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HEAD AND NECK

Relationships of orexigenic and anorexigenic hormones with body fat distribution in patients with obstructive sleep apnea syndrome

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Abstract

Purpose We aimed to examine the relationships of disease activity and risk factors with serum levels of orexigenic and anorexigenic hormones in patients with obstructive sleep apnea syndrome (OSAS).

Methods Fasting blood samples were taken for hormonal analysis of all participants, abdominal/neck bioimpedance measurements were recorded, and polysomnography (PSG) analyses were performed. According to the apnea–hypopnea index (AHI), 34 patients with newly diagnosed OSAS and 34 participants without OSAS were compared.

Results The median body mass index (BMI) measured in the OSAS group was 30.39 kg/m^2 and AHI was 18.95 and these values were 25.40 kg/m^2 and 1.55 in the control group. There was a higher level of visceral adiposity and neuropeptide Y (NPY) in the moderate-to-severe OSAS group compared to the mild OSAS and control groups, and in the mild OSAS group compared to the control group ($p=0.001$, $p<0.001$). A positive correlation between the level of NPY and AHI and BMI ($p<0.001$, $p=0.011$), and a negative correlation between NPY levels and oxygen saturation ($p=0.001$) was found. Oxygen saturation and desaturation rates were correlated with body fat percentage, body fat mass, abdominal adiposity, visceral adiposity, resting metabolic rate, and NPY levels.

Conclusions The visceral adiposity ratio and increase in NPY levels are important parameters that increase the severity of OSAS. Considering the negative effects of NPY on vascular endothelium, measurement of basal NPY level before PSG in patients with OSAS is considered a parameter related to disease severity.

Keywords Anorexigenic hormone · Neuropeptide Y · Obstructive sleep apnea syndrome · Orexigenic hormone · Body fat distribution

Introduction

The occurrence of the obesity pandemic in this century makes it imperative that obesity-related clinical conditions become much better recognized and more treatable. Obstructive sleep apnea syndrome (OSAS), one of the most common sleep disorders, is among the diseases closely related to obesity [1]. OSAS is characterized by recurrent blockages of the upper respiratory tract during sleep and excessive daytime sleepiness (EDS) associated with this condition; snoring may also be observed as well as cardiopulmonary dysfunctions [2]. There are many metabolic consequences of OSAS that affect appetite, energy consumption, and systemic inflammation. These results are mediated by peptide hormones (ghrelin, leptin, adiponectin, resisting, apelin, obestatin, and neuropeptide Y) [3]. The discovery of the

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roles of these peptide hormones in the pathophysiology of OSAS is broadening horizons.

Appetite is regulated by a complex system of central and peripheral hormonal and nervous signals that regulate the individual's response to food intake. Central control is carried out by various factors, including neuropeptidergic, monoaminergic, and endocannabinoid systems, while peripheral regulation includes satiety signals and fat signals. The main role in the regulation of central appetite is played by the arcuate nucleus (ARC) in the hypothalamus. ARC neurons secrete orexigenic substances such as neuropeptide Y (NPY) and agouti-related peptide (AGRP) and anorexigenic peptides such as pro-opiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART). Satiety signals are produced by the gastrointestinal tract through hormones, such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY) during meals. The inputs delivered to the nucleus tractus solitarius via the vagus nerve are directed to the ARC, and leptin, etc. satiety-forming hormone releases are stimulated [4]. Disruption of this regulation in orexigenic and anorexigenic hormones is the main pathophysiological basis of obesity, which is most often accompanied by an increase in appetite and a loss of feeling of satiety.

It is known that obesity also increases the levels of leptin and NPY. However, it has been reported that NPY also increases independently of obesity in patients with OSAS [5]. It has even been suggested that NPY has a potential role in the pathophysiological process of hypertension seen in OSAS [6]. A review of the literature indicates that leptin levels are related to body mass index (BMI) and adiposity rather than OSAS. It is observed that adiponectin and ghrelin levels are also affected by OSAS, while resistin and apelin levels are not associated with it [3].

