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Metabolic profile and insulin resistance in patients with obstructive sleep apnea syndrome

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Aim: The following metabolic parameters were assessed in patients with obstructive sleep apnea syndrome (OSAS) diagnosed by polysomnography (PSG): leptin, IFG (ımpaired fasting glucose), thyroid functions, thyroid autoantibodies, lipid parameters, insulin levels, HOMA-IR index, CRP, obesity, and metabolic syndrome frequency.

Materials and methods: Three patient groups were defined based on apnea-hypoapnea index (AHI) levels (Group I: n: 11 male (M)/19 female (F); Group II: n: 19 M/10 F; Group III: n: 21 M/10 F) and 2 control groups (obese (n = 18 M/12 F) and normal (n = 12 M/18 F)) were included with comparable BMI value and age.

Results: The frequencies of metabolic syndrome were compared between patient groups, and no significant difference was found, despite an increased frequency of metabolic syndrome from mild OSAS to severe OSAS. The following significant differences were observed for insulin values: normal controls versus obese controls ($P < 0.0001$), normal controls versus Group I ($P = 0.014$), normal controls versus Group II ($P = 0.001$), normal controls versus Group III ($P < 0.0001$), and Group I versus Group III ($P = 0.026$).

Conclusion: An increased frequency of metabolic syndrome and insulin resistance was found in OSAS patients. OSAS patients with metabolic syndrome and insulin resistance are at an increased risk of diabetes mellitus and cardiovascular diseases.

Key words: OSAS, Met-S, AHI, insulin resistance

Obstruktif uyku apne sendromlu hastalarda metabolik profil ve insülin direnci

Amaç: Bu çalışmada polisomnografi ile obstruktif uyku apne sendromu (OSAS) teşhisi konmuş hastaların aşağıda belirtilen metabolik parametreleri değerlendirildi: leptin, bozulmuş açlık glukozu, tiroid fonksiyonları, tiroid otoantikorları, lipid parametreleri, insülin seviyeleri, HOMA-IR indeks, obezite, ve metabolik sendrom sıklığı.

Yöntem ve gereç: Apne-hipoapne indeksi (AHI) temel alınarak 3 hasta grubu (Grup I: n: 11 Erkek (E)/ 19 Kadın (K); Grup II: n: 19 E/10 K; Grup III: n: 21 E/10 K) ve vücut kitle indeksi (BMI) değeri ve yaş karşılaştırılmasını içeren iki kontrol grubu (obez (n = 18 E/12 K) ve normal (n = 12E/18K)) tanımlandı.

Bulgular: Metabolik sendrom sıklığı hafif OSAS'dan ciddi OSAS' a doğru artmasına rağmen hasta grupları arasında anlamlı farklılık bulunamadı. İnsülin değerleri için farklılıklar gözlendi: normal kontrol obez kontrol karşısında ($P < 0,0001$): normal kontrol Grup I karşısında ($P = 0,014$); normal kontrol Grup II karşısında ($P = 0,001$); normal kontrol Grup III karşısında ($P < 0,0001$); Grup I Grup III karşısında ($P < 0,026$).

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Sonuç: OSAS'lı hastalarda artan metabolik sendrom sıklığı ve artan insülin direnci bulundu. Metabolik sendromlu ve insülin direnci olan hastalarda diabetes mellitus ve kardiyovasküler hastalık riski artmıştır.

Anahtar sözcükler: OSAS, Met-S, AHI, insülin direnci

Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by persistent and repetitive obstruction of the upper airways during sleep. The obstructive apnea represents the respiratory effort against a partially or totally blocked airway and causes loud snoring or arousal upon the restoration of airflow. While snoring is the most frequent night symptom of OSAS, excessive sleepiness is the most common daytime symptom (1-3). Factors such as age, gender, genetic factors, obesity (increased neck circumference and thick/short neck), craniofacial abnormalities (retrognathia, micrognathia), cigarette smoking, and the use of alcohol or hypnotic drugs are associated with an increased risk of OSAS. The male to female ratio is 2.5:1 in the general population (4).

In this study, we explored the metabolic profile and insulin resistance of OSAS patients attending the sleep laboratory unit of our hospital in order to assess possible relations between these conditions.

Materials and methods

This prospective study examines patients who attended the outpatient clinic of the Otorhinolaryngology Department of İstanbul Education and Research Hospital between August 2008 and January 2009 with the complaint of snoring. The Epworth Sleepiness Scale (ESS) was completed by all patients with symptoms of OSAS such as excessive snoring, morning fatigue, an inability to sleep comfortably at night, and frequent nocturnal urination. Patients with an ESS score of 9 or greater were referred to the sleep laboratory for polysomnography (PSG) examinations with an EMBLA S 7000 (USA) PSG device. For PSG procedures, patients were asked to visit the sleep laboratory in the evening hours. ECG, EOG, EEG, EMG, and pulse oximetry were monitored for one night of sleep via thoracoabdominal probes and nasal cannula attached to the patient. Using the data obtained from this observation, AHI, minimum oxygen saturation, mean oxygen saturation, and oxygen desaturation index (ODI) levels were estimated. According to AHI scores, patients were classified as follows: simple snoring (AHI < 5), mild OSAS (AHI = 5-15), moderate OSAS (AHI = 16-30), and severe OSAS (AHI > 30).

