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The serum copeptin levels in obstructive sleep apnea patients with prehypertensive

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Abstract. – OBJECTIVE: Copeptin is a precursor of AVP, an antidiuretic hormone, plays a pivotal role in the maintenance of cardiovascular homeostasis. Obstructive sleep apnea syndrome (OSAS) is related to cardiovascular disease. We sought to evaluate the serum copeptin levels in newly diagnosed prehypertensive patients with OSAS.

PATIENTS AND METHODS: Eighty-four prehypertensive patients were evaluated using polysomnography and were divided into two groups, an OSAS (n = 41) group and a control (n = 43) group. Serum copeptin levels were measured using the ELISA method.

RESULTS: Copeptin levels were significantly higher in the OSAS group compared to the control group (146 [93-739] pg/ml vs. 111 [33-253] pg/ml, respectively, $p < 0.001$). A regression analysis revealed that the apnea hypopnea index (AHI) and the lowest SpO_2 were related to serum copeptin levels (unstandardized $\beta = 1.02 \pm 0.40$, $p = 0.014$ and unstandardized $\beta = -3.1 \pm 0.9$, $p = 0.048$ respectively).

CONCLUSIONS: According to the results of our study, serum copeptin levels are higher in the prehypertensive patients with OSAS compared to those in the control group. Therefore, in assessing the severity of OSAS, serum copeptin levels can be a candidate for a biochemical marker in addition to polysomnographic findings.

Key Words:
Prehypertension, Obstructive sleep apnea, Copeptin, Vasopressin, Cardiac diseases.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a sleep disorder that results from a pharyngeal collapse during sleep, resulting in partial or complete airway obstruction[1]. The frequency of this disease is increasing gradually. Numerous studies show the relationship between OSAS and cardiovascular diseases, such as hypertension, coronary artery disease, heart failure, arrhythmia, and stroke[2-5]. In OSAS patients, accompanying cardiovascular complications increase the risk of morbidity and mortality[6].

Prehypertension independent of other cardiovascular risk factors increases the risk of major cardiovascular events. In the Seventh Report of the Joint National Committee (JNC-7), prehypertension was defined as systolic blood pressure between 120 mmHg and 139 mmHg and diastolic blood pressure between 80 mmHg and 89 mmHg[7,8].

Arginin vasopressin (AVP), an antidiuretic hormone, plays a pivotal role in the maintenance of cardiovascular homeostasis. It has a very short half-life and is, therefore, very hard to detect in plasma. Copeptin is a precursor of AVP; it has a longer half-life and is easier to detect in plasma at room temperature[9]. AVP increases during stress conditions, is released during life-threatening conditions and contributes to the maintenance of cardiac homeostasis. Increases in copeptin levels have been reported in acute myocardial infarction and chronic heart failure patients. They have also been shown to have a prognostic value in heart failure patients[10,11]. Repeated apnea episodes cause hypoxia and hypercapnia in OSAS patients, resulting in myocardial ischemia and compensatory activation of the sympathetic nervous system. This condition increases left ventricular afterload, decreases preload, and can lead to heart failure[12]. The aim of our study was to evaluate whether there is a relationship between serum copeptin levels and, apnea hipopnea index (AHI), shows the severity of obstructive sleep apnea, in prehypertensive OSAS patients.

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Patients and Methods

This study was conducted at our University Departments of Cardiology, Chest Disease, and Neurology. Patients who admitted to the above mentioned outpatient clinics were enrolled into the study. The study is a prospective randomized case-control study. Due to irrelevant reports in the literature, the study sample size was not calculated in the ethical board. Hence, the power analysis was obtained according to results of the comparison of OSAS and non-OSAS groups in plasma copeptin levels, which is an important variable of the study. The power of the study was 83.7%, with a reliability of 95%.