Hypocretin-1, NPY, leptin, ghrelin, and adiponectin are hormones that are influential both in metabolic pathways and in sleep regulation. EDS is not observed in all patients with OSAS. A study conducted based on this by Sánchez-de-la-Torre M and colleagues showed that EDS in patients with sleep apnea is associated with increased circulating levels of hypocretin-1 and decreased ghrelin [7].

It is notable that ghrelin levels are especially affected in sleep and respiratory disorder treatments (with positive airway pressure) [3]. Interestingly, in a study conducted with rats, it was shown that the elimination of obstruction in the upper airway triggers more eating due to an increase in the levels of hypothalamic NPY and plasma ghrelin, and obesity increases [8].

In examining the relationship between orexigenic and anorexigenic hormones and sleep-disordered breathing, it is necessary to study the relationship of both body fat composition and peptide levels with body fat ratio change and applied treatments together.

In our study, we aimed to investigate the relationship between levels of alpha melanocyte stimulating hormone (α-MSH), which has anorexigenic and sleep-regulating effects, CART, another anorexigenic, the orexigenic hormones AGRP and NPY with disease activity, and risk factors in patients with OSAS.

Materials and methods

Patient and study design

80 patients (age range; 19–74) who referred to Gazi University Hospital Department of Otorhinolaryngology with complaint of sleep apnea-related symptoms and agreed to participate in the study were included and underwent overnight polysomnography (PSG) between 2017 and 2020. The exclusion criteria were as follows: previous diagnosis of OSAS, diagnosis of upper airway pathology, severe systemic diseases that might make them susceptible to OSAS, heart failure, central nervous system disease, use of psychiatric drugs, diagnosis of solid or hematological malignancy, unstable angina pectoris and/or hypercapnia, hypoxemia unresponsive to oxygen therapy, severe respiratory insufficiency requiring mechanical ventilation, severe coagulopathy, having known eating behavior disorders, use of drugs that affect appetite control (liraglutide, etc.), and pregnancy and/or lactating. Based on these criteria, 12 patients were excluded and the study was performed with a total of 68 patients ($n=68$) (Fig. 1). After the PSG analyses, 34 participants were included in the OSAS group and 34 participants were included in the control group. Prior to the sleep study, all patient's data were registered including age, gender, height, and weight, medical history, current medication. Hospital's computer-based data system was also used to access medical information. When the patients who accepted to participate in the study came to receive the sleep study results, blood samples were taken and measurements were made in the Endocrinology and Metabolism Basal Metabolism Laboratory by a technician who was blinded to the study.

Polysomnography

The participants were hospitalized for one night at the sleep laboratory of our hospital. Standard overnight PSG with 6 electroencephalogram channels was performed in all subjects using the Nocturnal A1 system, versions 2.0 (Nox Medical ehf Katrinartuni 2 IS-105 Reykjavík, Iceland). All sleep data were evaluated by the same person. Apnea was defined as reduction in airflow of at least 90% for 10 s. Hypopnea was defined as a reduction in airflow of at least 30% for 10 s with $\geq 4\%$ oxyhemoglobin desaturation or an

