THE TEXAS HEART INSTITUTE® JOURNAL

Clinical Investigation

Relationship Between Obstructive Sleep Apnea Severity and Serum Endocan Levels in Patients With Hypertension

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Abstract

Background: Obstructive sleep apnea (OSA) is common in middle-aged adults and has been associated with various cardiovascular disorders; endothelial dysfunction may play a role in the pathogenesis of these disorders in patients with OSA. Endothelial cell specific molecule-1 (endocan) is a marker of vascular pathology, which is correlated with endothelial dysfunction. This study investigates the relationship between serum endocan levels and OSA severity in patients with hypertension.

Methods: A retrospective review included 48 patients with OSA and hypertension but without conventional cardiovascular risk factors, and 67 patients with OSA who did not have hypertension. The correlation between serum endocan levels and the apnea-hypopnea index (AHI) was investigated in both groups.

Results: There was a significant correlation between the serum endocan level and the AHI in patients with OSA and hypertension (r = 0.308; P = .033), but there was no such correlation in patients without hypertension (r = 0.193; P = .118). However, when both groups were combined (ie, all patients with OSA), there was a significant correlation between serum endocan levels and the AHI (r = 0.228; P = .014). On multiple logistic regression analysis, endocan levels were independent predictors of OSA severity in patients with OSA and hypertension (P = .029).

Conclusion: In patients with OSA and hypertension, serum endocan levels are significantly correlated with the AHI. Measurement of endocan may have a place in evaluating patients with OSA and hypertension for adverse cardiovascular events, and they may even help to guide OSA therapy for these patients.

Keywords: Hypertension; sleep apnea, obstructive; ESM1 protein, human

Introduction

Obstructive sleep apnea (OSA) is a syndrome characterized by repetitive obstructions—partial or complete—of the upper respiratory tract that result in arousals during sleep and in hypoxia followed by reoxygenation. The most critical demographic risk factors for OSA are obesity, advancing age, and male sex.[1] The severity of disease is classified by the apnea-hypopnea index (AHI): the number of episodes, per hour of sleep, of breathing cessation (apnea) and reductions in airflow (hypopnea) associated with desaturation or arousal. By convention, a value of fewer than 5 events per hour is usually considered normal, between 5 and 15 events per hour is considered mild OSA, between 15 and 30 events per hour is considered moderate OSA, and over 30 events per hour is considered severe OSA. Peppard et al[2] found that OSA has a prevalence of 13% in adult men and 6% in adult women in Wisconsin, but Köktürk et al[3] found the prevalence of OSA in Turkey is only 0.9% to 1.9%.

The intermittent hypoxia and recurrent arousals of OSA can lead to various adverse consequences including sympathetic activation, oxidative stress, insulin resistance, hypercoagulability, activation of inflammation, and endothelial dysfunction. Obstructive sleep apnea can cause multiple system disorders and has been recognized as an independent risk factor for cardiovascular disease (CVD), cerebrovascular disease, and metabolic disease.[4-6] It is also

Citation: Yazan S, Karakurt H, Püşüroğlu H. Relationship between obstructive sleep apnea severity and serum endocan levels in patients with hypertension. *Tex Heart Inst J.* 2023;50(1):e217664. doi:10.14503/THIJ-21-7664

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a strong independent predictor of future cardiovascular and all-cause mortality. A meta-analysis by Ge et al[7] showed that severe OSA increases the risk for all-cause death by 67% and the risk for cardiovascular death by 265%.

Endothelial dysfunction is characterized by a shift of the endothelium toward reduced vasodilation capability and a proinflammatory and prothrombotic state. It is associated with most types of CVD, including hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes mellitus (DM), and chronic renal failure.[8] Endothelial dysfunction has also been shown to occur in patients with OSA in studies that assessed forearm vascular flow, intima-media thickness, carotid-femoral pulse wave velocity, number of circulating endothelial progenitor cells, and vascular endothelial growth factor levels.[9] Endothelial cell specific molecule-1 (endocan) is a dermatan sulphate proteoglycan, measurable in the serum, that is synthesized by vascular endothelial cells.[10] Endocan plays a vital role in the pathogenesis of CVD, endothelial dysfunction, and inflammatory reactions,[11,12] but few studies have investigated the relationship between endocan levels and OSA severity.[13,14]

The present study may be the first to evaluate the relationship between the AHI and endocan levels in patients with OSA and hypertension. The aim of this study is to investigate the relationship between AHI and endocan levels in patients with OSA and hypertension, compared with those who have OSA without hypertension.