The convenience sampling criteria were as followings; being ages between 30-70, having complaints of snoring, sleepiness and apnea episodes during night time, being diagnosed as prehypertension and willing to be participated in the study. According to office blood pressure measurements, prehypertension was defined as systolic blood pressure between 120-139 mmHg and diastolic blood pressure between 80-89 mmHg. Then, the patients with prehypertension were included in the study, they were examined with polisomnography to detect whether they have OSAS or not. All study patients underwent echocardiographic and ambulatory blood pressure recordings to exclude heart disease and hypertension. Exclusion criteria were as followings: being diagnosed with chronic systolic and diastolic heart failure, history of coronary artery disease, severe valvular heart disease, chronic kidney failure, chronic liver disease, cerebrovascular disease, hypertension, antihypertensive drug users, chronic obstructive pulmonary disease, asthma, pulmonary hypertension, cor pulmonale, thyroid disorders, psychiatric disease, using nasal decongestant or antinflammatory drugs, antibiotic treatment within prior month of copeptin level assessment, and unwilling to be enrolled in the study. We especially excluded hypertension patients because they often have diastolic dysfunction. Therefore, we used echocardiography to excluded systolic and diastolic heart failure. The study began with the approval from local Ethics Committee ruling on the decisions of Helsinki Declaration and ethical rules. Patients were informed about the study and included in the study after they signed the informed consent. Medical histories of the patients were taken and physical examinations were done. They had ECG and undergone echocardiographic examinations.

Patients were divided into two groups according to the presence of OSAS. Age, sex, body mass index (BMI), office blood pressure (BP) measurements, smoking status, the presence of diabetes and hyperlipidemia were recorded for both groups. BMI was calculated as weight in kg divided by height in meters (kg/m^2).

After inclusion and exclusion criterias, 84 patients were enrolled in the study. Forty-one prehypertensive patient with newly diagnosed prehypertensive with OSAS (M=29, 70%) and 43 prehypertensive without OSAS control (M=29, 67%) patients, total 84 patients were included into this study.

Ambulatory Blood Pressure Measurements

The ambulatory blood pressure measurement device (Tonoport V, GE Healthcare, Berlin, Germany) was used blood pressure measurement for 24 hours. A collar was put on a non-dominant arm and removed after 24 hours. A device was programmed for blood pressure measurements 15 minutes apart for the daytime and 30 minutes apart for the nighttime. Time intervals of the day and night were individualized according to sleeping times of the patients. Participants were told to have routine daily activities and not to move and hold their arms at heart level while the device is making the measurement.

Records were accepted as eligible when there were at least 80% successfull day and night time systolic and diastolic blood pressure measurements. Each measurement was validated with computer and manually and extreme results (systolic BP < 80 mmHg or > 260 mmHg; diastolic BP < 40 mmHg or > 150 mmHg; and heart rate (HR) < 40 beats/min or >150 beats/min) were deleted. Patients with daytime systolic BP above 135 mm Hg and/or diastolic BP above 85 mm Hg, night time systolic BP above 120 mmHg diastolic BP above 70 mmHg and 24 hours mean systolic BP above 130 mmHg and diastolic BP above 80 mmHg were accepted as hypertensive and excluded from study[13].

Polysomnographic Examination

Participants were informed about the study and warned not to have caffeine containing food and beverages, alcohol and drugs that may interfere regular sleep pattern before the procedure. Polysomnographic examinations were done in a dark, quiet, temperature-controlled room without a companion. Polysomnography findings were

obtained using a computerized system (Embla N7000; Somnologica, Broomfield, CO, USA). Electroencephalography, electrooculography, electromyography of submental and tibialis anterior muscle, nose and mouth airflow measurements by using nasal cannula and nasal-oral thermistor, arterial oxygen saturation measurement by using pulse oxymeter, torax and abdominal movements, snoring and electrocardiographic reports were recorded. All these records were evaluated by a neurologist who is an expert about sleep. Sleeping score was done according to American Academy of Sleep Medicine 2007 criteria[14].

Obstructive apnea was defined as cessation of airflow from mouth or nose for 10 seconds or more, and hypopnea was defined as at least 50% or more decrease in the airflow for 10 seconds or more accompanying 3% the decrease in the oxygen saturation. Apnea hypopnea index (AHI) was obtained by dividing the number of the total apnea-hypopnea episodes to the duration of the total sleeping time. Patients who had AHI ≥ 5 were accepted to have obstructive sleep apnea (OSA). AHI < 5 was accepted as normal, namely non OSAS groups. According to AHI, patients were divided into three groups as mild OSA (AHI 5-14), moderate OSA (AHI 15-29) and severe OSA (AHI > 30).

