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Original Research Article

Increased Serum Levels of Growth Hormone in Patients with Obstructive Sleep Apnea Syndrome

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Abstract

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of upper airway obstruction which occurs during sleep and usually associated with a reduction in oxygen saturation, and it is one of the common health problems with significant mortality and morbidity. It is very well-known that OSAS alters the serum levels of several hormones by the effect of hypoxia on central neurotransmitters that causes changes in the hypothalamic-pituitary-adrenal axis (HPA) in relation with sleep fragmentation. Growth hormone secretion (GH) is affected by several factors such as age, sex, obesity, body composition and sleep quality. Also, the oxygen content of the inhaled air affects the secretion of GH. On the other hand, intermittent hypoxemia increases GH secretion. In this study, we aimed to examine the serum level of GH in patients with OSAS.

Keywords: Apnea, Growth hormone, Hypopnea, Hypoxia, Obstructive sleep apnea, Obesity

INTRODUCTION

OSAS is a serious disease that is characterized by partial or intermittent complete upper airway occlusion episodes leading to apnea and asphyxia and resulting in hypoxia (Lanfranco et al., 2010a). Body mass index (BMI) is identified as the most important risk factor for OSAS, and others include advanced age and male gender (Guilleminault et al., 1994).

The strict association between OSAS and obesity is known for a long time, and it is reported that the incidence of OSAS among morbidly obese patients is 12- to 30-fold higher than in general population (Young et al., 2005). On the other hand, it is also reported that OSAS itself may predispose individuals to worsening obesity in consequence of sleep fragmentation and disrupted metabolism (Svatikova et al., 2005; Gami et al., 2003).

OSAS is characterized by alterations in the serum levels or secretory patterns of several hormonesso that it is associated with several metabolic disorders such as increased insulin resistance, hypertension and diabetes which occur in OSAS (Lanfranco et al., 2010a; Julian et al., 2014). Additionally, a disrupted Hypothalamus-Pituitary-Adrenal (HPA) axis activity is described in OSAS (Lanfranco et al., 2010b) and an impairment of both basal and stimulated GH secretion has been shown in obese patients with OSAS (Gianotti et al., 2002).

In this study, we aimed to examine the serum level of GH in Turkish patients with OSAS.

MATERIALS AND METHODS

Patients

This study was performed on 60 OSAS patients who were treated Düzce University Medical Faculty, Department of Chest Diseases, Düzce (a city located in the Marmara-northern-west region of Turkey) and 28 healthy age and gender matched control participants who were obtained from Kütahya Health Sciences University, Medical Faculty, Department of Chest Diseases, Kütahya

(a city located in the Aegean part of Turkey) were placed in this study.

The gold standard diagnostic test for OSAS is Supervised Overnight Polysomnography (PSG) and the classification of OSAS is made according to apnea/hypopnea index (AHI; the occurrence of an average five or more episodes of obstructive respiratory events per hour). The diagnosis of OSAS was established on the basis of criteria proposed by the guideline establishes clinical practice recommendations for the diagnosis of OSAS in adults. The patients who were at high risk for OSAS with major symptoms at the time of polyclinic admission and underwent PSG in Düzce University Sleep Laboratory for definitive diagnosis resulting in AHI > 5 were diagnosed as OSAS according to the international guidelines (Kapur et al., 2017).

All of the participants were ethnically Caucasian and male gender. Individuals with high clinical suspicion for OSAS and definitively diagnosed as OSAS by PSG were included in the study. On the other hand, patients who have concomitant comorbidities were excluded from the study. So the study group consists of patients who have isolated OSAS. All of the procedures were explained to the subjects and written informed consent forms were obtained from all participants. The study protocol conforms to the ethical guidelines of declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Düzce University.

Enzyme-Linked Immunosorbent Assay (ELISA) Analyses and Oxidative Stress Index calculation

Peripheral blood samples (5 mL) were obtained from each subject by venipuncture. After collecting the whole blood from each participant into a blood tube without any agent, we left the tubes at room temperature for approximately 20–30 min to allow the blood to clot. In order to isolate the fibrinogen precipitate, we centrifuged the clot at 3000 rpm for 15 min, resulting at serum. Then, all serum samples were stored at Eppendorf. After centrifugation, the serum of everyone was stored at - 80 °C until Enzyme-Linked Immunosorbent Assay (ELISA) analysis.

Serum concentrations of GH (Rel Assay Diagnostics, Turkey) were analyzed by ELISA kits without stimulation.

