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Can we use serum copeptin levels as a biomarker in obstructive sleep apnea syndrome?

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ABSTRACT

Objective: The aim of this study was to compare serum copeptin levels in patients with obstructive sleep apnea syndrome (OSA) and simple snorers without sleep apnea; and to investigate relationships between copeptin levels and polysomnographic parameters.
Methods: Serum copeptin levels were determined using enzyme-linked immunosorbent assay in 47 patients with OSA and 12 patients without OSA (control group). Full-night polysomnography was performed in each patient. Patients with OSA were divided into three groups according to their Apnea Hypopnea Index (AHI) scores: mild OSA ($5 < AHI < 15$), moderate OSA ($15 < AHI < 30$), and severe OSA ($AHI > 30$).
Results: A total of 59 patients were included in the study. There were 23 female (39.0 %) and 36 male (61.0 %) subjects. The range of ages of study subjects was between 27 and 63 (mean 44.75 ± 9.64) years. According to the AHI values, patients were classified into four groups: simple snoring ($n = 13$), mild OSA ($n = 10$), moderate OSA ($n = 15$), and severe OSA ($n = 21$). Statistically significant differences between AHI groups in terms of age, Epworth score, and neck circumference. According to multiple comparison results for age, the difference between simple snoring and moderate OSA was statistically significant. According to multiple comparison results for Epworth score, the difference between simple snoring and severe OSA was statistically significant. According to multiple comparison results for neck circumference, a similar result was found like Epworth Sleepiness Scale score. The difference between AHI groups by gender was tested by a Pearson χ^2 test and was found to be statistically significant. There was no statistically significant difference among AHI groups in terms of copeptin. There was a statistically significant correlation of copeptin with AHI during rapid eye movement (REM) sleep; however, the correlation coefficient was not sufficiently large.
Conclusions: Increased serum copeptin concentration may reflect a response to stress in some diseases. This is well documented especially in cardiovascular diseases; however, we could not find any difference in OSA groups in terms of copeptin levels.

1. Introduction

Obstructive sleep apnea (OSA) is a major public health problem with an estimated prevalence of 24% in middle-aged men and 9% in middle-aged women (Dyken and Im, 2009; Tuomilehto et al., 2013). OSA is characterized by collapse of the upper airway, which causes complete or partial obstruction of breathing during sleeping (Querciola et al., 2010; Ozben et al., 2013).

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The arginine vasopressin (AVP) and copeptin have gained interest because of their diagnostic and prognostic values in variety of diseases in recent years (Yalta et al., 2013). AVP has osmoregulatory effects and reflects the individual stress response (Seligman et al., 2012). Copeptin represents vasopressin levels and is more stable in plasma and serum because of its favorable structural properties; copeptin has been used instead of AVP in clinical studies (Voors et al., 2009; Yalta et al., 2011). Copeptin has also been suggested as a marker of individual stress levels (Katan et al., 2008a). Copeptin levels seem to show moderate levels of stress better than cortisol levels (Katan et al., 2008b).

Airway obstruction and hypoxia in OSA causes sympathetic activation and oxidative stress. Copeptin is expected to increase in OSA and might be useful as a biomarker of increased risk; however, a recent study showed low levels of serum copeptin in patients with OSA (Ozben et al., 2013).

Therefore, the aim of this study was to evaluate copeptin levels in patients with OSA and to compare these levels with those in patients with simple snoring (control group). In addition, the study evaluated the use of copeptin as a biomarker that could be useful in the diagnosis, prognostication, treatment, and follow-up of OSA by comparing copeptin levels with polysomnographic parameters.

2. Material and methods

The study was performed at Antalya Research and Teaching Hospital, Otolaryngology and Sleep Medicine Clinic and Health Sciences Research and Application Center of Akdeniz University. The study was approved by the Antalya Research and Teaching Hospital local ethical committee. All patients gave written informed consent before inclusion in the study.