Overall, 120 patients who underwent a PSG and 60 healthy controls were included. Before the study procedures, informed consent was obtained from all patients. A total of 30 patients with a PSG were excluded from the study because they met the exclusion criteria, which included a history of diabetes mellitus (DM), thyroid surgery and/or medical treatment for thyroid disease, or use of antidepressants. Patient groups were defined by PSG results. Group I included patients with simple snoring and mild OSAS (n = 30), Group II with moderate OSAS (n = 29), and Group III with severe OSAS (n = 29). The control group consisted of healthy individuals with no signs of OSAS at ESS. In addition, control subjects underwent an ENT examination before the study and were required to demonstrate no history of snoring or alcohol or cigarette use. The 2 control groups differed only with regard to BMI, which was <25 and >30 in Groups I (n = 30) and II (n = 30), respectively. The decision to include 2 separate control groups was based on the high prevalence of obesity among OSAS patients. Group I and Group II were designated as normal controls and obese controls, respectively.

The height (m), weight (kg), and waist circumference (cm) of each subject was recorded and BMI was calculated (kg/m^2). Information on alcohol and cigarette use, history of diabetes, use of blood pressure lowering agents, thyroid disease, and nocturia was obtained. In addition, symptoms associated with OSAS were recorded.

Venous blood samples were collected between 0800 and 1000 following 8-10 h of fasting. The samples were then placed in tubes containing clot activator gel (BD Vacutainer® SSTTM II, BD Diagnostics, Franklin Lakes, USA). The samples were kept at

room temperature for 30 min before being subject to centrifugation for 10 min at 1600 × *g* (4000 rpm).

Total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were determined spectrophotometrically by an Abbott Aeroset 2.0 device. FT4, TSH, anti-TG, anti-TPO, and insulin levels were determined via ECLIA (Electrochemiluminescence Immunoassay) with a Roche Hitachi E-170 device. For CRP estimations, an Image 800 (Beckman Coulter) device was used with a nephelometric method. Leptin levels were determined by a Leptin kit (DRG International Inc., USA) using the sandwich ELISA method. Absorbance measurements for leptin were performed in a microplate ELISA reader (GVD Reader-Washer) at 450 nm.

Statistical analysis

SPSS 11.5 for Windows was used for statistical analyses. The Kolmogorov-Smirnov test was used to test the normality of continuous variables. Variables with a Gaussian distribution (age, BMI, HDL, waist circumference) were expressed as mean ± SD and variables with a non-Gaussian distribution (glucose, total cholesterol, triglycerides, low density cholesterol, insulin, HOMA-IR, TSH, FT4, A-TPO, CRP, leptin) were expressed as median value (in the interquartile range). Between-group comparisons for logarithmic or square root transformed variables with a normal distribution were performed with a one-way ANOVA analysis; Tukey and Tamhane's T2 tests were used for post-hoc analyses. Between-group comparisons of variables without a normal distribution after transformation was done with the Kruskal-Wallis test; for post-hoc comparisons, the non-parametric Tukey-Kramer test was used. For the comparison between the expected and observed frequencies, chi-square tests were used and Spearman's correlation coefficient (r_s) was used for the correlation between variables. Dichotomous dependent variables (patients and controls) for independent variables (leptin, HOMA, CRP, age, BMI) were analyzed by logistic regression analysis. The odds ratios (OR) from the regression analysis are presented with 95% confidence intervals (CI). Statistical significance was set at a P value (2-tailed) of less than 0.05.

Findings

This study was undertaken between August 2008 and January 2009 with 150 voluntary participants at Istanbul Education and Research Hospital. The demographic characteristics of patients are shown in Table 1.

The distributions of continuous variables in all 5 groups were evaluated with the Kolmogorov-Smirnov test. Variables with a non-Gaussian group distribution were expressed as median (25-75th percentile), and those with a Gaussian distribution as X ± SD (Table 2).

The frequencies of metabolic syndrome were compared between patient groups using the chi-square test and no significant difference was found (P = 0.331), despite an increased frequency of metabolic syndrome from mild OSAS (69% (n = 20)) to severe OSAS (74.2% (n = 23)). The prevalence in Group I was determined to be 56.7% (n = 17).

The Pearson chi-square test did not show any statistically significant difference between the 5 groups in terms of impaired fasting glucose (P = 0.102).