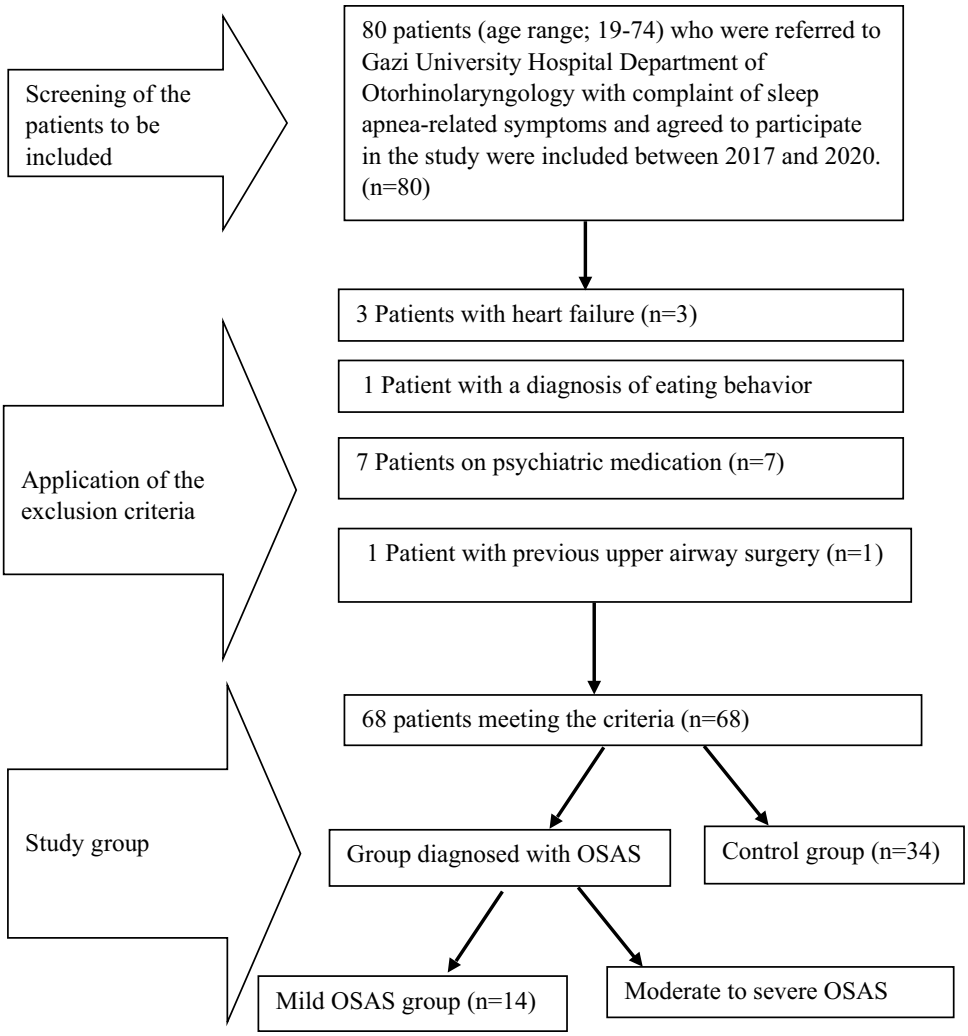


Fig. 1 Determination of the patient groups. *OSAS* obstructive sleep apnea syndrome

electroencephalogram (EEG) arousal. Apnea–hypopnea index (AHI) was defined as the number of apnea and hypopnea per sleep hour. Subjects with an AHI score below 5 were considered normal, between 5 and 15 mild, 15 and 30 moderate, and if it is more than 30, it is considered severe obstructive sleep apnea syndrome. In addition, the average spo2 and spo2 desaturation percentages of the patients were recorded.

Blood collection

After PSG, fasting blood samples were collected early in the morning and centrifuged at 3200×*g* for 10 min. Serum samples were immediately transferred into a sterile Eppendorf tubes and all samples were stored at − 80 °C until analyzed.

Fasting blood AGRP (pg/mL), CART (ng/mL), GLP-1(pg/mL), α-MSH (ng/mL) and NPY (ng/mL) parameters were measured by enzyme-linked immunosorbent assay (ELISA) method.

For each biochemical analyte, tests were performed using commercial kits: AGRP ELISA (Catalog#MBS267449, Lot#30300452, assay sensitivity: 5 pg/mL). Intra-assay and inter-assay coefficient of variation were less than 8% and 12%, respectively. CART ELISA (Catalog#MBS3800386, Lot#03/2020, assay sensitivity: 0.1 ng/mL), GLP1 ELISA (Catalog # MBS771621, Lot#202003, assay sensitivity: 0.1 pg/mL). Intra-assay and inter-assay CV (%) were less than 10% and 15%, respectively. α-MSH (Catalog#MBS166701, Lot#202002008, assay sensitivity: 5.07 ng/mL). Intra-assay and inter-assay coefficient of variation were less than 8% and 10%, respectively. NPY ELISA (Catalog#MBS3801243, Lot#08/2020, assay sensitivity: 1 ng/mL). All kits were obtained from MyBiosource, San Diego, USA. In addition, all tests were run in an ELISA processor. A calibration curve using standard duplicates was performed for each analyte in every run.

