of variation in hypertension could be explained with the Model (Table II).

The calculated AUC for AOPP and endocan (independent predictors for hypertension according to multivariable logistic regression analysis) were ranking from 0.600 to 0.700 [i.e., AUC for AOPP=0.638 (0.550-0.719), p=0.01 and AUC for endocan=0.679 (0.593-0.757), p<0.001] which demonstrated sufficient clinical accuracy towards hypertension[16]. On the contrary, the Model showed very good clinical accuracy [AUC= 0.825 (0.749-0.900), p<0.001] (Figure 1) indicating that these tested markers together could be used to discriminate patients with hypertension, from normotensive ones.

Discussion

The present study shows higher endocan and AOPP levels in patients with hypertension, compared with normotensive counterparts.

Higher endocan levels were also reported in some recent reports[8,9,17,18]. However, to our knowledge, this is the first study that evaluated the mutual effect of endocan and variety of oxidative stress markers in hypertensive subjects. Among examined oxidative stress biomarkers in this study [i.e., AOPP, PAB, total protein sulfhydryl (SH-) groups)], and despite the fact that PAB also correlated with hypertension in univariable logistic regression analysis, only AOPP remained its independent predictor. Moreover, endocan and AOPP, when tested together in the Model, were independently correlated with hypertension in adult population showing very good clinical accuracy

Table I. Clinical data of study population.

	Patients with hypertension N=90	Control group N=44	p
Male/Female (N)	37/53	14/30	0.298
Smokers, yes/no (N)	20/70	10/34	0.947
Hypolipidemics, yes/no (N)	27/63	7/37	0.078
Antihypertensives, yes/no (N)	71/19	0/44	-
–	-Angiotensin converting enzyme inhibitors, N=58 -Calcium channel blockers, N=13 -Angiotensin receptor blockers, N=11 -Beta-blockers, N=29 -Thiazide diuretics, N=39	–	–
SBP, mmHg	138 (128-149)	126 (118-129)	**<0.001**
DBP, mmHg	86 (80-94)	78 (74-84)	**<0.001**
Age, years	62±9	56±9	**0.001**
BMI, kg/m²*	28.8 (27.9-29.6)	27.2 (26.0-28.5)	**0.038**
Glucose, mmol/L**	5.6 (5.3-6.0)	5.4 (5.2-5.6)	0.183
HbA1c, %	5.4±0.3	5.3±0.3	0.120
Urea, mmol/L**	5.5 (4.7-6.5)	5.2 (4.3-6.0)	0.119
Creatinine, μmol/L	74±15	71±10	0.279
Uric acid, μmol/L	289±7	264±10	**0.050**
eGFRMDRD, mL/min/1.73m²	81±15	83±11	0.357
hsCRP, mg/L**	1.43 (0.64-2.61)	0.88 (0.45-1.41)	0.106
AOPP, μmol/L**	42.20 (37-60-54.60)	37.60 (31.85-49.70)	**0.046**
PAB, HKU**	102.40 (66.47-131.67)	124.57 (96.60-134.80)	0.204
Total SH- groups, μmol/L	0.27 ± 0.09	0.26±0.07	0.503
Endocan, pg/mL**	4.03 (2.06-9.11)	2.36 (1.70-3.77)	**0.006**

Data are presented as mean ± SD.
* Log-transformed data are presented as geometric mean (95% CI).
** Skewed distributed data are presented as median (interquartile range).

(AUC>0.8) and suggesting that these two biomarkers could be reliable ones to discriminate hypertensive patients from normotensive ones.

Endothelial dysfunction represents the key pathophysiological change that underlies hypertension[19] and previous reports show that endocan may be the convenient biomarker for its monitoring, since it is secreted by endothelial cells and has influence on neo-vascularization, cell adhesion and leukocyte migration[4]. In addition, its expression is controlled by several cytokines (interleukin-1, tumor necrosis factor-alpha) and vascular endothelial growth factor (VEGF).

Recently, Sun et al[20] suggested a potential target for endothelial dysfunction induced by intermittent hypoxia, showing significant upregulation of endocan by the hypoxia-inducible factor-1 alpha/VEGF-A pathway under intermittent hypoxia in endothelial cells, which takes an important part in intensifying adhesion between endothelial cells and monocytes. Additionally, they showed the upregulation of expression of adhesion molecules, vascular cell adhesion molecule-1 (VCAM-1) and inter-cellular adhesion molecule-1 (ICAM-1) by endocan, whereas endocan silencing has led to suppression mentioned adhesion molecules. It is already known that ICAM-1 and VCAM-1 are endothelial cells receptors and are upregulated by inflammatory cytokines stimuli, which further lead to leukocytes migration and adhesion to injured endothelium[21].