Tukey multiple comparisons following one-way ANOVA analysis for the logarithmic glucose values showed significant differences between normal controls and Group II (P = 0.002) as well as those found between normal controls and Group III (P = 0.009).

No significant between-group differences were observed in TSH and FT4 levels (P values of 0.455 and 0.472, respectively) and in A-TG and A-TPO positivity (P values of 0.531 and 0.082, respectively).

Tukey multiple comparisons after one-way ANOVA analysis for logarithmic total cholesterol values showed the following significant differences: between normal controls and Group II (P = 0.002); between normal controls and Group III (P < 0.001); between obese controls and Group II (P = 0.005); and between obese controls and Group III (P = 0.002). The same comparison for triglyceride levels showed the following significant differences: between normal controls and Group I (P = 0.024); between normal controls and Group II (P < 0.001); and between normal controls and Group III (P < 0.0001). For HDL cholesterol, the following differences were detected:

Table 1. Demographic characteristics of patients.

Demographic variables	Group I (mean ± SD) (mild)	Group II (mean ± SD) (moderate)	Group III (mean ± SD) (severe)	Normal controls (mean ± SD)	Obese controls (mean ± SD)	P value
Male/Female	11/19	19/10	21/10	12/18	18/12	= 0.035*
Age (years)	50 ± 8	47 ± 12	49 ± 10	34 ± 10	34 ± 9	< 0.0001**
BMI (kg/m^2)	31.6 ± 5.5	31.8 ± 5.9	33.4 ± 4.8	22.6 ± 2.2	31.2 ± 3	< 0.0001**
Waist circumference (cm)	104 ± 12	107 ± 12	111 ± 10	83 ± 11	104 ± 10	< 0.0001**
Smoking (%)	23.3% (n = 7)	37.9% (n = 11)	32.3% (n = 10)	-	-	= 0.474*
Alcohol use (%)	16.7% (n = 5)	27.6% (n = 8)	32.3% (n = 10)	-	-	= 0.360*
Antihypertensive medication use (%)	46.7% (n = 14)	27.6% (n = 8)	41.9% (n = 13)	-	-	= 0.295*

Age, BMI and waist circumference are presented as mean ± SD
*P value obtained from chi-square test
** P value obtained from one-way ANOVA

normal controls versus Group II (P = 0.037); and normal controls versus Group III (P = 0.043). For LDL cholesterol, the following differences were observed with Tamhane's T2 multiple-comparison: normal controls versus Group II (P = 0.037); normal controls versus Group III (P = 0.002); and obese controls versus Group III (P = 0.005).

The following significant differences were observed for insulin values with Tukey's multiple comparison tests after one-way ANOVA analysis: normal controls versus obese controls (P < 0.0001); normal controls versus Group I (P = 0.014); normal controls versus Group II (P = 0.001); normal controls versus Group III (P < 0.0001); and Group I versus Group III (P = 0.026).

Tukey-Kramer multiple comparisons after Kruskal-Wallis analysis for CRP revealed the following differences between the groups: normal controls versus Group II (P < 0.0001); normal controls versus Group III (P < 0.0001); obese controls versus Group II (P = 0.006); and obese controls versus Group III (P < 0.0001).

Tamhane's T2 test after one-way ANOVA analysis showed the following between-group differences for HOMA-IR: normal controls versus obese controls (P < 0.0001); normal controls versus Group I (P = 0.013); normal controls versus Group II (P < 0.001); and normal controls versus Group III (P < 0.0001).

The effect of gender on leptin levels was explored with univariate analysis of variance which showed a significant interaction between gender and leptin levels (P = 0.002). Thus, leptin levels in groups were assessed separately for male and female participants.

Leptin levels are presented as median (25th-75th percentile) and logarithmic transformation was done before the comparison of the groups using one-way ANOVA (Table 3).

Tamhane's T2 test after one-way ANOVA analysis showed the following significant differences for leptin levels for male participants: normal controls versus obese controls (P = 0.009), normal controls versus Group I (P < 0.0001), normal controls versus Group II (P < 0.0001), and normal controls versus

Table 2. Biochemical profile of the groups.