Abbreviations and Acronyms

AHI	apnea-hypopnea index
AOS	average oxygen saturation
BMI	body mass index
CVD	cardiovascular disease
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
HbA_{1c}	glycated hemoglobin
hsCRP	high-sensitivity C-reactive protein
MOS	minimum oxygen saturation
OR	odds ratio
OSA	obstructive sleep apnea
WBC	white blood cell

Patients and Methods

This retrospective study assessed the records of 115 patients without a history of CVD who reported snoring and were suspected of having OSA. All patients were evaluated at the outpatient clinic between February 2014 and February 2015. The exclusion criteria were obstructive or restrictive pulmonary disease (the former was defined as a forced expiratory volume 1/forced vital capacity ratio <70%), use of noninvasive mechanical ventilation, substantial cardiac failure, acute coronary syndrome (unstable angina pectoris and myocardial infarction), valvular heart disease, congenital heart disease, uncontrolled hypothyroidism, renal or hepatic dysfunction, active inflammatory disease, acute infection, malignancy, and use of medication that could potentially interfere with endocan levels (eg, lipid-lowering therapy, vitamins, or antioxidants).

Patients with confirmed OSA were assigned to hypertensive and nonhypertensive subgroups. All patients underwent 58-channel overnight polysomnography (PSG; Compumedics), during which the following recordings were taken: 12-channel electroencephalography, 2-channel electrooculography, jaw and leg electromyography, electrocardiography, airflow measurement via an oronasal thermistor, monitoring of chest and abdominal respiratory movements, oxygen saturation using a fingertip pulse oximeter, monitoring for snoring with a tracheal microphone, and body posture. Sleep stages were scored based on Rechtschaffen and Kales' standard criteria.[15] Apnea was defined as an interruption in oronasal airflow longer than 10 seconds; hypopnea was defined as a decrease in oxygen saturation by 3% for 10 seconds or longer, or as a decrease of 50% or more in airflow because of arousal; and the AHI was determined using the apnea and hypopnea counts per hour. A diagnosis of OSA was made with an AHI of 6 or greater. Sleep stages were scored using standard criteria over 30-second epochs; the results were reviewed and verified by a certified sleep physician.

Hypertension was defined as an office blood pressure of 140/90 mm Hg or greater, or as active use of antihypertensive medication.[16] The diagnosis of DM was made using American Diabetes Association criteria (fasting serum glucose ≥126 mg/dL [≥7 mmol/L], nonfasting glucose ≥200 mg/dL [≥11.1 mmol/L], or active use of antidiabetic medication). Body mass index (BMI) was calculated by dividing the patient's weight in kilograms by their height in meters squared. Current smokers were defined as those who had smoked more than 100 cigarettes in their lifetime and had smoked any cigarettes during the last month.

Hyperlipidemia was defined as a fasting total serum cholesterol above 240 mg/dL, low-density lipoprotein cholesterol above 130 mg/dL, serum triglycerides above 180 mg/dL, or the use of lipid-lowering medications for hypercholesterolemia. A family history of CVD was de-

fined as premature CVD occurring in first-degree relatives younger than 55 years for men and younger than 65 years for women.

This study was approved by the ethics committee of the University of Health Sciences, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital. All patients signed written informed consent for study participation, and the study was performed following the principles of the Declaration of Helsinki.

Blood Sampling

Standard laboratory parameters—including hematocrit, creatinine levels, and lipid profiles—were determined using standard methods. High-sensitivity C-reactive protein (hsCRP) levels were measured in whole blood using a turbidimetric method (cobas c 501; Roche Diagnostics USA). Serum endocan levels were measured using an enzyme-linked immunosorbent assay kit (endothelial cell-specific molecule-1 [ESM1] [Endocan] [Human]; Aviscera Bioscience) and the ELx800 absorbance reader (BioTek Instruments, Inc) with an intra-assay coefficient of variability of 6% to 8% and an interassay coefficient of variability of 10% to 12%.

