Original Article

Do serum copeptin levels change with positive airway pressure treatment in patients with severe obstructive sleep apnea?

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ABSTRACT

Objectives: The aim of this study was to evaluate serum copeptin levels in patients with obstructive sleep apnea (OSA) before and after the positive airway pressure (PAP) treatment.

Patients and Methods: A total of 16 patients (14 males, 2 females; median age 48 years; range, 38 to 60 years) with severe sleep apnea based on the Apnea Hypopnea Index (AHI) >30 and 20 healthy controls (10 males, 10 females; median age 35.5 years; range, 22 to 47 years) were included in this study between October 2014 and December 2015. Full-night polysomnography was applied to each patient. Serum copeptin levels were determined using the enzyme-linked immunosorbent assay in both groups. Serum copeptin level measurement was repeated in the patient group after one year of PAP treatment.

Results: After one year of PAP treatment, serum copeptin levels of the patients with OSA decreased, although there was no statistically significant difference before and after treatment.

Conclusion: Increased serum copeptin concentration may reflect a response to moderate stress in many diseases, particularly cardiovascular diseases. Based on our study results, there was no significant difference between the severe OSA group and healthy volunteers and before and after treatment among the patients with severe OSA.

Keywords: Copeptin, severe obstructive sleep apnea, sleep apnea, vasopressin.

Obstructive sleep apnea (OSA) is the most common sleep disorder.[1,2] It is characterized by collapses of the upper airway during sleeping with complete or partial obstruction of breathing.[3,4] This type of obstruction causes hypoxia in OSA, leading to sympathetic activation and oxidative stress.

In recent years, there has been an increasing interest in copeptin owing to its diagnostic and prognostic value in a variety of diseases.[5]

Received: July 03, 2020 **Accepted:** September 07, 2020 **Published online:** September 21, 2020

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Doi: http://dx.doi.org/10.5606/Tr-ENT.2020.91885

Citation:
Osma Ü, Selçuk ÖT, Eyigör M, Renda L, Türkoğlu Selçuk N, Eyigör H, et al. Do serum copeptin levels change with positive airway pressure treatment in patients with severe obstructive sleep apnea? Tr-ENT 2020;30(2):52-57.

Copeptin has been also shown as a marker of individual stress level.[6] Copeptin is expected to increase in OSA, although recent studies have shown different levels of serum copeptin in patients with OSA.[4,7,8]

In the present study, we aimed to evaluate serum copeptin levels in patients with severe OSA and compare these levels with those of healthy volunteers (control group) and to evaluate copeptin levels before and after positive airway pressure (PAP) treatment in severe OSA patients.

PATIENTS AND METHODS

This study was conducted at Antalya Training and Research Hospital, Department of Ear, Nose and Throat outpatient clinic between October 2014 and December 2015. A written informed consent was obtained from each participant. The study protocol was approved by the Antalya Training and Research Hospital, Local Ethics Committee (No:47/3). The study was conducted in accordance with the principles of Declaration of Helsinki.

A total of 16 patients (14 males, 2 females; median age 48 years; range, 38 to 60 years) with severe sleep apnea based on the Apnea Hypopnea Index (AHI) >30 and 20 healthy controls (10 males, 10 females; median age 35.5 years; range, 22 to 47 years) were included in this study. Inclusion criteria for the patient group were snoring, witness apnea, and daytime sleepiness, and no history of cardiovascular and pulmonary diseases. All patients were evaluated with a full-night polysomnography (PSG). Those who were diagnosed with severe OSA underwent PAP treatment for one year. The pulmonary function tests of all participants were evaluated. Patients suspected of narcolepsy, hypersomnolence, periodic limb movement disorder, previous history of OSA surgery, previous history of PAP treatment, and obesity hypoventilation syndrome were excluded from the study. Patients with psychiatric or neurological disorders and major systemic co-morbidities were also excluded. The Epworth Sleepiness Scale (ESS) score was calculated for each patient using the validated Turkish version of the ESS questionnaire.[9] The body mass index (BMI) was calculated as weight (kg) divided by the height-squared (m^2).

Blood samples were taken from the anterior cubital vein after a minimum of 8-h fasting between 07:00 and 08:00 A.M. and blood samples were kept at -4°C until centrifugation. After centrifugation, plasma was stored at -70°C until analysis. Copeptin levels were quantified with a human copeptin ELISA kit (Phoenix Pharmaceuticals Inc., CA, USA) according to the manufacturer's instructions.