Statistical analyses

Statistical analyses were performed by SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) 16.0 package program. Power analysis was performed by calculating the statistical power for OSAS and control group using two-tailed test and 80% power of confidence interval with alpha = 5% level of significance. Serum levels of interest parameters were given as mean ± standard error of the mean (SEM). Serum levels of relevant parameters were given as mean ± standard deviation. The data obtained were evaluated using the Mann–Whitney Utest. All p-values <0.05 were accepted as statistically significant.

RESULTS

Mean age was 52 for the study group (min. 45-max. 60) and 48 for the control group (min. 40-max. 55) and all of the study participants were male. There was no significant difference in means of age and gender between the two groups (p> 0.05).

Serum GH levels were found to be significantly higher in OSAS group (0.04±0.002ng/ml) compared to the control group (0.02±0.001ng/ml) (p=0,000). (Figure 1)

DISCUSSION

Abnormalities in anatomical structure and physiological function are both important factors that are involved in the pathogenesis of OSAS (Silva et al., 2014). Excess in pharyngeal tissue, structural changes of the upper airways and weakness or relaxation of the pharyngeal musculature are the major problems causing occlusion of the lumen of the upper airway during sleep. This occlusion leads to increasing respiratory efforts to overcome the obstruction and also sleep deprivation and restriction which are seen in OSAS (Berkmann et al., 2021).

It is a known fact that sleep is a basic physiological need for human life and different sleep stages are characterized by a specific neurochemical environment of neurotransmitters and hormones so that sleep loss leads to alterations in hormone secretion (Steiger, 2011).

GH is a peptide hormone that is produced and released by the anterior pituitary gland (Pilecka et al., 2007). GH secretion is affected by age, gender, food intake and obesity, blood glucose, serum free fatty acids, body composition and sleep quality (Lanfranco et al., 2010a). A marked increase in GH release is reported during sleep accompanied by down-regulation of the HPA axis (Steiger, 2011). Increased release of growth hormone leads to overgrowth of soft tissues in the upper airway structure (Attal and Chanson, 2010) and therefore OSAS can be defined as a consequence of the anatomical changes in the upper airway caused by growth hormone excess (Berkmann et al., 2021).

Somatomedins are the polypeptides that are synthesized dependent-on GH. GH stimulates the synthesis of somatomedin C, also named as insulin-like growth factor-1 (IGF-I), mainly in the liver and also other tissues. In this regard, IGF-I is reported as the main mediator of GH (Lanfranco et al., 2010a).

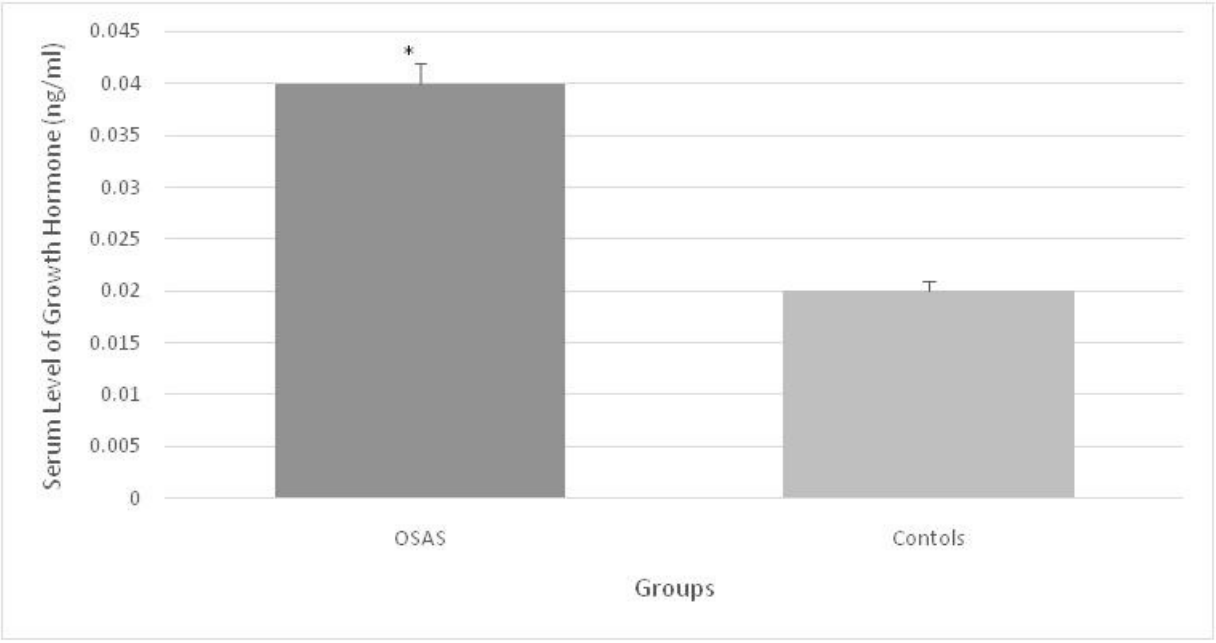

Figure 1. Serum levels of growth hormone. OSAS; Obstructive Sleep Apnea Syndrome.
*; p=0,000