Evaluation of metabolism measurements

Body bioimpedance measurement was performed in all participants while fasting in the morning, with a bioimpedance device located within the Department of Endocrinology and Metabolism of Gazi University (Abdominal fat analyzer AB-140M, Body Composition Analyzer BC-418MA). Basal metabolic rate (BMR), BMR percentage, visceral fat, abdominal fat, neck fat and body fat percentages, body fat mass, lean body mass (FFM), and total body water (TBW) measurements were recorded.

Statistical analysis

The data of the study were analyzed in SPSS 23.0. The qualitative data are presented in terms of numbers and percentages, while the quantitative data are presented in terms of means and medians. The chi-square test was used to compare the qualitative data. The Kolmogorov–Smirnov test was used to determine the normality of the data, nonparametric tests (Mann–Whitney *U* test, Kruskal–Wallis test) were used for the normalized data, and parametric tests (independent *t* test, ANOVA) were used for the non-normalized data. Pearson and Spearman correlation tests were used according to whether the data were normally distributed or not. $p < 0.005$ was considered statistically significant.

In our study, there were control groups consisting of 34 OSAS patients and 34 healthy volunteers. Considering that the prevalence of obesity in the population is 30% and that the average 70% of the patients with OSAS are obese, the power of the study was calculated 90.5% by taking the potential type-I error of 5% (in the Epi-Info program).

Results

Our study was performed with a total of 68 participants. The participants were initially divided into two groups: the patient group diagnosed with OSAS ($n = 34$) and the non-OSAS control group ($n = 34$).

Forty-six of the participants were male. There were 25 male participants in the OSAS group and 21 in the control group. There was no significant difference in terms of sex between the groups ($p = 0.30$).

The mean age of the participants was 50.4 (±9.81) in the OSAS group and 36.47 (±12.61) in the control group. There was a significant difference between the groups in terms of age ($p = 0.001$).

Median BMI was 30.39 (23.84–44) kg/m^2 and AHI was 18.95 (7–82.80) in the OSAS group, while these values were, respectively, 25.40 (20.31–35.27) kg/m^2 and 1.55 (0.30–4.90) in the control group. Both BMI and AHI were higher in the OSAS group ($p = 0.001$, $p = 0.001$, respectively).

The OSAS group itself was divided into two according to AHI. Those with AHI < 15 were evaluated as having mild OSAS ($n = 14$) and those with AHI ≥ 15 were evaluated as having moderate to severe OSAS ($n = 20$).

There was a significant difference between the groups in terms of BMI, fat mass, total body water, abdominal region adiposity, and resting metabolic rate (Table 1).

When the groups were compared according to abdominal visceral adiposity, neck fat, and hormone levels, there was a significant difference between visceral fat and NPY levels (Table 2).

A moderate positive correlation was found between the level of NPY and AHI and BMI ($p < 0.001$, $p = 0.011$). There was a moderate negative correlation between NPY level and oxygen saturation ($p = 0.001$) (Fig. 2).

Table 1 Comparison of bioimpedance measurement results between the groups

	Mild OSAS ($n = 14$) Mean ± SD	Moderate to Severe OSAS ($n = 20$) Mean ± SD	Normal ($n = 34$) Mean ± SD	*p
Lean body mass	58.37 ± 18.17	64.87 ± 11.54	56.67 ± 10.82	0.08
BMI	29.06 ± 3.75	31.44 ± 4.99	26.09 ± 4.10	< 0.001
Fat percentage	28.90 ± 8.62	29.31 ± 7.75	24.67 ± 8.37	0.089
Fat mass	25.68 ± 8.93	27.58 ± 8.65	18.85 ± 7.78	0.001
Total body water	45.35 ± 7.36	47.48 ± 8.43	41.51 ± 7.96	0.029
Abdominal region adiposity	37.19 ± 8.64	38.27 ± 7.03	31.35 ± 9.05	0.009
Resting metabolic rate	1642.50 ± 233.34	1829.95 ± 268.04	1571.64 ± 297.17	0.006
Percentage of resting metabolic rate	96.14 ± 13.69	102.70 ± 9.25	95.47 ± 12.54	0.093

BMI body mass index, *OSAS* obstructive sleep apnea syndrome

*One-way ANOVA

Table 2 Comparison of visceral and neck adiposity ratios with hormone levels between the groups