Biochemical Analysis

A venous blood sample was drawn after at least 12 hours of fasting. These samples were centrifugated. Fasting plasma glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides (TG), creatinine levels were measured with Roche Sysmex XT-2000i autoanalyzer (Roche Diagnostics, Paris, France) machine. Dyslipidemia was defined as total cholesterol (TC) ≥ 220 mg/dL, low density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL, triglyceride (TG) ≥ 150 mg/dL[15] and diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL and HbA1C ≥ 6.5[16]. The blood sample drawn for the measurement of copeptin were put in a tube containing EDTA and centrifugated for 10 minutes at 5000 rpm and kept at –80 degrees refrigerator. Copeptin levels were measured according to the instructions of the producer company with Copeptin ELISA kit (Hangzhou Eastbiopharm Co. Ltd., Hangzhou, China) Results were given as pg/ml. The intra and inter variability values for Copeptin were < 10% vs <12% respectively. Detection range was 4-2000 pg/ml. The normal values of copeptin in healthy individuals were not given by producer companies of the kits.

Transthoracic Echocardiograpy

All of the patients had an echocardiographic examination by an experienced cardiologist with Vivid S5 (GE Vingmed Ultrasound AS, Horten, Norway) machine. Two dimensional, M-Mode measurements were done. Left ventricular measurements were done at parasternal long axis view according to recommendations of American Echocardiography Association[17]. Measurements were done from parasternal long axis while patients were lying at left lateral decubitus position and in addition to aorta, left atrium, left ventricular systolic and diastolic diameters, left vetricular ejection fraction (LVEF) according to Simpson method were measured.

Statistical Analysis

Data were analyzed with PASW Statistics Windows 18 (SPSS Inc., Chicago, IL, USA) program. Distribution of the variables was analyzed with Shapiro-Wilk test. Parametric continuous variables were given as mean ±standard deviation and non-parametric continuous variables were given as median (minimum-maximum) and categorical variables were given as numbers and ratios. In a comparison of the two independent group student *t* test was used for even distribution and Mann Whitney U test was used for uneven distribution. Categorical variables were compared with chi square test or Fisher test when necessary. According to univariate linear regression analysis, the variables with $p < 0.10$ were included in multivariate linear regression analysis to find out the relation between copeptin levels and demographic variables and polysomnographic parameters. *p* values below 0.05 were accepted as statistically significant.

Results

Mean age of the patients in the OSAS group was 50.5±9.8 years and control group was 50.2±11.1 years. There was no difference with regard to age and the sex between to groups. (p = 0.878 vs p = 0.744 respectively). There were also no difference according to BMI, diabetes, hyperlpidemia, smoking ratio, fasting plasma glucose TC, LDL-C, HDL-C, TG, creatinine, left ventricular ejection fraction between two groups (Table I).

Table I. Demographic, polysomnographic parameters and copeptin levels in OSAS and control group.

	OSAS group (n=41)	Control group (n=43)	*p* values
Age, years	50.5 ± 9.8	50.2 ± 11.1	0.878
Gender (M), n (%)	29 (70)	29 (67)	0.744
BMI, kg/m^2	34.2 ± 8.4	32.7 ± 5.2	0.337
Systolic BP, mmHg	129 ± 4.8	127 ± 5.2	0.608
Diastolic BP, mmHg	83 ± 3.6	82 ± 4.1	0.711
Diabetes mellitus, n (%)	6 (15)	11 (25)	0.212
Hyperlipidemia, n (%)	4 (10)	9 (20)	0.157
Smoking, n (%)	9 (22)	9 (21)	0.909
Fasting glucose, mg/dL	112 (70-195)	108 (74-165)	0.441
TC, mg/dL	180 ± 27	186 ± 24	0.651
LDL-C, mg/dL	120 ± 30	125 ± 33	0.613
HDL-C, mg/dL	38 (25-72)	41 (28-77)	0.242
TG, mg/dL	200 (101-254)	212 (98-241)	0.256
Creatinine,	1.12 ± 0.4	1.06 ± 0.5	0.610
LVEF, %	56.9 ± 9.8	57.7 ± 3.2	0.808
AHI	26.8 (6-102)	2 (1-4)	< 0.001
Mean SpO_2, %	93 ± 2	94 ± 3	0.844
Lowest SpO_2, %	77 ± 8	90 ± 5	< 0.001
Copeptin, pg/mL	146 (93-739)	111 (33-253)	< 0.001

AHI: apnea-hypopnea index, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, LVEF: left ventricular ejection fraction, OSAS: obstructive sleep apnea syndrome, SpO_2: oxygen saturation, TC: total cholesterol, TG: triglyceride.