In literature, it is stated that endocrine secretions are evidently disturbed by sleep deprivation and restriction including decreased concentrations of GH and GH-related growth factor IGF-1 (Maggio et al., 2013; Chennaoui et al., 2014; Rabat et al., 2016). Also, Saini et al. reported the reduced spontaneous GH secretion in OSAS, which is possibly due to sleep respiratory disturbances, and pointed out the close relationship between sleep fragmentation and low circulating GH levels in untreated OSAS patients (Saini et al., 1993). They have also shown that a single night continuous positive airway pressure (nCPAP) treatment is able to increase the duration of slow wavesleep and to normalize GH levels in obese subjects with OSAS. Thus, the authors concluded that reduced GH secretion is restored by nCPAP treatment and the treatment increased the amplitude of GH secretory bursts but not the frequency (Saini et al., 1993). Additionally, reduced IGF-I levels have also been shown in patients with OSAS independent of BMI and age (Grunstein et al., 1989; Ursavas et al., 2007; McArdle et al., 2007).

A reduction in both spontaneous and stimulated GH secretion together with reduced IGF-I concentrations and impaired peripheral sensitivity to GH is detected in obese patients with OSAS (Lanfranco et al., 2010b). On the other hand, Grunstein et al. indicated the role of hypoxemia rather than sleep fragmentation at the basis of hormonal alterations which are common in OSAS (Grunstein et al., 1989). They have reported a significant increase in IGF-I levels 3 months after the initiation of nCPAP treatment (Grunstein et al., 1989). Therefore, hypoxia itself might impair both growth hormone function and peripheral sensitivity to GH. Reduced synthesis and release of GH both by acute and prolonged hypoxia has been shown in animal studies (Zhang and Du, 2000). Furthermore, hypoxia reduces IGF-I mRNA expression in vitro and low IGF-I levels have been shown in animal models (Bernstein et al., 1992).

Conversely, it has been reported that intermittent hypoxemia increases growth hormone secretion (Konet al., 2010). Oxygen content of inspirated air appears to affect the secretion of GH and IGF-I. In fact, chronic hypoxemia is associated with a decrease in IGF-I without any changes observed in GH, while intermittent hypoxemia has been shown to affect GH secretion (Bernstein et al., 1992). In animals, hypoxia inhibits GH release or biosynthesis and hyperoxia increases the expression of IGF-I and its type I receptor (Konet al., 2010).

Consequently, GH/IGF-I axis activity disruption seems to be responsible from the metabolic alterations that are seen in OSAS and the reduction in GH and IGF-1 levels in OSAS have been reported several times. However, our study showed increased serum GH levels in patients with OSAS. So, in this meaning, our results are not compatible with the literature.

Of course, there are some limitations of our study. For instance, one of the biggest concerns is small sample size. Also, we did not have an opportunity to measure the serum level of IGF-1, which is a biological marker of growth-hormone secretion.

Additionally, as we see from the literature, PSG is the

"goldstandard" diagnostic test for OSAS and nCPAP therapy is the main stay of treatment of OSAS (Sharma et al., 2014). In our study, the definitive diagnosis of OSAS is made by PSG however, we could not have the chance for treatment and to evaluate GH levels after nCPAP therapy which is a major concern.

So, it is a fact that, further studies should be performed with large sample size and long-term patient follow-up detecting levels of hormones which are a part of HPA axis and also serum somatomedin levels.

CONCLUSION

Today we know that circulating level of GH is effected also by its polymorphisms. We suggest that increased serum GH levels in patients with OSAS can be related with these polymorphisms. For this reason, further studies conducted in different ethnical groups and populations are needed to clarify the role of GH axis in OSAS in order to identify its polymorphisms. Moreover, understanding the role of hormonal alterations in OSAS may lead to the discovery of new treatment approaches and effective management strategies in the future. Eventually, correct management of OSAS may adjust endocrine disorders, improve quality of life and prevent OSAS-related morbidity and mortality.

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