Statistical Analysis

Statistical analyses were performed using SPSS software, version 25 (IBM). The distribution of continuous variables was analyzed using the Kolmogorov-Smirnov test. The mean (SD) was determined for continuous variables, and percentages were determined for categorical variables. A Student *t* test was used to determine the significance of differences between groups for continuous variables. The χ^2 test was used for categorical variables. Pearson correlation analysis was used to assess correlations between serum endocan levels, AHI, and other variables. Univariate and multiple logistic regression analyses were performed to identify independent predictors of OSA severity. Outliers were detected using the multiple value assignment method. A *P* value less than .05 was considered statistically significant.

TABLE I. Characteristics and Laboratory Findings in the Study Population

Variable	Total OSA (N = 115)	Nonhypertensive OSA (n = 67)	Hypertensive OSA (n = 48)	*P* value[a]
Age, mean (SD), y	52.3 (7.1)	51.1 (6.6)	54.5 (7.3)	.011
Male sex, No. (%)	80 (69.0)	50 (74.6)	30 (62.5)	.174
BMI, mean (SD), kg/m^2	34.6 (5.3)	34.1 (5.3)	35.2 (5.4)	.297
Smoking, No. (%)	61 (53)	38 (57)	23 (48)	.235
DM, No. (%)	27 (23.5)	6 (9)	21 (43.8)	<.001
Hyperlipidemia, No. (%)	10 (8.7)	4 (6)	6 (12.5)	.250
Creatinine, mean (SD), mg/dL	0.78 (0.34)	0.78 (0.20)	0.8 (0.50)	.637
eGFR, mean (SD), mL/min/1.73 m^2	107.9 (24.8)	109.5 (30)	105.6 (24.5)	.413
Glucose, mean (SD), mg/dL	115.2 (33.5)	113.8 (31.9)	117.0 (35.9)	.593
HbA_{1c}, mean (SD), %	6.0 (0.9)	5.8 (7.6)	6.3 (1.1)	.014
hsCRP, mean (SD), mg/dL	5.5 (6.1)	4.3 (3.9)	7.0 (8.0)	.039
WBC count, mean (SD), $\times 10^3$/μL	7.1 (1.9)	6.8 (1.9)	7.5 (1.9)	.047
Neutrophil, mean (SD), $\times 10^3$/μL	4.0 (1.5)	3.80 (1.4)	4.3 (1.5)	.057
Lymphocyte, mean (SD), $\times 10^3$/μL	2.4 (0.7)	2.4 (0.7)	2.4 (0.7)	.638
AHI, mean (SD)	32.9 (25.7)	27.1 (21.9)	50.0 (28.3)	.006
MOS, mean (SD), %	77.6 (12.1)	80.2 (8.7)	4.1 (15.1)	.015
AOS, mean (SD), %	90.9 (5.4)	92.0 (4.3)	89.6 (6.5)	.019
Endocan, mean (SD), ng/mL	22.5 (35.2)	22.7 (21.9)	22.2 (28.4)	.944

AHI, apnea-hypopnea index; AOS, average oxygen saturation; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein; MOS, minimum oxygen saturation; OSA, obstructive sleep apnea; WBC, white blood cell.

[a] Comparisons are between patients with and without hypertension; $P < .05$ is considered significant.

TABLE II. Correlation Between Variables and AHI in Patients With OSA

Variable	Total OSA (N = 115)		Nonhypertensive OSA (n = 67)		Hypertensive OSA (n = 48)	
	P value[a]	*r*	*P* value[a]	*r*	*P* value[a]	*r*
Age	.047	0.185	.406	0.103	.285	0.157
BMI	.085	0.161	.708	0.047	.096	0.243
Creatine level	.130	0.142	.126	0.189	.428	0.117
eGFR	.523	−0.060	.947	−0.008	.597	−0.780
Glucose level	.189	0.127	.993	0.001	.119	0.234
HbA_{1c} level	.010	0.240	.635	0.059	.047	0.288
hsCRP level	.124	0.144	.080	0.215	.838	0.030
WBC count	.001	0.295	.019	0.286	.109	0.234
Neutrophil count	.004	0.266	.082	0.214	.088	0.249
Lymphocyte count	.010	0.238	.008	0.322	.325	0.145
MOS	<.001	−0.617	<.001	−0.624	<.001	−0.578
AOS	<.001	−0.644	<.001	−0.707	<.001	−0.564
Endocan level	.014	0.228	0.118	0.193	.033	0.308

AHI, apnea-hypopnea index; AOS, average oxygen saturation; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein; MOS, minimum oxygen saturation; OSA, obstructive sleep apnea; WBC, white blood cell count.