Biochemical variables	Group I*	Group II**	Group III***	Normal Controls ¶	Obese Controls ¶¶	P value
Glucose (mg/dL)	96.5 (92.8-101)	98 (93-113)	97 (91-110)	89.5 (84.2-96)	97.5 (91.5-105.3)	= 0.003
Total cholesterol (mg/dL)	216.5 (188.8-235.2)	228 (195.5-257)	217 (207-251)	174.5* (160-200.5)	180 (151-230.5)	< 0.0001
Triglyceride (mg/dL)	160.5 (101-204.8)	169 (133-211.5)	189 (140-221)	92 (74-149)	131 (99.8-174)	< 0.0001
LDL cholesterol (mg/dL)	143.5 (122.5-156.3)	147 (123.5-179)	140 (132-170)	107 (95-139)	115.5 (88.4-154)	< 0.0001
HDL cholesterol (mg/dL)	42.1 ± 9.9	38.9 ± 8.7	39.1 ± 9.6	46 ± 11.1	39.2 ± 9.3	= 0.018
Insulin (μU/mL)	12.5 (8.8-17.3)	12.7 (8.6-22.8)	18.24 (15.04-22.09)	7.66 (6.24-10.32	16.9 (9.3-20.8)	< 0.0001
HOMA-IR	2.8 (1.9-4.5)	3.2 (2.2-5.7)	4.6 (3-5.6)	1.63 (1.36-2.46)	3.8 (2.1-5.5)	< 0.0001
TSH (mIU/L)	1.84 (1.01-2.54)	1.57 (1.13-2.69)	1.56 (1.13-2.21)	2.32 (1.25-3.75)	1.75 (1.31-2.2)	= 0.455
FT4 (ng/dL)	1.17 ± 0.15	1.22 ± 0.14	1.16 ± 0.16	1.22 ± 0.16	1.20 ± 0.17	= 0.472
Positive A-TG (IU/mL) (%)	10% (n = 3)	3.4% (n = 1)	16.1% (n = 5)	6.7% (n = 2)	10% (n = 2)	= 0.531
Positive A-TPO (IU/mL) (%)	13.3% (n = 4)	10.3% (n = 3)	16.5% (n = 5)	10% (n = 3)	6.7% (n = 3)	= 0.0816
CRP (mg/dL)	0.42 (0.17-0.71)	0.43 (0.26-0.78)	0.6 (0.26-0.94)	0.1 (0.1-0.19)	0.28 (0.15-0.35)	< 0.0001
Leptin (ng/mL)	47.4 (17.7-144.9)	22.1 (9.3-52.9)	35.98 (10.17-85.61)	7.1 (2.8-13.7)	16.8 (8.1-30.1)	< 0.0001

HDL cholesterol and FT4 data are presented as mean ± SD. Glucose, total cholesterol, triglyceride, LDL cholesterol, TSH, CRP, leptin, and HOMA data are presented as median (25th-75th percentile).

The Kruskal-Wallis test was used for the comparison of groups with regard to glucose and TSH levels.

For insulin, total cholesterol, triglyceride, LDL cholesterol, and leptin data, logarithmic transformation was done and groups were compared using one-way ANOVA.

Square-root transformation was done for HOMA-IR data before one-way ANOVA.

The chi-square test was used to compare the groups with regard to the prevalence of positive results for A-TG and A-TPO. The Kruskal-Wallis test was used to compare the groups for CRP levels.

Glucose:¶-**: P = 0.002; ¶-***: P = 0.009

Total cholesterol: ¶-**:P = 0.002; ¶-***: P < 0.001; ¶¶-**:P = 0.005; ¶¶-***:P = 0.002

Triglyceride: ¶ -*: P = 0.024; ¶-**: P < 0.001; ¶-***: P < 0.0001

LDL: ¶-**: P = 0.037; ¶-***: P = 0.002; ¶¶-***: P = 0.005

HDL: ¶-**: P = 0.037; ¶-***: P = 0.048

Insulin: ¶-¶¶: P < 0.0001; ¶-*: P = 0.014; ¶-**: P = 0.001; ¶-***: P < 0.0001; *-***: P = 0.026

HOMA-IR: ¶-¶¶: P < 0.0001; ¶-*: P = 0.013; ¶-**: P < 0.001; ¶-*** :P < 0.0001

CRP: ¶-**: P < 0.0001; ¶-***: P < 0.0001; ¶¶-**: P = 0.006; ¶¶-***: P < 0.0001

Table 3. Leptin levels of the groups.

		Group I*	Group II**	GroupIII***	Normal controls ¶	Obese controls ¶¶	P value
Leptin	Male n = 81	16.6 (10.3-25.1)	10.5 (6.9-30.4)	16.9 (8.5-37.6)	2.6 (2.0-3.9)	9.1 (5.1-13.3)	P < 0.0001
	Female n = 69	68.5 (45.7-180.6)	56.3 (45.0-122.5)	171.1 (83.5-259.6)	11.6 (7.6-19.7)	32.7 (27.2-39.3)	P < 0.0001

Males:
¶-¶¶:P = 0.009; ¶-*:P < 0.0001; ¶-**:P < 0.0001; ¶-***:P < 0.0001
Females:
¶-¶¶:P < 0.0001; ¶-*:P < 0.0001; ¶-*:P = 0.002; ¶-***:P < 0.001; ¶¶-***:P = 0.003

Group III (P < 0.0001). For female participants these differences were as follows: normal controls versus obese controls (P < 0.0001), normal controls versus Group I (P < 0.0001), normal controls versus Group II (P = 0.002), normal controls versus Group III (P < 0.0001), and obese controls versus Group III (P = 0.003).