There were no difference in systolic blood pressure and diastolic blood pressure between two groups. Mean SpO_2 was similar in two groups (93% ± 2 in the OSAS group and 94 ± 3% in the control group p = 0.844), however lowest SpO_2 levels were lower in the OSAS group (77 ± 8% in the OSAS group and 90±5% in the control group, p < 0.001). Mean AHI was 26.8 (6-102) in the OSAS group and 2 (1-4) in the control group (p < 0.001). Copeptin levels were significantly higher in the OSAS group (146 (93-739) pg/ml in the OSAS group, 111 (33-253) pg/ml in the control group, p < 0.001) (Figure 1).

Univariate and multivariate linear regression analysis were done in order to find out the relation between copeptin levels and diabetes, coronary artery disease, smoking, age, AHI, lowest SpO_2, BMI, LVEF. AHI and lowest SpO_2 levels were the only parameters that was found to be related to copeptin levels (unstandardized = 1.02 ± 0.40, p = 0.014 vs unstandardized = -3.1 ± 0.9, p = 0.048 respectively) (Table II).

Discussion

In this study, we have measured the serum copeptin levels in prehypertensive patients with and without OSAS. Interestingly, we found higher serum copeptin levels in OSAS patients who are at greater risk of developing cardiovascular diseases. In addition, there was a relationship between copeptin levels and the AHI and the lowest oxygen saturation values. There was no difference between the two groups with regard to age, sex, BMI, presence of diabetes mellitus, hyperlipidemia, smoking status, fasting plasma glucose, TC, LDL-C, HDL-C, TG,

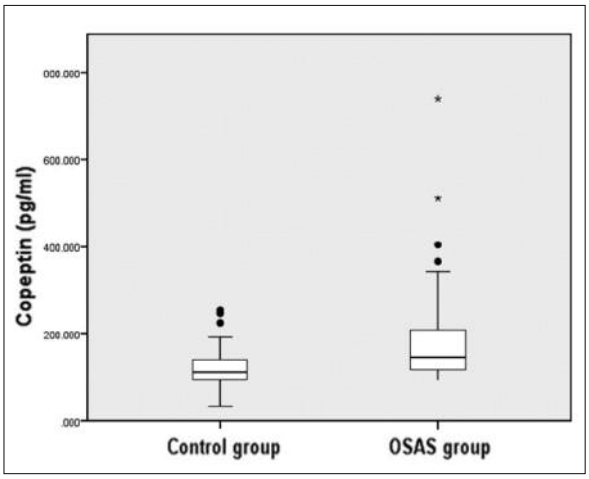

Figure 1. Serum copeptin levels in prehypertensive patients with or without OSAS: obstructive sleep apnea syndrome.

Table II. Univariate and multivariate linear regression analysis of the copeptin levels with demographic variables and polysomnographic parameters.

	Unstandardized coefficients		
	B	Std Error	*p* values
Univariate			
Hyperlipidemia	45.5	30.6	0.141
Diabetes mellitus	15.2	27.8	0.587
Smoking	27.2	27.1	0.320
Age	0.74	1.07	0.494
AHI	0.906	0.39	0.024
Lowest SpO_2	-3.8	1.1	0.041
BMI	1.93	1.61	0.232
LVEF	3.1	3.6	0.392
Multivariate			
AHI	1.02	0.40	0.014
Lowest SpO_2	-3.1	0.9	0.048

AHI: apnea-hypopnea index, BMI: body mass index, CAD: coronary artery disease, LVEF: left ventricular ejection fraction, SpO_2: oxygen saturation.

creatinine levels, LVEF, and mean peripheral capillary oxygen saturation (SpO_2) levels. The similar distributions of the cardiovascular risk factors, such as age, sex, presence of diabetes, hyperlipidemia and smoking status, between the two groups make the results of our study more valuable.

