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Original Article

Obstructive sleep apnoea syndrome is associated with relative hypocortisolemia and decreased hypothalamo–pituitary–adrenal axis response to 1 and 250 μg ACTH and glucagon stimulation tests

Zuleyha Karaca [a], Sevda Ismailogullari [b], Selda Korkmaz [b], Ilkay Cakir [a], Murat Aksu [b,*], Recep Baydemir [b], Fatih Tanriverdi [a], Fahri Bayram [a]

[a] Erciyes University Medical School, Department of Endocrinology, Turkey
[b] Erciyes University Medical School, Department of Neurology, Turkey

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ABSTRACT

Objective: The investigations regarding the effect of obstructive sleep apnoea syndrome (OSAS) on hypothalamo–pituitary–adrenal (HPA) axis revealed conflicting results. We aimed to evaluate the effects of OSAS on HPA-axis with dynamic tests.
Methods: This study was carried out on 26 patients with OSAS and 15 subjects without OSAS which, were defined according to the International Classification of Sleep Disorders. Patients were enrolled from either Endocrinology outpatient clinic or Neurology Sleep Center. Participants for the control group were included from the patients admitting to Endocrinology Department with the complaint of obesity or volunteers from hospital staff. All the participants were evaluated by polysomnography (PSG) and dynamic tests of HPA axis (dexamethasone suppression test, 1 and 250 μg ACTH and glucagon stimulation tests).
Results: Serum basal and peak cortisol levels were found to be lower in OSAS patients when compared to the control group during 1 μg ACTH and glucagon stimulation tests. When the area under curve (AUC) of cortisol responses to dynamic stimulation tests were calculated according to trapezoid formula, patients with OSAS were found to have lower values compared to control group. AUC responses of all three dynamic stimulation tests were found to be negatively correlated with AHI.
Conclusion: OSAS is associated with relative hypocortisolemia in the morning with reduced responses to 1 and 250 μg ACTH and glucagon stimulation tests.

1. Introduction

Obstructive sleep apnoea syndrome (OSAS) is a common health problem characterized by repetitive upper airway occlusion episodes leading to apnoea and asphyxia. It typically occurs 100–600 times per night and airway patency is reestablished by arousals from sleep [1]. The pathophysiology of OSAS is not well understood, but obesity and male gender are important risk factors [2].

The effect of OSAS on hypothalamo pituitary adrenal (HPA) axis has aroused interest among scientists dealing with sleep medicine. The nocturnal hypoxia associated with repetitive arousals may lead to increased cortisol secretion in patients with OSAS. However, many studies have failed to find differences in serum cortisol levels between patients with OSAS and healthy controls. Furthermore, treatment of OSAS by the gold standard method continuous positive airway pressure (CPAP) has shown conflicting results regarding reduction in cortisol levels in OSAS patients and the removal of CPAP has not been shown to result in immediate cortisol increase either [3–7].

Serum or salivary morning cortisol levels were used for the investigation of HPA axis in many of the studies [8–12]. More extensive evaluation of circadian rhythm by measurement of cortisol in every 30 minutes, revealed unchanged or increased cortisol levels during sleep without any change in 24 h mean cortisol levels in patients with OSAS [7,13].

The response of HPA axis to challenge in OSAS patients has previously been investigated with dexamethasone suppression and CRH stimulation tests. CRH administration was not shown to result in different ACTH and cortisol responses in patients with OSAS [7], but OSAS was shown to be associated with less suppression of salivary cortisol following dexamethasone administration compared to obese subjects without OSAS. Although basal and late night salivary cortisol levels were found to be similar in both groups [9].

The aim of the present study was to evaluate the HPA axis in patients with OSAS and subjects without OSAS. Therefore, we used

* Corresponding author. Address: Erciyes University Medical School, Department of Neurology, 38039 Kayseri, Turkey. Tel.: +90 352 2076600; fax: +90 352 4375273.
E-mail address: aksu@erciyes.edu.tr (M. Aksu).

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three well-defined dynamic stimulation tests of the HPA-axis (1 and 250 μg ACTH and glucagon stimulation tests), which have not previously been carried out in OSAS patients, at least according to our knowledge.

2. Materials and methods

2.1. Study participants and baseline tests

This study was carried out on 26 patients with OSAS and 15 subjects without OSAS. OSAS was diagnosed according to the International Classification of Sleep Disorders 2. An apnoea-hypopnoea index (AHI) $\geqslant$ 5 on PSG with at least one of the following: (i) unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue or insomnia, (ii) the patient wakes with holding of breath, gasping or choking, (iii) the bed partner reports loud snoring, breathing interruptions, or both during the patient's sleep or (iv) AHI $\geqslant$ 15 in the absence of another current sleep disorder, medical or neurological disorder, medication or substance use [14]. We excluded all medical conditions (other than controlled hypertension), smoking more than 10 cigarettes/day and any drug use (other than antihypertensives including angiotensin converting enzyme inhibitors, angiotensin receptor blockers or calcium-channel blockers).

Serum fasting glucose and lipid levels were measured. Thyroid function tests, PRL, FSH, LH and estradiol levels in females and total testosterone in males were measured and found to be in the normal ranges (data not shown).