There was a moderately positive correlation between HOMA and CRP, BMI and HOMA, and BMI and CRP in the normal control group, while no correlations were observed between HOMA and leptin or CRP and leptin. In obese controls, there was a moderately positive correlation between HOMA and CRP, and BMI and HOMA, a strong positive correlation between BMI and CRP, and a weak positive correlation between HOMA and leptin levels, with no correlation between CRP and leptin. In the patient group, a moderate positive correlation was observed between CRP and leptin, a strong positive correlation was discovered between BMI and HOMA, BMI and leptin, and BMI and CRP, and weak correlations were found between HOMA and leptin and HOMA and CRP (Table 4).

Two separate models were developed for logistic regression analysis in which the patient group (n = 90) and normal controls (n = 30) were incorporated as dependent variables and leptin, HOMA, CRP, gender, age, and BMI as independent variables (Table 5).

Model 1: x = -2.37 + 0.61(leptin) + 0.63(HOMA) + 1.66(CRP)

Model 2: x = -28.5 + 0.11 (leptin) – 0.3 (HOMA) -1.15 (CRP) + 0.082 (age) + 0.95 (BMI) + 1.37 (gender)

(x < 0: patient ; x > 0: normal control)

Table 4. Correlations between HOMA, CRP, leptin, and BMI in the groups.

	Normal controls (n = 30)	Obese controls (n = 30)	Patient groups (n = 90)
HOMA-Leptin	r_s= 0.107 (P = 0.574)	r_s= 0.218 (P = 0.247)	r_s= 0.251 (P = 0.017)
HOMA-CRP	r_s= 0.507 (P = 0.04)	r_s= 0.365 (P = 0.048)	r_s= 0.217 (P = 0.040)
CRP-Leptin	r_s= 0.056 (P = 0.767)	r_s= 0.121 (P = 0.525)	r_s= 0.450 (P < 0.0001)
BMI-HOMA	r_s= 0.482 (P = 0.007)	r_s= 0.491 (P = 0.006)	r_s= 0.551 (P < 0.0001)
BMI-Leptin	r_s= -0.279 (P = 0.135)	r_s= -0.047 (P = 0.805)	r_s= 0.670 (P < 0.0001)
BMI-CRP	r_s= 0.412 (P = 0.024)	r_s= 0.558 (P < 0.001)	r_s= 0.522 (P < 0.0001)

r_s: Spearman correlation coefficient

Table 5. Logistic regression analysis for Model 2.

Variable	β	SE	OR (95% CI)	P value
Constant value	-28.5	8.1	0.0001	P < 0.0001
Leptin	0.11	0.07	1.12 (0.97-1.29)	P = 0.116
HOMA	-0.3	0.4	0.7 (0.3-1.5)	P = 0.364
CRP	-1.15	1.4	0.3 (0.02-4.9)	P = 0.41
Age	0.082	0.049	1.08 (0.98-1.19)	P = 0.093
BMI	0.95	0.34	2.6 (1.32-5.1)	P = 0.005
Gender	1.37	1.74	3.94 (0.13-118.9)	P = 0.43

β: regression coefficient
SE: standard error
OR: odds ratio
95% CI: 95% confidence interval

In Model 1, both leptin (P = 0.031) and HOMA (P = 0.012) had significant effects on the categorization of the patient group, while only BMI showed a significant effect on this parameter (OR: 2.6 [1.32-5.1]; P = 0.005) in Model II, where age, BMI, and gender were also included. Leptin and HOMA emerged as BMI-dependent variables.

The frequency of metabolic syndrome in patient groups is shown in Figure 1.

The frequency of impaired glucose tolerance (IGT) in the study groups is shown in Figure 2.

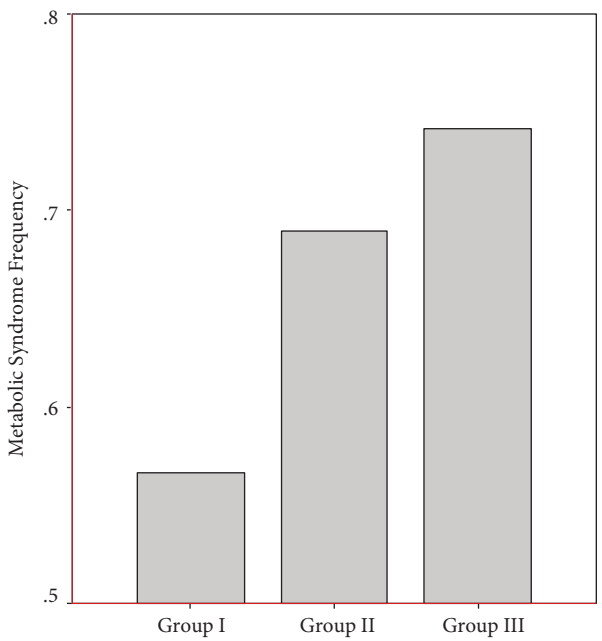

Figure 1. The frequency of metabolic syndrome in patient groups.