Polysomnography analysis

Full-night PSG recording was applied with a Grass-Telefactor PMA AS40 (Natus Medical Incorporated, Pleasanton, CA, USA) in the sleep laboratory of our department. The PSG recordings were scored manually by a single examiner. Measured parameters included electroencephalography (C4/A1, O2/A1, F4/A1, F3/A2), electrooculography, electrocardiogram, oronasal airflow either by nasal cannula or thermal sensors, pulse oximetry, thoracoabdominal movements, submental and pretibial electromyography, and snoring noises. Staging was performed according to the guidelines of the 2012 American Sleep Academy Association criteria.[10]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in median (min-max) or number and frequency, where applicable. Since the number of observations was few, differences between two independent groups were analyzed using the Mann-Whitney U test and differences between two related groups using the Wilcoxon signed-rank test. A p value of 0.05 was considered statistically significant.

RESULTS

Of a total of 36 participants, 16 were in the patient group and 20 were in the control group. The median BMI value was found to be lower in the male participants. After treatment, the median serum copeptin levels of the patients decreased for both sexes. Baseline demographic characteristics of males and females are shown in Table 1.

The PSG parameters of the sex groups are shown in Table 2. Accordingly, the median

Table 1. Demographic characteristics and copeptin levels of participants according to sex

	Male		Female		Total	
	Median	Min-Max	Median	Min-Max	Median	Min-Max
Age (year)	48.00	38.0-60.0	49.50	46.0-53.0	48.00	38.0-60.0
Body mass index (kg/m^2)	31.50	27.0-41.0	34.50	29.0-40.0	31.50	27.0-41.0
Epworth score	9.50	1.0-21.0	12.50	4.0-21.0	9.50	1.0-21.0
Copeptin (before treatment)	0.71	0.60-1.16	0.76	0.74-0.78	0.73	0.60-1.16
Copeptin (after treatment)	0.665	0.32-0.98	0.675	0.67-0.68	0.675	0.32-0.98

Min: Minimum; Max: Maximum.

AHI values were low in the female group. The median apnea duration was 23.05 (range, 16.4 to 43.1) min. The median longest non-rapid eye movement apnea value was higher in the female group. The median oxygen saturation (SO_2) values were similar in both groups.

For the patient group, comparisons of serum copeptin levels before and after treatment are shown in Table 3. Accordingly, there was no statistically significant difference in the patient group in terms of copeptin levels before and after treatment. A comparison was made between

Table 2. Polysomnographic parameters of severe obstructive sleep apnea sex groups

	Male		Female		Total	
	Median	Min-Max	Median	Min-Max	Median	Min-Max
AHI	73.70	31.0-101.3	53.95	53.0-54.9	72.20	31.0-101.3
Non-REM AHI	74.00	25.7-102.3	48.45	43.9-53.0	72.60	25.7-102.3
REM AHI	67.75	20.3-89.4	44.80	0.0-89.6	67.75	0.0-89.6
REM apnea index	59.10	1.0-89.4	39.55	0.0-79.1	59.10	0.0-89.4
Hypopnea index	12.25	0.4-54.3	24.70	18.6-30.8	15.70	0.4-54.3
Total apnea index	55.60	12.5-96.8	29.30	22.3-36.3	54.45	12.5-96.8
Average apnea duration	24.00	16.4-43.1	21.05	19.5-22.6	23.05	16.4-43.1
Longest apnea non-REM	51.80	28.5-135.2	70.75	36.4-105.1	51.80	28.5-135.2
Average SO_2	92.25	9.3-95.9	93.15	90.8-95.5	92.25	9.3-95.9
Minimum SO_2	72.50	67.0-91.0	73.50	67.0-80.0	72.50	67.0-91.0
Average desaturation	51.80	24.8-78.1	44.35	41.7-47.0	51.70	24.8-78.1
<90 desaturation	77.80	12.8-150.5	114.50	32.7-196.3	77.80	12.8-196.3

Min: Minimum; Max: Maximum; AHI: Apnea Hypopnea Index; REM: Rapid eye movement; SO_2: Oxygen saturation.

Table 3. Comparison of copeptin levels before and after treatment

	Before treatment		After treatment		
	Median	Min-Max	Median	Min-Max	*p*
Copeptin	0.73	0.60-1.16	0.675	0.32-0.98	0.156

Min: Minimum; Max: Maximum.

Table 4. Comparison of treatment and control groups in terms of demographic characteristics

	Treatment group		Control group		
	Median	Min-Max	Median	Min-Max	*p*
Age (year)	48.00	38.0-60.0	30.50	22.0-47.0	<0.001
Copeptin (before treatment)	0.73	0.60-1.16	0.81	0.42-1.04	0.077

Min: Minimum; Max: Maximum.

the treatment and control groups in terms of age and copeptin. A statistically significant difference was found in the age between the patient and control groups. The results are shown in Table 4.