Hypoxia that results from repeated episodes of apnea and hypopnea in OSAS patients activates the sympathetic nervous system, causes endothelial dysfunction, and plays a role in the development of cardiovascular complications[2,18]. Several cardiac biomarkers, such as C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), adiponectin, brain natriuretic peptides (BNPs), and interleukin-1, have been suggested to be used in the early diagnosis, treatment and estimation of the prognosis for cardiovascular complications in OSAS patients[19-22]. Hypoxic episodes in OSAS cause an inflammatory response that has been proved by the increase in inflammatory mediators, and this may ultimately result in endothelial dysfunction, the development of atherosclerosis, and a decrease in cardiac function due to myocardial depression. Previous studies[23,24] have revealed that intermittent hypoxia increases sympathetic activity and norepinephrine levels in patients with OSAS. In one study[25], serum copeptin levels were increased with 3,4-methylenedioxymethamphetamine (MDMA). Thus, it was considered to play a role in the transport of norepinephrine and serotonin. Interestingly, this effect was blocked with the administration of the serotonin and norepinephrine transporter inhibitor.

Copeptin is a nonspecific marker of the endogenous stress response. Jayasinghe et al[26] measured the copeptin and troponin levels in acute coronary syndrome patients admitted to an emergency department. Copeptin and troponin levels were found to be increased and are suggested to be used to evaluate acute coronary syndrome patients. In another study, the relationship between the development of heart failure after acute myocardial infarction (AMI) and serum copeptin levels was evaluated in 224 patients. Copeptin levels were found to be stronger markers compared to brain natriuretic peptide (BNP) and NT-proBNP levels in patients who had heart failure after AMI[27]. Higher copeptin levels in prehypertensive patients with OSAS compared to patients without OSAS can be explained by the increase in sympathetic activity triggered by hypoxia in OSAS patients. To our knowledge there has been not any study that shows the relationship between prehypertension and copeptin levels. However, it has been demonstrated that serum copeptin levels are significantly higher in hypertensive patients in adolescence compared to the control group[28]. In addition, there are many studies about the role of AVP in the pathogenesis of hypertension.

The renin-angiotensin-aldosterone system in the brain releases vasopressin from the hypothalamic-pituitary system and, in combination with the autonomic nervous system, regulates cardiovascular, fluid, and electrolyte homeostasis. It has been demonstrated that AVP releases neurons regulating the sympathetic nervous system[29-31]. Regarding the data that mentioned above, it might be plausible to expect an increase in serum copeptin levels in OSAS patients due to adrenergic stimulation secondary to intermittent hypoxia. The results of our study have demonstrated that serum copeptin levels are higher in OSAS patients compared to the control group. However, it is interesting to note that Ozben et al[32] found lower copeptin levels in OSAS patients. To our knowledge, this is the one and only study in the literature to report this finding. Ozben et al[32] attributed this finding to the dysregulation of the antidiuretic hormone (ADH) or arginine vasopressin. However, most of the patients in their study were hypertensive.

In fact, serum copeptin levels are higher in hypertensive patients[28,33]. The patients in our study were prehypertensive. Hypertensive patients were excluded from our study based on the results of ambulatory blood pressure monitoring. Because we do not have hypertension as a confounding factor, our results show the relationship between copeptin levels and the severity of OSAS better.

We would like to underline that, if we could have measured the adrenalin in serum and urine and showed the relationship with copeptin levels, the power of our study would have increased. The reported copeptin levels in this study are not consistent with prior research because the manufacturer of copeptin kits do not report the normal level for the copeptin. The serum copeptin levels in this study seem to exceed the normal range reported in previous studies[32]. We think that our entire sample consistent of a cohort with cardiovascular diseases. We studied patients with snoring, sleepiness and apneic events during sleep. There exists a relationship between snoring and CVD[34,35]. Therefore, the propensity for elevated copeptin levels in the study is high for both the OSAS and control groups. In addition, we could not design and analyze the study according to how mild, moderate, severe OSAS because the limited sample size.

Conclusions

According to the results of our study, serum copeptin levels are higher in prehypertensive patients with OSAS compared to the control group. In addition, there is a relationship between serum copeptin levels and the lowest SpO_2 and the AHI. For this reason, serum copeptin levels should be assessed in prehypertension patients, higher levels may indicate the need for polysomnography. The findings of this study have important implication on who should and should not undergo polysomnograhy. There is a need for large studies that support the relationship between serum copeptin levels and the presence of OSAS in prehypertensive patients.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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