Discussion

OSAS is associated with a number of co-morbid conditions, particularly with endocrinological disturbances. For instance, 1.2% to 11% of patients with OSAS have been reported to have hypothyroidism (5-7).

In a study by Winkelman et al. involving 255 patients, hypothyroidism occurred at an incidence of 1.6% and 2.9% in subjects with clinical sleep disorder and in subjects with a diagnosis of OSAS, respectively. In that study, the need for the evaluation of thyroid functions in high-risk OSAS patients (>60 years of age, female gender) with clinical signs of hypothyroidism was emphasized (7). Skjodt et al. reported newly diagnosed hypothyroidism in 1.5% of PSG patients and in 2.4% of patients with

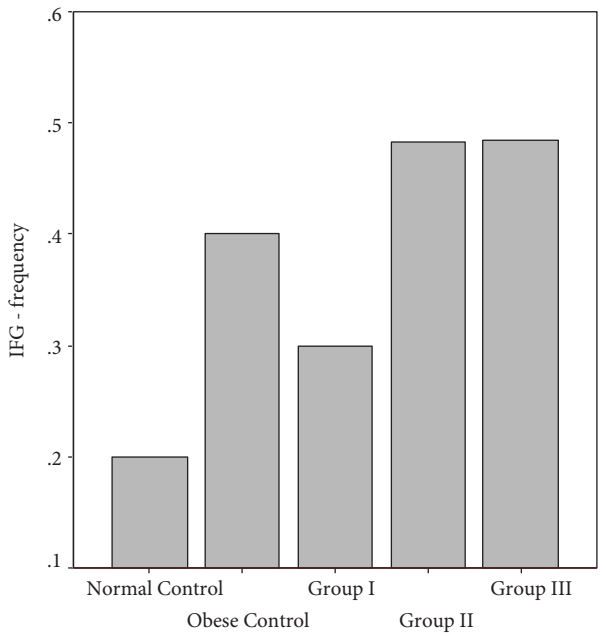

Figure 2. The frequency of impaired glucose tolerance (IGT) in the study groups.

suspected OSAS, proposing that routine screening for hypothyroidism may provide cost savings by eliminating the need for unnecessary investigations for sleep disorders such as "primary sleep apnea" (8). Lin et al. found hypothyroidism in 3.1% of 65 patients with OSAS, recommending routine use of thyroid function tests in all OSAS patients; however, these authors considered routine PSG unnecessary in patients with hypothyroidism (5). Popovici et al. detected hypothyroidism in 11% of 53 patients with suspected OSAS, pointing out the common co-existence of these 2 conditions (6). In our study, a clinical diagnosis of hypothyroidism was made with a TSH > 4.2 μIU/mL and FT4 < 0.93 ng/dL. Using these cut-off values, 3 patients (3.3%), 2 of whom had severe OSAS, were diagnosed as having hypothyroidism. Our results are comparable to previous reports.

In a study by Wolk et al., the association between obesity and OSAS was evaluated, reporting obesity in 70% of OSAS patients, and OSAS in 40% of obese subjects. In addition, a 10% increase in body weight was reported to increase the risk of sleep apnea by an order of 6, while a 10% decrease was reported to decrease AHI by 26%. A mutual and multifactorial interaction was also reported for the development of OSAS and obesity. The adverse effect of inadequate nocturnal sleep on daytime physical activity was also reported to play an important role in the progression of obesity in OSAS (9).

In our study, similar to previous reports, obesity (BMI > 30 kg/m^2) was present in 58 patients (64%), confirming the strong association between OSAS and obesity once more. In addition, hypertension was found to be significantly associated with OSAS in a variety of studies. In line with these observations, 39% of our OSAS patients (n = 35) were on antihypertensives. The first major study involving 7511 patients was carried out in 1985 showing a 1.94- and 3.13-fold increase in hypertension incidence in snoring men and women, respectively (10). At present, approximately 60% of OSAS patients are estimated to be hypertensive, and the severity of hypertension increases with the level of AHI (11).

An association between CRP and OSAS was shown in a variety of studies and both adipose tissue and obesity are known to play a role in the appearance of low-grade inflammation (12). Increased CRP levels represent an important risk factor for atherosclerosis, cardiovascular diseases, and cerebrovascular mortality. Recent studies also show an association between increased waist to hip ratio, increased BMI, and CRP (13). In addition, increased CRP levels were reported in OSAS patients and levels were shown to decrease upon CPAP treatment (14). In a study by Guilleminault et al., no association between OSAS and CRP was observed in less obese patients, while only BMI was shown to be associated with CRP (15). Shamsuzzaman et al. found increased CRP levels in 22 newly diagnosed OSAS patients compared to 20 healthy age- and BMI-matched controls (16).