[a] $P < .05$ is considered significant.

TABLE III. Correlation Between Between Measurements and Endocan Levels

Variable	Total OSA (N = 115)		Nonhypertensive OSA (n = 67)		Hypertensive OSA (n = 48)	
	P value[a]	*r*	*P* value[a]	*r*	*P* value[a]	*r*
AHI	.014	0.228	.118	0.193	.033	0.308
MOS	.171	−0.128	.121	−0.191	.514	−0.097
AOS	.098	−0.155	.041	−0.251	.615	−0.074
eGFR	.441	0.073	.607	0.064	.557	0.087

AHI, apnea-hypopnea index; AOS, average oxygen saturation; eGFR, estimated glomerular filtration rate; MOS, minimum oxygen saturation; OSA, obstructive sleep apnea.

[a] $P < .05$ is considered significant.

Results

Of the 115 patients with OSA who met inclusion criteria, 48 had hypertension (hypertensive OSA) and 67 did not (nonhypertensive OSA). There were few notable differences between groups regarding patient age, sex, DM status, glycated hemoglobin (HbA_{1c}) measurement, white blood cell (WBC) count, high-sensitivity C-reactive protein (hsCRP) level, AHI, minimum oxygen saturation, and average oxygen saturation (Table I).

There was a significant correlation between serum endocan levels and AHI in the total study cohort (total OSA, $r = 0.228$; $P = .014$; Table II) and in patients with hypertensive OSA ($r = 0.308$; $P = .033$). However, there was no significant correlation between serum endocan levels and AHI in patients with nonhypertensive OSA ($r = 0.193$; $P = .118$; Table II). There was no significant correlation between BMI and AHI ($r = 0.161$; $P = .085$) or between hsCRP and AHI ($r = 0.144$; $P = .124$) in the total OSA cohort (Table II). There was, however, a significant correlation between AHI and the WBC count, neutrophil count, lymphocyte count, and HbA_{1c} for the total OSA cohort (Table II).

Although endocan levels were significantly correlated with AHI in the total OSA cohort and in the hypertensive OSA group, the oxygen saturations recorded during polysomnography did not correlate significantly with endocan levels (Table III).

TABLE IV. Multivariate Logistic Regression Analysis of Obstructive Sleep Apnea Severity

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value[a]	OR (95% CI)	*P* value[a]
Total OSA (N = 115)				
BMI	1.04 (1.01-1.06)	.005	1.03 (0.99-1.06)	.058
Hypertension	2.68 (1.25-5.75)	.011	2.49 (1.05-5.90)	.039
HbA_{1c} level	1.67 (1.08-2.57)	.020	1.36 (0.83-2.22)	.214
Creatinine level	10.49 (1.31-83.69)	.027	13.01 (1.44-117.35)	.022
Hypertensive OSA (n = 67)				
Endocan level	1.06 (1.00-1.13)	.029	1.06 (1.00-1.13)	.043
Glucose level	1.03 (1.00-1.06)	.050	1.01 (0.98-1.04)	.259
Nonhypertensive OSA (n = 48)				
BMI	1.03 (1.00-1.07)	.050	1.02 (0.98-1.07)	.177
Male sex	12.57 (1.54-102.25)	.018	8.31 (0.61-113.00)	.112
Smoking	3.10 (1.03-9.34)	.044	2.43 (0.71-8.34)	.156
Creatinine level	26.98 (1.59-455.32)	.022	13.04 (0.56-299.57)	.108

BMI, body mass index; HbA_{1c}, glycated hemoglobin; OR, odds ratio; OSA, obstructive sleep apnea.

[a] $P < .05$ is considered significant.

Univariate logistic regression analysis showed that endocan ($P = .029$) and glucose levels ($P = .05$) were predictors of OSA severity for the hypertensive OSA group (Table IV). On multiple logistic regression analysis, only the endocan level was an independent predictor of OSA severity in the hypertensive OSA group ($P = .043$; Table IV).