In line with this, Cimen et al[22] reported a significant decrease in serum endocan concentration after successful reperfusion in patients diagnosed with acute coronary syndrome. Also, Tadzic et al[23] reported that reduction of endocan concentration could diminish the activation of endothelial cells, leading to delay of atherosclerosis progression. On the contrary, Ağaç et al[10] showed that en-

Table II. Associations of hypertension with clinical data.

Predictors	Unadjusted OR (95% CI)	p	Nagelkerke R^2
Age, years	1.068 (1.024-1.114)	0.002	0.104
BMI, kg/m^2	1.097 (1.000-1.205)	0.050	0.041
Glucose, mmol/L	2.457 (1.089-5.544)	0.030	0.054
HbA1c, %	2.383 (0.793-7.160)	0.122	0.025
Urea, mmol/L	1.293 (0.976-1.712)	0.073	0.035
Creatinine, µmol/L	1.020 (0.992-1.048)	0.166	0.021
Uric acid, µmol/L	1.008 (1.002-1.014)	0.004	0.091
eGFRMDRD, mL/min/1.73m^2	0.988 (0.962-1.014)	0.357	0.009
hsCRP, mg/L	1.436 (1.080-1.908)	0.013	0.084
AOPP, µmol/L	1.038 (1.005-1.071)	0.022	0.065
PAB, HKU	0.989 (0.978-0.999)	0.039	0.045
Total SH- groups, µmol/L	4.239 (0.062-295.319)	0.500	0.005
Endocan, pg/mL	1.300 (1.121-1.506)	< 0.001	0.170
Model	**Adjusted OR (95% CI)**	**p**	**Nagelkerke R^2**
Age, years	1.049 (0.998-1.104)	0.062	0.399
BMI, kg/m^2	0.989 (0.972-1.121)	0.865	
Glucose, mmol/L	1.387 (0.522-3.684)	0.511	
Uric acid, µmol/L	1.003 (0.996-1.011)	0.345	
hsCRP, mg/L	1.424 (1.002-2.118)	0.081	
AOPP, µmol/L	1.042 (1.002-1.084)	0.037	
PAB, HKU	0.988 (0.975-1.001)	0.079	
Endocan, pg/mL	1.322 (1.126-1.552)	0.001	

Model: age, BMI, glucose, uric acid, hsCRP, AOPP, PAB, endocan (all continuous variables).

docan was not reliable marker for the occurrence of asymptomatic target organ damage in patients with hypertension.

Oxidative stress is one of the main culprits in the pathogenesis of hypertension[2]. In line with our results, Yıldırım et al[24] also found higher AOPP levels in patients with hypertension, compared with normotensive controls. The AOPP are indicators of oxidative damage of proteins that are involved in inflammation of endothelium by the overexpression of VCAM-1 and ICAM-1[3]. Endothelial dysfunction is characterized by a reduction in vasodilatation in response to nitric oxide (NO) deficiency. AOPP can also be involved in inhibition of production of NO through activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase[25]. NADPH oxidase activation stimulates angiotensin II type 1 receptors, which may cause increase in production of ROS and concomitant decrease in NO in patients with hypertension[25].

In addition to this, Li et al[26] have recently proposed a novel pathophysiological mechanism of causal link between the accumulation of AOPP and renal tubulointerstitial fibrosis in diabetic nephropathy via activation of the protein kinase C (PKC) signaling pathway (mostly the PKCη iso-

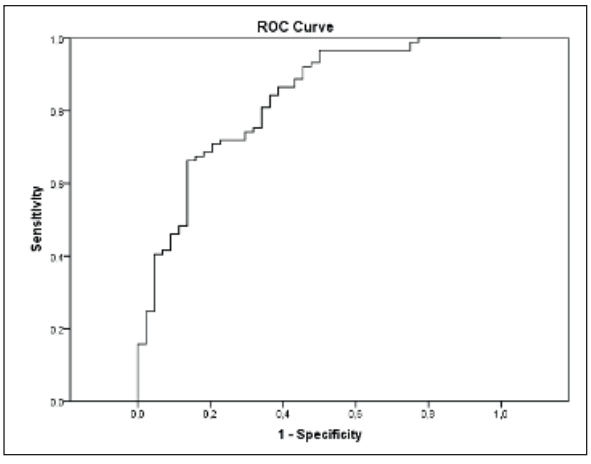

Figure 1. Discriminatory ability of Model regarding hypertension presence.
Model: age, BMI, glucose, hsCRP, AOPP, PAB and endocan (all continuous variables).

form). Namely, the accumulation of AOPP initiates CD36-dependent mitochondrial oxidative distress via activation of PKCη signaling, whereas inhibition of the PKC signaling can reverse AOPP-induced proteinuria and renal insufficiency[26].