In our study, CRP levels of OSAS patients were significantly higher compared to normal and obese controls. In addition, a strong positive correlation was found between BMI and CRP, similar to the findings of previous studies. Obesity is a central component of other metabolic syndrome features such as increased waist circumference, hypertension, and hyperinsulinemia and it plays key role in the development of diabetes. The risk of diabetes mellitus in OSAS should also be borne in mind since these components are frequently found in these patients.

Marshall et al. found a diabetes prevalence of 4.7% in a group of patients without apnea compared to 17.7% in those with severe apnea, corresponding to an estimated odds ratio (OR) of 4.37. The incidence of diabetes in a 4-year period was 2.2% in those without apnea, and 20% in those with severe apnea (OR: 11.2). Another prospective study by Reichmuth et al. found an OR of 4.06 for patients with AHI > 15 compared to those with an AHI < 5 (17). These findings suggest that apnea may play an important role in the development of DM. In France, Meslier et al. found an increased incidence of type 2 DM and IGT among patients with OSAS compared to the general population (30.1% and 20% increase, respectively). In that country, the incidence of type 2 DM is between 3.5% and 8.6% for those between 45 and 74 years of age (18).

Higher BMI and waist circumference measurements and higher levels of triglyceride, total cholesterol, and LDL cholesterol among patient groups compared to controls (i.e. presence of risk indicators for the development of DM) together with the association of AHI with increased prevalence of impaired fasting glucose suggests a tendency towards the development of diabetes mellitus in OSAS patients. Thus, the findings of the study, particularly the higher prevalence of impaired fasting glucose in OSAS patients, underline the need for OGTT screening in these patients.

In a case-control study by Coughlin et al., the presence of metabolic syndrome criteria was examined in OSAS patients. An independent relation was found for 61 patients with AHI > 15 and for 43 patients with AHI < 5 and the odds ratio for metabolic syndrome was 9.1 for OSAS patients. An independent relation was also found between OSAS and several other criteria, including systolic and diastolic blood pressure, fasting insulin, triglyceride, HDL cholesterol, and total cholesterol levels (19). In a retrospective study by Parish et al., OSAS patients had a higher prevalence of metabolic syndrome compared to subjects without the condition (60% versus 40%) (20).

In this study, there was an increase in the prevalence of metabolic syndrome with increasing OSAS severity: 56.6%, 69%, and 74.2% in patients with mild, moderate, and severe OSAS, respectively. When all OSAS patients were considered, the frequency of metabolic syndrome was 67%. There is a remarkable difference between the frequencies of metabolic syndrome among OSAS patients and that of the general population, clearly suggesting a tendency towards diabetes and cardiovascular disease. The higher prevalence of metabolic syndrome among patients with OSAS indicates that these patients should also be evaluated for the risk of diabetes and cardiovascular disease.

Hyperglycemia and insulin resistance play key roles in metabolic syndrome. Tkacova et al. estimated insulin resistance in 98 patients with or without OSAS using HOMA-IR formula. The results of 28 patients without OSAS, 39 patients with moderate OSAS, and 21 patients with severe OSAS were compared. Fasting insulin levels and HOMA-IR values were significantly higher in relation to the increasing severity of the disease. Insulin resistance was present in 33%, 44%, and 74% of subjects without OSAS, with moderate OSAS, and with severe OSAS, respectively. In addition, study subject's apnea-hypopnea index was moderately positively correlated with fasting insulin and HOMA-IR levels ($r = 0.484$ and $r = 0.546$, respectively). In that study, the 10-year cardiovascular disease (CVD) risks of the patients were also estimated using NCEP ATP III criteria; a cardiovascular disease risk greater than 10% was estimated in 21% of patients without OSAS, whereas corresponding figures were 28% and 65% for patients with moderate and severe OSAS, respectively. The odds of having a CVD risk > 10% was 8 times higher among patients with severe OSAS compared to those patients who did not suffer from the condition (odds ratio: 8.36) (21). Ip et al. examined the insulin resistance of 185 OSAS patients with AHI > 5 using the HOMA model and found an increase in insulin resistance with age and obesity. In that study, a multiple linear regression analysis was performed and obesity emerged as the main causal factor for insulin resistance (22). A study by Vgontzas et al. examined 14 obese patients with OSAS and 11 obese patients without OSAS (age- and BMI-matched) for insulin resistance and found higher levels of fasting blood glucose and fasting insulin in patients with OSAS compared to patients without this condition (23). Brooks et al. demonstrated that insulin sensitivity in obese diabetic patients with OSAS improved with