	Mild OSAS ($n=14$) Median (min–max)	Moderate to severe OSAS ($n=20$) Median (min–max)	Normal ($n=34$) Median (min–max)	*p
Visceral adiposity	14.25 (7.50–22)	18.50 (2.50–22.50)	9.25 (2.50–21)	0.001
Neck adiposity	1.50 (1–3.50)	2 (1–4)	2 (1–4.50)	0.287
AGRP	94.50 (69–116)	254.51 (54.42–435.65)	252.22 (70.74–439.15)	0.154
CART	6.53 (5.06–7.39)	6.60 (4.55–15.29)	6.40 (1.42–15.67)	0.527
GLP-1	5.47 (1.21–8)	4.99 (1.36–10.13)	6.01 (1.28–10.06)	0.159
α-MSH	1245.58 (897.25–2310.58)	1326 (694.75–2384.75)	1471.83 (640.58–2463.08)	0.476
NPY	23.75 (4.01–67.12)	91.60 (5.01–181.26)	10.34 (2.82–56.95)	< 0.001

AGRP agouti-related peptide, *α-MSH* alpha melanocyte stimulating hormone, *CART* cocaine and amphetamine regulated transcript, *GLP-1* glucagon-like peptide-1, *NPY* neuropeptide Y, *OSAS* obstructive sleep apnea syndrome

*Kruskal–Wallis test

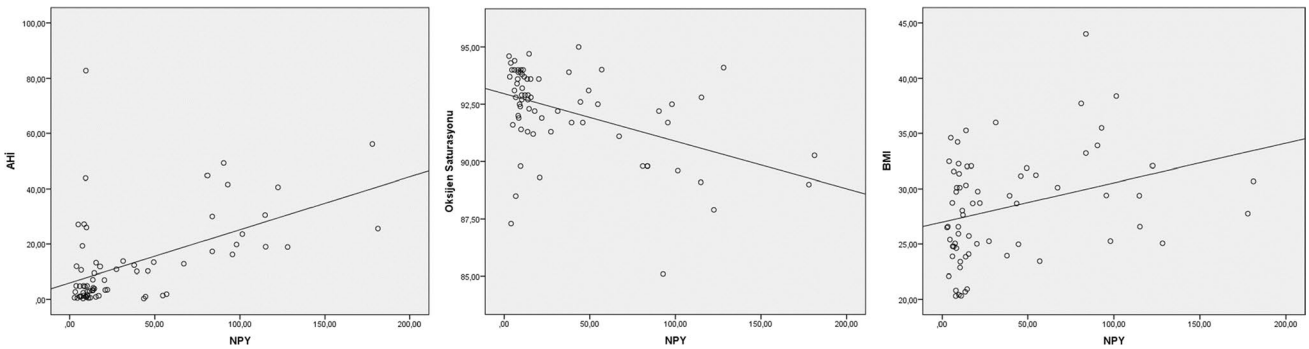


Fig. 2 Relationship of NPY with BMI, AHI and oxygen saturation. *AHI* apnea hypopnea index, *BMI* body mass index, *NPY* neuropeptide Y

The correlation of oxygen saturation and desaturation rate with bioimpedance measurements and hormone levels was examined. Oxygen saturation and desaturation rate was correlated with body fat percentage, body fat mass, abdominal adiposity, visceral adiposity, BMR, and NPY levels. A correlation was found between the desaturation rate and GLP-1 levels (Table 3).

Of the hormones in the patient group, only AGRP showed a moderate correlation with FFM and TBW ($p=0.023$, $p=0.032$). There was no correlation between AGRP level and BMI, AHI, or mean spo2 (pdec0.097, $p=0.242$, $p=0.437$).

Logistic regression was performed to investigate the effect of body fat and hormone measurements on the presence of OSAS, but no significant results were found for any of the measurements.

Discussion

In our study, the levels of NPY and visceral adiposity were parallel to the severity of OSAS. In this context, we found a correlation between the level of NPY and BMI, AHI, and average oxygen saturation.