DISCUSSION

Obstructive sleep apnea is associated with various systemic diseases such as, obesity, metabolic syndrome, increased insulin resistance, hypertension, myocardial infarction, congestive heart failure, stroke, pulmonary hypertension cognitive dysfunction, and impotence, with subsequent deterioration of the patient's quality of life.[2,4,11] It has a complex pathophysiology with repetitive upper airway collapses which cause obstruction of breathing, and oxygen desaturation, resulting in sleep fragmentation.[2] This chronic, intermittent hypoxemia induces an inflammatory process which, then, triggers oxidative stress and sympathetic activation associated with endothelial dysfunction and results in an increase in the cardiovascular and cerebrovascular morbidity.[4]

The hormones of the arginine vasopressin (AVP) cascade system including AVP and copeptin have been recently attracted a great interest owing to their diagnostic and prognostic value in a variety of diseases.[12] The AVP is produced in the hypothalamus and, then, stored in the pituitary gland. Hypoxia, hypotension, hyperosmolarity, acidosis, and infections stimulate AVP release.[13] The AVP has osmoregulatory effects and reflects the individual stress response.[13] Copeptin has been suggested as a marker of individual stress level similar to AVP.[6,14] Serum AVP has molecular instability and a short half-life which limits its use in clinical trials.[12] Copeptin is the C-terminal portion of provasopressin. It is co-synthesized with vasopressin. Copeptin represents vasopressin levels. Since it is more stable in plasma and serum, copeptin has been used instead of AVP in clinical studies.[12,15]

Serum cortisol levels are well known to be related to the degree of internal and external stress. In severe situations such as sepsis, cortisol levels may predict the outcome.[16] It has been shown that copeptin and cortisol levels have a significant correlation in patients and copeptin levels seem to show moderate levels of stress better than cortisol levels.[16]

Most studies regarding the use of copeptin have been conducted on cardiovascular diseases such as acute myocardial infarction, coronary artery disease, heart failure, and vasodilatory shock.[5] However, in recent years, several researches for the use of copeptin in various non-cardiovascular diseases including hyponatremia, lower respiratory tract infections, sepsis and septic shock, acute dyspnea, diabetes insipidus, kidney disease, diabetes mellitus, metabolic syndrome, central nervous system diseases, pre-eclampsia, sinusitis and OSA have been conducted.[5,7,13,17] In a study, copeptin levels were found to be significantly higher in hospitalized patients compared to healthy controls.[6] However, in the current study, no statistically significant difference was observed between the OSA group and healthy controls.

Obstructive sleep apnea is characterized with intermittent hypoxemia that causes sympathetic activation, inducing oxidative stress. To date, there are only three studies investigating serum copeptin levels in patients with OSA.[4,7,8] Interestingly, the results were conflicting. In the study by Ozben et al.,[4] serum copeptin levels were found to be significantly lower in 60 patients with moderate and severe OSA

compared to 26 healthy controls. These results were explained as the negative effect of increased atrial natriuretic peptide (ANP) levels on the secretion of antidiuretic hormone (ADH).[4] In contrast with the results of Ozben et al.,[4] no statistically significant difference was found between the AHI groups and simple snorers in terms of copeptin in another study by Selcuk et al.[7] However, a correlation was found between the AHI and copeptin levels which may represent the developing oxidative stress level without the negative effect of increased ANP levels on the secretion of ADH in patients with OSA. In another study, copeptin levels were evaluated in 116 OSA patients and healthy volunteers and the authors reported increased levels of copeptin in patients with OSA, compared to the control group.[8] In the current study, no significant difference was found between the severe OSA group and healthy volunteers. A decrease in serum copeptin levels was also obtained after one year of PAP treatment in the severe OSA group, although there was no statistically significant difference in the patient group in terms of copeptin levels before and after PAP treatment.

This study has some limitations including small sample size. In addition, these results only represent the findings of the sleep laboratory group. On the other hand, this study is the first to compare serum copeptin levels with PAP treatment in patients with severe OSA.

In conclusion, increased serum copeptin concentration may reflect a response to moderate stress in many diseases, particularly cardiovascular diseases. Based on our study results, there was no significant difference between the severe OSA group and healthy volunteers and before and after PAP treatment among the patients with severe OSA. However, further large-scale, prospective studies are needed to confirm these findings.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

This study was funded by the Antalya Training and Research Hospital, Scientific Research Support Fund.

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