2.2. Polysomnography

All the participants were evaluated with PSG recordings. A full-night PSG recording was performed using a computerized recording system (Grass Telefactor®, West Warwick, RI, USA) consisting of (1) sleep scoring through six channel electroencephalography (EEG) (EEG leads; F4-M1, C4-M1, O4-M1, F3-M2, C3-M2, O3-M2), two channel electrooculography (EOG), and one channel electromyography (EMG); (2) respiration monitoring through a thermistor as well as a nasal pressure sensor for apnoea–hypopnoea detection, piezo-crystal effort belts for thoraco-abdominal movement detection and a pulse-oximeter; (3) a two lead electrocardiogram (ECG); and (4) bilateral tibial EMG and a body position detector.

All recordings were scored based on 30 second epochs according to the American Academy of Sleep Medicine (AASM) criteria [15]. Sleep stages were scored as W (wake), N1 (stage 1 sleep), N2 (stage 2 sleep), N3 (SWS), and R (REM sleep). Sleep parameters were assessed based on the sleep recordings and included (1) sleep scoring data; total sleep time (TST; in minutes), sleep latency (SL; lightsout to first epoch of any sleep in minutes), percent sleep efficiency ([TST/total recording time] $\times$ 100), wake after sleep onset (WASO; stage W during total recording time, minus SL, in minutes), percent of TST in each stage (time in each stage/TST), Stage REM latency (sleep onset to first epoch of stage REM in minutes); (2) respiratory events; apnoea hypopnoea index (AHI; total number of apnoeas and hypopnoeas $\times$ 60/TST). An obstructive apnoea was defined as a drop in the peak thermal sensor excursion by $\geqslant$90% of baseline lasting at least 10 second accompanied by respiratory effort movement. An obstructive hypopnoea was defined as nasal pressure signal excursions drop by $\geqslant$30% of baseline with $\geqslant$4% desaturation from pre-event baseline, or $\geqslant$50% of baseline with $\geqslant$3% desaturation from pre-event baseline or the event is associated with arousal, associated with respiratory effort; (3) movement events; periodic leg movements of sleep (PLMS) index (PLMI; number of PLMS $\times$ 60/TST) according to the AASM criteria. The data were scored by a sleep medicine specialist who was masked to the status of subjects. Participants filled out the Epworth Sleepiness Scale (EPSS) and a score of equal or higher than 10 was accepted as having sleepiness.

2.3. Dynamic tests evaluating HPA-axis

Overnight dexamethasone suppression test was performed in the study-participants. 1 mg dexamethasone was given at 11 pm and serum cortisol was measured in the following morning at 8 am.

Dynamic tests were performed at 8 am in the morning on different days after an overnight fast, leaving at least 48 h between tests. 0.25 mg intravenous Tetracosactrin (1–24) (Synacthen, Novartis, Switzerland) was used for ACTH stimulation tests. 0.25 mg Tetracosactrin was mixed with 250 ml 0.9% NaCl solution and preserved at +4 °C for not more than a month and 1 μg ACTH was obtained from this mixture. 1 and 250 μg ACTH stimulation tests were performed and blood samples for the measurement of cortisol were obtained in the basal state and 30, 60, 90 and 120 minutes after the administration of 1 and 250 μg intravenous ACTH, respectively.

One mg glucagon (GlucaGen hypokit, Novo Nordisk, Denmark) was applied intramuscularly and blood samples were obtained in the basal state and after 90, 120, 150, 180, 210 and 240 minutes following administration of glucagon.

No adverse reactions were reported during ACTH or glucagon stimulation tests. Unfortunately, 250 μg ACTH stimulation test could only be carried out in 16 patients and eight control subjects since 0.25 mg intravenous Tetracosactrin (1–24) (Synacthen, Novartis, Switzerland) was unavailable for the others. The other tests were completed successfully in all participants.

2.4. Assays

Serum cortisol levels were measured by radioimmunoassay (RIA) method with DSL-2100 (Texas, USA) with an intraassay coefficient of variation: 8.4%, interassay coefficient of variation: 9.1% and sensitivity of 0.3 μg/dl.

Total cholesterol and HDL-cholesterol and triglyceride levels were measured by enzymatic reactions (Beckman Coulter, Syncron LX20/LX20 pro) in the morning after an overnight fast. LDL-cholesterol was calculated according to the Friedewald formula.

This study was approved by Local Ethics Committee and the study participants signed the written informed consent.

2.5. Statistical analysis

All statistical analysis were done by Statistical Package for Social Sciences (SPSS for Windows, version 15; Chicago, IL). The results are presented as mean ± standard deviation. Normal distribution of the data were tested by Kolmogorov–Smirnov test. The correlations were tested with Pearson's correlation analysis. Student *t*-test or Mann–Whitney *U* test were used as parametric and non-parametric tests for comparison of the groups, where appropriate. Chi-square test was used for comparison of the categorical variables. Analysis of covariance was used for comparison of cortisol levels for BMI correction. $p < 0.05$ was considered as statistically significant.

3. Results

The demographic characteristics of the patients are presented in Table 1. Patients with OSAS were found to be older than the control subjects. The sex distribution and body mass indices of the participants were similar in both groups. The groups did not show