For many years, OSAS has been considered and treated as a local abnormality of the respiratory tract. In the 1990s, the demonstration of increased pro-inflammatory cytokines in OSAS, increased levels of TNF-alpha independent from obesity in sleep apnea, IL-6 levels, insulin resistance, and the relationship of OSAS with visceral adipose tissue led to the evaluation of OSAS in the category of systemic diseases today [9]. OSAS has a strong association with metabolic diseases, especially insulin resistance, type 2 diabetes mellitus (T2D), obesity, and non-alcoholic fatty liver disease (NAFLD) [1].

Seventy percent of OSAS patients are obese [10]. An increase in visceral adipose tissue is an important risk factor for OSAS [11]. In our study, this information is supported. We found that there was higher visceral adiposity in the moderate-to-severe OSAS group compared to the mild OSAS and control groups, and in the mild OSAS group compared to the control group. With increasing severity of obesity, fat tends to accumulate in the upper parts of the body, especially in the neck. Some studies have suggested that the accumulation of fat in the neck is associated with OSAS, causing a decrease in the diastolic function of the respiratory tract [11, 12]. However, the role of adiposity in the

Table 3 Relationship between oxygen saturation and desaturation rate and adiposity, bioimpedance measurements, and hormones

Spearman rho	Median oxygen saturation		SpO2 desaturation rate	
	p	*ρ*	*p*	*ρ*
Fat percentage	< 0.001	− 0.511	< 0.001	0.467
Fat mass	< 0.001	− 0.656	< 0.001	0.623
Lean body mass	0.028	− 0.267	0.004	0.349
Total body water	0.027	− 0.268	0.003	0.352
Abdominal region adiposity	< 0.001	− 0.500	< 0.001	0.479
Visceral adiposity	< 0.001	− 0.598	< 0.001	0.605
Neck adiposity	0.342	0.117	0.296	− 0.129
Resting metabolic rate	0.001	− 0.385	< 0.001	0.420
Percentage of resting metabolic rate	0.066	− 0.224	0.062	0.228
AGRP	0.437	0.096	0.202	− 0.157
CART	0.173	− 0.167	0.581	0.068
GLP-1	0.294	0.129	0.047	− 0.242
α-MSH	0.918	0.013	0.478	− 0.087
NPY	0.001	− 0.406	< 0.001	0.431

AGRP agouti-related peptide, *α-MSH* alpha melanocyte stimulating hormone, *CART* cocaine and amphetamine regulated transcript, *GLP-1* glucagon-like peptide-1, *NPY* neuropeptide Y, *OSAS* obstructive sleep apnea syndrome

pathogenesis of OSAS is not limited to this. In recent years, the importance of adipokines, especially leptin, released from adipose tissue in the pathogenesis of OSAS has been revealed. New literature data on decreasing adiponectin and increasing resistin and visfatin in OSAS are emerging every day [1]. In our study, we did not find any association between neck adiposity and hormone levels, the average SpO2, or SpO2 desaturation rate. We think that this may have been due to both the OSAS group and the control group being composed of BMI > 25 kg/m^2 patients or the number of participants. On the other hand, OSAS can also be seen in individuals who are not obese. OSAS can even predispose non-obese patients to the development of metabolic syndromes [13, 14]. This information indicates that although the amount of fat measured metabolically in OSAS is important, it does not appear to be an absolute determinant.

While there is a strong association between the severity of OSAS (AHI and respiratory disturbance index) and high ghrelin levels, it has been found that the ghrelin levels of patients with OSAS are less likely to be associated with BMI. Interestingly, it has been shown that PAP treatment in OSAS can reduce ghrelin levels independent of BMI [3, 15]. There are many studies showing that leptin levels are also high in OSAS. It has been reported that the level of leptin decreases with PAP therapy independent of BMI in two meta-analyses [3]. In the study by Yosunkaya et al., it was suggested that OSAS-related parameters and PAP treatment did not affect leptin levels [16]. As these and similar literature data have emerged, we found that the OSAS–BMI relationship is a relatively crude perspective, and we think that molecular mechanisms originating from adipose tissue/hypothalamus that have not yet been elucidated in the pathophysiology of OSAS may be at the forefront and OSAS parameters such as EDS may be related to peptide hormone levels rather than BMI.