Taking all these findings into consideration, the therapeutic strategy for inhibition of endocan and/or reducing oxidative stress might be the challenge for hypertension prevention/treatment in future prospective studies.

There are several limitations of this study. Due to its cross-sectional design, only associations (between endocan, AOPP and hypertension) but not causality can be established. Also, we were not able to examine any relationship between endocan and/or AOPP and endothelial dysfunction (e.g., cIMT) due to limited diagnostic procedures. However, this would be useful strategy for future studies in order to extend current investigation and to obtain deeper insight into the pathophysiological mechanisms of hypertension. Additionally, in the current study we did not examine the relationship of endocan and AOPP with insulin resistance, since insulin resistance represents one of the important underlying factors of hypertension and cardiovascular disease[6]. However, we have recently shown higher endocan and AOPP levels in patients with type 2 diabetes than in the diabetes-free individuals[6]. Moreover, we have shown the relationship between HbA1c and endocan and AOPP, respectively, in patients with prediabetes and diabetes. Even more, endocan was shown to be the independent predictor of HbA1c in those participants. Finally, except for antihypertensive medications in hypertensive group, some of the examinees used lipid-lowering therapy (i.e., statins) in both groups (i.e., both in case and control group) which might influence the obtained results[27-29]. Namely, previous investigations have reported that antilipemic agents lower oxidative stress biomarkers[27] and endocan levels[29], whereas antihypertensive medications, such as valsartan and amlodipine may lower serum endocan levels[28]. However, our results are in line with those of Musialowska's et al[18] who also showed higher circulating endocan levels in subjects with treated hypertension compared with normotensive ones.

Conclusions

These results showed that endocan and AOPP are independently correlated with hypertension in adult population and these markers when tested together could be reliable parameters to discriminate patients with hypertension from normotensive ones.

Acknowledgements

This work was financially supported in part by a grant from the Ministry of Science, Montenegro and the Ministry of Education, Science and Technological Development, Republic of Serbia (Project No. 175035).

Conflict of Interests

The authors declare that they have no conflict of interest.

References

1) Dikalov SI, Dikalova AE. Crosstalk between mitochondrial hyperacetylation and oxidative stress in vascular dysfunction and hypertension. Antioxid Redox Signal 2019; 31: 710-721.
2) Guzik TJ, Touyz RM. Oxidative stress, inflammation, and vascular aging in hypertension. Hypertension 2017; 70: 660-667.
3) Bigagli E, Lodovici M. Circulating oxidative stress biomarkers in clinical studies on type 2 diabetes and its complications. Oxid Med Cell Longev 2019; 2019: 5953685.
4) Zhao T, Kecheng Y, Zhao X, , Hu X, Zhu J, Wang Y, Ni J. The higher serum endocan levels may be a risk factor for the onset of cardiovascular disease: a meta-analysis. Medicine (Baltimore) 2018; 97: e13407.
5) Ekiz-Bilir B, Bilir B, Aydin M, Soysal-Atile N. Evaluation of endocan and endoglin levels in chronic kidney disease due to diabetes mellitus. Arch Med Sci 2019; 15: 86-91.
6) Klisic A, Kavaric N, Stanisic V, Vujcic S, Spasojevic-Kalimanovska V, Ninic A, Kotur-Stevuljevic J. Endocan and a novel score for dyslipidemia, oxidative stress and inflammation (DOI score) are independently correlated with glycated hemoglobin (HbA1c) in patients with prediabetes and type 2 diabetes. Arch Med Sci 2020; 16: 42-50.
7) Klisic A, Kavaric N, Abenavoli L, Stanisic V, Spasojevic-Kalimanovska V, Kotur-Stevuljevic J, Ninic A. Is endocan a novel potential biomarker of liver steatosis and fibrosis? J Med Biochem 2020; 39: 363-371.
8) Poon PY, Ng JK, Fung WW, Chow KM, Kwan BC, Li PK, Szeto CC. Relationship between plasma endocan level and clinical outcome of Chinese peritoneal dialysis patients. Kidney Blood Press Res 2019; 44: 1259-1270.
9) Oktar SF, Guney I, Eren SA, Oktar L, Kosar K, Buyukterzi Z, Alkan E, Biyik Z, Erdem SS. Serum endocan levels, carotid intima-media thickness and microalbuminuria in patients with newly diagnosed hypertension. Clin Exp Hypertens 2019; 1-8. doi: 10.1080/10641963.2019.1652632.