Discussion

Serum endocan levels are significantly correlated with the AHI in patients with hypertensive OSA but not nonhypertensive OSA. Only a few studies have assessed the relationship between serum endocan levels and OSA severity.[13,14] Endocan levels are significantly higher in patients with OSA than in the control groups of these studies, and there is a significant correlation between the severity of OSA and the endocan level. The present study might be the first to evaluate the relationship between AHI and endocan levels in patients with hypertensive OSA.

It is well known that OSA is closely related to cardiovascular events and mortality.[17,18] Many factors observed in patients with OSA—such as hypoxemia, systemic hypertension, and increased sympathetic activity—are considered to lead to the development of atherosclerosis.[19]

Launois et al[20] showed that the incidence of OSA increases with age, and there is a correlation between OSA and mortality and morbidity. The present study found a significant correlation between age and OSA severity in the study cohort as a whole, but this correlation was not significant in either subgroup (hypertensive OSA or nonhypertensive OSA). As in Ciavarella et al,[21] this study did not find a significant correlation between BMI and AHI in patients with OSA; this lack of correlation was consistent in patients with and without hypertension. Papanas et al[22] showed a significant linear correlation between AHI and HbA_{1c} and fasting glucose levels in patients with OSA but without DM. The present study found a significant correlation between HbA_{1c} and AHI in the total OSA cohort, independent of DM status. This correlation held true for the hypertensive OSA group but not the nonhypertensive OSA group.

Endocan is secreted from the vascular endothelial system, especially when inflammation is present. Therefore, it may play a role in vascular pathology and inflammation. Serum endocan levels are associated with some types of cancer and with inflammation and cardiovascular events.[23] Endocan stimulates smooth muscle proliferation and migration and can cause intimal disruption, which leads to the onset of atherosclerosis. Kose et al[24] examined serum endocan levels in patients with acute coronary syndrome and found a significant increase compared with patients in the control group, but there was no correlation with the severity of disease. Hypertension and endothelial dysfunction are interrelated conditions, and their relationship probably represents an inflammatory process caused by oxidative stress. Serum endocan levels are significantly higher in patients with hypertension than in individuals with normal blood pressure.[25]

The present study has several limitations. First, this was a nonrandomized study and therefore subject to selection bias. Also, endothelial dysfunction was not assessed using flow-mediated dilation or other validated techniques.

In conclusion, there is a significant relationship between serum endocan levels and AHI in patients with OSA and hypertension but not in patients with OSA who do not have hypertension. Endocan measurement may have a place in evaluating patients with hypertensive OSA for adverse cardiovascular events, and it may even help guide OSA therapy for these patients. More investigation is needed to evaluate the relationship between serum endocan levels and OSA severity in patients with OSA but without hypertension.

Published: 1 February 2023

Author Contributions: All authors made substantial contributions to the conception and design of the study or to data acquisition, analysis, or interpretation. All authors reviewed and approved the final manuscript. Dr Serkan Yazan and Dr Hüseyin Karakurt take full responsibility for the integrity of the submission and publication and were involved in the study design.

Conflict of Interest Disclosures: None

Funding/Support: This study did not receive any financial support.