The level of leptin in OSAS was mostly high in relation to obesity, while the study by Barcelo et al. showed that the level of NPY was high in OSAS regardless of obesity [5]. Because NPY has effects, such as vascular hypertrophy and vasoconstriction, it has been suggested that it may play a role in the pathogenesis of cardiovascular disease in OSAS [5, 6, 17]. In parallel with our results, the study by Tang and colleagues also showed that the level of NPY was associated with the severity of OSAS. Moreover, it has been suggested that cognitive functions in OSAS may also be related to the level of NPY [18].

As a result of our study, we have shown that the levels of AGRP, CART, GLP-1, and α-MSH hormones in OSAS do not cause significant differences. In 2011, a similar result was shown by Papaioannou et al. for leptin, ghrelin, and PYY levels. However, in our study, there was a significant relationship between OSAS severity and NPY, in contrast to the study by Papai Decannou and colleagues [19]. NPY receptors are located in the brain stem and hypothalamus at the highest rate among various brain regions. Therefore, it can be concluded that the level of NPY is an important regulator of sleep and breathing [20]. In fact, in our study result, we attempted to confirm this hypothesis by showing that the level of NPY in OSAS indicates the severity of the disease. However, genetic data have not yet confirmed this. It was found that the frequency of the NPY gene allele did not differ between the groups with and without OSAS [21]. In a study conducted on rats, it was also shown that the levels of NPY mRNA in the hypothalamus and brain stem did not change due to hypercapnia [20]. The fact that intermittent hypoxia increases the level of NPY, while the level of NPY mRNA does not change with hypercapnia exposure suggests that the underlying pathogenetic mechanism may be due to the influence of NPY receptor synthesis [20, 22].

Chronic intermittent hypoxia can affect the central expression of NPY and the release of peripheral NPY. Due to the negative potential effects of NPY on vascular endothelium, a goal of diagnosis and treatment regarding the relationship between cardiovascular and cerebrovascular diseases and OSAS, which is the first disease that comes to mind when we consider chronic intermittent hypoxia, using NPY can be set [22, 23]. For this reason, we think that the level of NPY may be decisive in the diagnosis and treatment of OSAS-related complications in the future.

There are a number of limitations in our study. As expected, BMI differed between the OSAS group and the control group. However, even if BMI were matched it would not rule out potential differences in body fat distribution. The prevalence of respiratory disorders in sleep is higher in men than in women (20–30%/10–15%, respectively). At the same time, its incidence increases with age. The fact that the patient population constituting the OSAS group in our study consists of individuals of more advanced age seems to be compatible with the general society data. The majority of male individuals in both the OSAS and the control group also ensured balance between the groups [24, 25]. Considering that OSAS becomes more severe at an older age, the high average age of the OSAS group also affects our study results. In addition, the generalizability of the results is limited due to the number of patients in our study. According to the TURDEP-II study data, the prevalence of obesity in the adult population in Turkey is 31.2%; however, according to the World Health Organization data, it is around 29.5%. We also showed that our study has sufficient statistical power with the result of the power analysis made when we take the obesity prevalence as 30% in the population [26, 27].

Looking at the literature, our study is the first to examine the relationship between detailed body bioimpedance measurement results and hormone levels (AGRP, CART, GLP-1, α-MSH, and NPY) in OSAS. There are data indicating that PAP treatment in OSAS also promotes weight gain by a mechanism that has not yet been elucidated [25, 28]. In our study, we used the PSG data of newly diagnosed OSAS patients who have not yet received PAP treatment to rule out this confounding factor. In addition, we tried to rule out other confounding factors by applying a wide range of exclusion criteria.

Conclusions

Compared to the increase in adiposity in the neck area, visceral adiposity and an increase in the level of NPY are associated with the severity of OSAS. Considering the negative effects of NPY on vascular endothelium, measurement of basal NPY level before PSG in patients with OSAS is found to be a parameter associated with disease severity that can provide information about mortality and morbidity.

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Data availability The original data are available upon reasonable request.

Declarations

Conflict of interest No potential conflict of interest was reported by the authors.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethics committee approval was obtained from the Clinical Research Ethics Committee of Gazi University (Project No: 176). Written and oral informed patient consent was obtained from all participants.

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