2.1. Patient selection

A total of 59 patients between the ages of 18 and 64 years who had symptoms including snoring, witnessed apnea, and daytime sleepiness and who were consecutively evaluated with a full-night polysomnography (PSG) recording between December 2013 and March 2014 and were without a history of cardiovascular and pulmonary disease were included in the study. All patients' pulmonary function test results were evaluated. Patients suspected of narcolepsy, hypersomnolence, periodic limb movement disorder, previous history of OSAS surgery, previous history of positive airway pressure treatment, and obesity hypoventilation syndrome were excluded from the study. Patients with psychiatric or neurological disorders and major systemic co-morbidities were also excluded. Epworth Sleepiness Scale (ESS) scores were assessed for all patients using the validated Turkish version of the ESS questionnaire (Izci et al., 2008). Body mass index (BMI) was calculated as weight (kg) divided by the height-squared (m^2). Blood samples were taken from the antecubital vein after a minimum of 8 h of fasting between 07:00 and 08:00 and blood samples were kept at −4 °C until centrifugation. After centrifugation, plasma was stored at −70 °C until assay.

2.2. Measurement of copeptin levels

Copeptin levels were quantified with a Human Copeptin ELISA Kit (Eastbiopharm, China) according to the manufacturer's instructions.

2.3. Polysomnography analysis

Full-night polysomnographic recording was performed by Grass-telefactor–PMA AS40 in the sleep laboratory of our department. Polysomnograms were scored manually by the same examiner. Measured parameters included electroencephalography (C4/A1, O2/A1, F4/A1, F3/A2), electro-oculography, electrocardiography, oronasal airflow by either nasal cannula or thermal sensors, pulse oximetry, thoracoabdominal movements, submental and pretibial electromyography, and snoring noises. Staging was performed according to the guidelines of American Sleep Academy Association 2007 criteria (Iber et al., 2007).

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 21.0. Numeric variables were given as mean ± standard deviation (SD), and categorical variables were given as percentages. The goodness-of-fit test of numeric variables of normal distribution was determined using Shapiro–Wilk test. Equality of variances of numeric variables was tested by the Levene test.

The difference between OSA groups in terms of age and EES scores was tested by one-way analysis of variance (ANOVA), and the difference between AHI groups in terms of BMI, copeptin, and neck circumference (cm) was tested by the Kruskal–Wallis test. If a significant difference was found in ANOVA and the Kruskal–Wallis test, the Tukey post hoc test and Mann–Whitney test with Bonferroni adjustment were used to determine significant groups, respectively. For categorical variables, the Pearson χ^2 test was used to test differences among AHI groups. Finally, to test the correlation between age, BMI, copeptin, neck circumference, and polysomnographic findings, the Spearman rho test was used. A p-value of less than 0.05 was accepted as significant.

3. Results

A total of 59 patients were included in the study. There were 23 female (39.0%) and 36 male (61.0%) subjects. Ages of study subjects ranged between 27 and 63 (mean, 44.75 ± 9.64) years. According to their Apnea Hypopnea Index (AHI) scores, patients were classified into four groups: simple snoring (n = 13), mild OSA (n = 10), moderate OSA (n = 15), and severe OSA (n = 21). Demographic characteristics of AHI groups are shown in Table 1. A statistically significant difference between AHI groups was found in terms of age ($p = 0.019$), ESS score ($p = 0.011$), and neck circumference ($p = 0.009$) According to multiple comparison results for age, the difference between simple snoring and moderate OSA was statistically significant ($p = 0.013$). According to multiple comparison results for ESS scores, the difference between simple snoring and severe OSA was statistically significant ($p = 0.011$). According to multiple comparison results for neck circumference, results were similar to those for the ESS score ($p = 0.004$). The difference between AHI groups for gender was tested by the Pearson χ^2 test and was found statistically significant ($p = 0.006$). No statistically significant difference among AHI groups in terms of copeptin was found ($p = 0.071$).

Correlation coefficients and significance levels between age, BMI, copeptin, neck circumference, and polysomnographic findings are given in Table 2. There was a statistically significant correlation of copeptin with REM AHI (Spearman rho = 0.280, p = 0.032) and hypopnea index (Spearman rho = 0.429, p = 0.001); however, the correlation coefficient was not sufficiently large. REM AHI was positively correlated with almost every variable. Like neck circumference, ESS score was found to be negatively correlated with average SO_2 and minimum SO_2, whereas it was positively correlated with other variables.

4. Discussion

OSA is the most common sleep disorder, with a prevalence of 24% in men and 9% in women, and causes excessive daytime