10) Ağaç MT, Kahyaoğlu B, Aksoy MMN, Cinemre FB, Vatan MB, Gündüz Y. Is endocan a biochemical marker for asymptomatic target organ damage in hypertensive patients? Anatol J Cardiol 2019; 21: 76-82.
11) Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; Task Force Members. 2013 ESH/ESC guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and for the European Society of Cardiology (ESC). J Hypertens 2013; 31: 1281-1357.
12) American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In Standards of Medical Care in Diabetes-2017. Diabetes Care 2017; 40: S11-S24.
13) Witko-Sarsat V, Friedlander M, Capeillère-Blandin C, Nguyen-Khoa T, Nguyen AT, Zingraff J, Jungers P, Descamps-Latscha B. Advanced oxidation protein products as a novel marker of oxidative stress in uremia. Kidney Int 1996; 49: 1304-1313.
14) Ellman GI. Tissue silfhydryle groups. Arc Biochem Biophys 1959; 82: 70-77.
15) Alamdari DH, Paletas K, Pegiou T, Sarigianni M, Befani C, Koliakos G. A novel assay for the evaluation of the prooxidant-antioxidant balance, before and after antioxidant vitamin administration in type II diabetes patients. Clin Biochem 2007; 40: 248-254.
16) Šimundić AM. Measures of diagnostic accuracy: basic definitions. EJIFCC 2009; 19: 203-211.
17) Turgunova L, Koichubekov B, Turmuhambetova A, Sorokina M, Laryushina YE, Korshukov I, Shalygina A, Baidildina B. Biochemical markers of hypertension, prehypertension. Ann Cardiol Angeiol (Paris) 2018; 67: 161-166.
18) Musialowska D, Zbroch E, Koc-Zorawska E, Musialowski P, Malyszko J. Endocan concentration in patients with primary hypertension. Angiology 2018; 69: 483-489.
19) Kossaify A, Karam M. Markers in hypertension: insights for an enhanced blood pressure management. J Hypertens 2014; 3: 165.
20) Sun H, Zhang H, Li K, Wu H, Zhan X, Fang F, Qin Y, Wei Y. ESM-1 promotes adhesion between monocytes and endothelial cells under intermittent hypoxia. J Cell Physiol 2019; 234: 1512-1521.
21) Hua S. Targeting sites of inflammation: intercellular adhesion molecule-1 as a target for novel inflammatory therapies. Front Pharmacol 2013; 4: 127.
22) Cimen AO, Emet S, Elitok A. Endocan: a biomarker predicting successful reperfusion after coronary artery by-pass surgery of acute coronary syndrome patients. Eur Rev Med Pharmacol Sci 2019; 23: 338-342.
23) Tadzic R, Mihalj M, Vcev A, Ennen J, Tadzic A, Drenjancevic I. The effects of arterial blood pressure reduction on endocan and soluble endothelial cell adhesion molecules (CAMs) and CAMs ligands expression in hypertensive patients on Ca-channel blocker therapy. Kidney Blood Press Res 2013; 37: 103-115.
24) Yildirim E, İpek E, Bavunoğlu I, Yildirim N, Cengiz M, Yavuzer S, Yavuzer H, Erman H, Uzun H. The impact of protein oxidation on sustained and white coat hypertension. Anatol J Cardiol 2017; 17: 210-216.
25) Hopps E, Caimi G. Protein oxidation in metabolic syndrome. Clin Invest Med 2013; 36: 1-8.
26) Li X, Xu L, Hou X, Geng J, Tian J, Liu X, Bai X. Advanced oxidation protein products aggravate tubulointerstitial fibrosis through protein kinase C-dependent mitochondrial injury in early diabetic nephropathy. Antioxid Redox Signal 2019; 30: 1162-1185.
27) Parizadeh SM, Azarpazhooh MR, Moohebati M, Nematy M, Ghayour-Mobarhan M, Tavallaie S, Rahsepar AA, Amini M, Sahebkar A, Mohammadi M, Ferns GA. Simvastatin therapy reduces prooxidant-antioxidant balance: results of a placebo-controlled cross-over trial. Lipids 2011; 46: 333-340.
28) Celik T, Balta S, Karaman M, Ahmet Ay S, Demirkol S, Ozturk C, Dinc M, Unal HU, Yilmaz MI, Kilic S, Kurt G, Tas A, Iyisoy A, Quarti-Trevano F, Fici F, Grassi G. Endocan, a novel marker of endothelial dysfunction in patients with essential hypertension: comparative effects of amlodipine and valsartan. Blood Press 2015; 24: 55-60.
29) Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP. Lipid lowering agents and the endothelium: an update after 4 years. Curr Vasc Pharmacol 2012; 10: 33-41.