References

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med.* 2002;165(9):1217-1239. doi:10.1164/rccm.2109080
2. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol.* 2013;177(9):1006-1014. doi:10.1093/aje/kws342
3. Köktürk O, Tatlıcıoğlu T, Kemaloğlu Y, Fırat H, Çetin N. Prevalence of obstructive sleep apnea syndrome in patients with habitual snoring. *Tuberk Toraks.* 1997;45:7-11.
4. Chami HA, Resnick HE, Quan SF, Gottlieb DJ. Association of incident cardiovascular disease with progression of sleep-disordered breathing. *Circulation*. 2011;123(12):1280-1286. doi:10.1161/CIRCULATIONAHA.110.974022
5. Durgan DJ, Bryan RM Jr. Cerebrovascular consequences of obstructive sleep apnea. *J Am Heart Assoc.* 2012;1(4):e000091. doi:10.1161/JAHA.111.000091
6. Jean-Louis G; Zizi F; Clark LT; Brown CD; McFarlane SI. Obstructive sleep apnea and cardiovascular disease: role of the metabolic syndrome and its components. *J Clin Sleep Med.* 2008;4(3):261-272.
7. Ge X, Han F, Huang Y, et al. Is obstructive sleep apnea associated with cardiovascular and all-cause mortality? *PLoS One.* 2013;8(7):e69432. doi:10.1371/journal.pone.0069432
8. Endemann DH, Schiffrin EL. Endothelial dysfunction. *J Am Soc Nephrol.* 2004;15(8):1983-1992. doi:10.1097/01.ASN.0000132474.50966.DA
9. Parati G, Lombardi C, Hedner J, et al; EU COST Action B26 members. Recommendations for the management of patients with obstructive sleep apnoea and hypertension. *Eur Respir J.* 2013;41(3):523-538. doi:10.1183/09031936.00226711
10. Sarrazin S, Adam E, Lyon M, et al. Endocan or endothelial cell specific molecule-1 (ESM-1): a potential novel endothelial cell marker and a new target for cancer therapy. *Biochim Biophys Acta.* 2006;1765(1):25-37. doi:10.1016/j.bbcan.2005.08.004
11. Aparci M, Isilak Z, Uz O, Yalcin M, Kucuk U. Endocan and endothelial dysfunction. *Angiology.* 2015;66(5):488-489. doi:10.1177/0003319714568791
12. Zhang SM, Zuo L, Zhou Q, et al. Expression and distribution of endocan in human tissues, *Biotech Histochem.* 2012;87(3):172-178. doi:10.3109/10520295.2011.577754
13. Kanbay A, Ceylan E, Köseoğlu Hİ, et al. Endocan: a novel predictor of endothelial dysfunction in obstructive sleep apnea syndrome. *Clin Respir J.* 2018;12(1):84-90. doi:10.1111/crj.12487
14. Pusuroglu H, Somuncu U, Bolat I, et al. Assessment of the relationship between endocan and obstructive sleep apnea severity. *Arch Med Sci.* 2020;16(6):1346-1352. doi:10.5114/aoms.2020.97764
15. Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. University of California, Brain Information Service/Brain Research Institute; 1968.
16. Williams B, Mancia G, Spiering W, et al; ESC Scientific Document Group. 2018 ESC/ESH guidelines for the management of arterial hypertension *Eur Heart J.* 2018;39(33):3021-3104. doi:10.1093/eurheartj/ehy339
17. Won CH, Chun HJ, Chandra SM, Sarinas PS, Chitkara RK, Heidenreich PA. Severe obstructive sleep apnea increases mortality in patients with ischemic heart disease and myocardial injury. *Sleep Breath.* 2013;17(1):85-91. doi:10.1007/s11325-012-0653-y
18. Baratta F, Pastori D, Fabiani M, et al. Severity of OSAS, CPAP and cardiovascular events: a follow-up study. *Eur J Clin Invest.* 2018;48(5):e12908. doi:10.1111/eci.12908
19. Mooe T, Rabben T, Wiklund U, Franklin KA, Eriksson P. Sleep-disordered breathing in men with coronary artery disease. *Chest.* 1996;109(3):659-663. doi:10.1378/chest.109.3.659
20. Launois SH, Pépin JL, Lévy P. Sleep apnea in the elderly: a specific entity? *Sleep Med Rev.* 2007;11(2):87-97. doi:10.1016/j.smrv.2006.08.005
21. Ciavarella D, Tepedino M, Chimenti C, et al. Correlation between body mass index and obstructive sleep apnea severity indexes - a retrospective study. *Am J Otolaryngol.* 2018;39(4):388-391. doi:10.1016/j.amjoto.2018.03.026
22. Papanas N, Steiropoulos P, Nena E, et al. HbA_{1c} is associated with severity of obstructive sleep apnea hypopnea syndrome in nondiabetic men. *Vasc Health Risk Manag.* 2009;5:751-756. doi:10.2147/vhrm.s7057
23. Aciksari G, Kavas M, Atici A, et al. Endocan levels and endothelial dysfunction in patients with sarcoidosis. *Angiology.* 2018;69(10):878-883. doi:10.1177/0003319718775283
24. 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):727-731. doi:10.1177/0003319714548870
25. Celık T, Balta S, Karaman M, et al. Endocan, a novel marker of endothelial dysfunction in patients with essential hypertension: comparative effects of amlodipine and valsartan. *Blood Press.* 2015;24(1):55-60. doi:10.3109/08037051.2014.972816