4-month CPAP treatment (24). On the other hand, Smurra et al. failed to demonstrate such a favorable effect of CPAP on insulin resistance (25). In this study, insulin levels of all groups were significantly different when compared to normal controls. In addition, the difference between obese controls and normal controls with regard to insulin levels may indicate that obesity is a causal factor for insulin resistance, a theory which may also be supported by the lack of any difference between obese controls and other patient groups. In other words, although insulin resistance increased along with increased severity of the disease among patient groups, it was significantly higher than normal controls. The presence of insulin resistance in OSAS was in line with previous studies. The high positive correlation between BMI and HOMA-IR that we found among the patient groups may be helpful in explaining the role of obesity in insulin resistance. In addition, we performed a correlation analysis to investigate a possible increase in inflammation due to obesity and found a high positive correlation between BMI and CRP. On the other hand, in the patient group, we found that the relation between inflammation and insulin resistance offered a weak positive correlation between CRP and HOMA-IR.

The high incidence of obesity among patients with OSAS prompted the investigation of leptin, which is secreted by adipose tissue and known to have a role in nutrition and energy metabolism. In addition to this, hyperleptinemia appears to lead to hypertension by increasing extracellular sodium through sympathetic nervous system activation and renal effects (26). The increased levels of leptin with inflammation and the role of obesity as a causal factor for inflammation indicate a strong interaction between these 3 factors (27). Leptin levels of OSAS patients were found to be higher compared to those of the matched obese control groups; the mechanism behind this is still unknown, however. A decrease in leptin levels with CPAP treatment suggests that leptin may interfere with respiration. In addition, the correlation between insulin resistance and leptin in patients with OSAS needs to be explained. The use of a CPAP device, the most effective treatment of OSAS, has been shown to decrease leptin levels and improve insulin resistance (28). This study demonstrated that CPAP treatment has the potential to decrease cardiovascular disease risk by improving insulin resistance and leptin levels. Impaired leptin receptors may explain the development of obesity and increased tendency to OSAS owing to the effects on food intake and energy consumption (29). In a study by Sanner et al., 86 OSAS patients underwent polysomnography and received 6-month CPAP treatment; however, serum leptin levels were unchanged (30). Vgantzas et al. found higher leptin levels among male OSAS patients compared to BMI- and age-matched controls (23). Kapsimalis et al. studied 67 male OSAS patients and found increasing leptin levels with increased AHI (31). Chin et al. demonstrated a decrease in serum leptin levels in 22 OSAS patients on a similar diet after 3 to 4 days of CPAP treatment, without any change in body weight (32). Although controversial results have been obtained from studies examining the relationship between leptin and OSAS, the effect of obesity on leptin levels is primarily emphasized.

Since leptin levels are known to be higher among females, we examined our patients with regard to gender. Leptin levels of our male patients in the normal control group were significantly different when compared to other patient groups and obese controls. The lack of any significant difference between obese controls and patient groups may indicate that the increased leptin levels may be BMI-dependent, which is further supported by the strong positive correlation between BMI and leptin levels. These results are consistent with previous studies. Leptin levels of female participants were higher than those of their male counterparts, which is also parallel with the findings of previous studies. Similarly, leptin levels of females were significantly higher in all patient groups and obese controls compared to normal controls. Since leptin originates from adipose tissue, this was an expected result. Another important finding was the significant difference between obese controls and patients with severe OSAS, suggesting that the relation between OSAS and leptin among females may not be solely caused by a high BMI. As demonstrated in previous studies, a decrease in AHI together with a reduction in leptin levels despite no concomitant change in BMI suggests an independent relation between leptin and OSAS. We believe that CPAP treatment may correct high leptin levels, which is a pathophysiological consequence of OSAS, independent of obesity.

In conclusion, the relationship relation between obesity and OSAS and its potential role in OSAS pathogenesis have been emphasized in all previous studies. Correction of obesity appears to be associated with improvements in all pathological conditions and parameters associated with OSAS such as metabolic syndrome, insulin resistance, cardiovascular disease risk, hypertension prevalence, and leptin levels.

Rather than being a simple social problem, snoring should be regarded as a serious health issue; all patients should be evaluated by both ESS and physical examination for the presence of OSAS and referred to a sleep laboratory where necessary. Currently, the CPAP device is the most widely accepted form of treatment for OSAS. The treatment of obesity is also of particular importance in order to decrease the risk of OSAS and metabolic disease. The high prevalence of metabolic syndrome and insulin resistance indicates a high risk of diabetes and cardiovascular disease among patients with OSAS. Thus, a multidisciplinary approach with the contributions of cardiologists, endocrinologists, psychiatrists, and dietitians would be most helpful in the treatment of patients with OSAS.

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