



Comorbidity analysis in obstructive sleep apnea patients

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Abstract

Aim: Obstructive sleep apnea (OSA) is a syndrome that causes complete or partial cessation of breathing and as a result of several pathways, hypertension (HT), type 2 diabetes mellitus (DM), and hyperlipidemia (HL) are usually seen as comorbidities. The main problem in the literature is, due to the presence of some confounders, especially body mass index (BMI), it is still not clear that if OSA is an independent risk factor for these comorbidities. This issue may be shown more clearly with BMI and age-matched subjects since they are strongly related to metabolic diseases and HT. Comparison of the ratios of the presence of DM, HL, and hypertension between the age and BMI matched groups is primarily aimed in the present study to see if moderate and severe OSA could be an independent risk factor for these comorbidities.

Materials and Methods: Patients admitted with sleep problems were retrospectively scanned from the patient files and cases with polysomnography and routine blood test were included. The body mass indexes, ages, smoking, and alcohol habits of the cases were noted. Two groups were formed based on polysomnography, taking a threshold value of the apnea-hypopnea index (AHI) of 15. Group 1 had cases with AHI <15 (normal and mild apnea patients) and Group 2 had cases with AHI ≥15 (moderate/severe apnea patients). Subjects were accepted as having DM, HL, or HT if they are on medication or if their examination and/or laboratory results show the presence of these diseases. The ratios of these diseases within the groups were compared.

Numerical variables were given as mean ± standard deviation. Categorical variables were shown as a number. Categorical variables were tested with the Chi-Square test or Fisher's exact test and an independent T-test was used for two independent groups. Statistical significance was accepted as $p < 0.05$.

Results: There were 22 cases with an AHI <15 and 17 cases with an AHI ≥15, with similar mean BMI and age ($p = 0.206$, $p = 0.054$ respectively). The ratio of hypertension was found significantly higher in moderate/severe OSA patients (47% vs 5%; $p = 0.005$). On the other hand, the ratios of DM and HL were found statistically similar ($p = 0.49$, $p = 1.0$ respectively).

Conclusion: This study aimed to show the possible independent role of sleep apnea in metabolic diseases and HT, by creating two groups with similar BMI, age, and cigarette and alcohol habits. The results support moderate/severe OSA as an independent risk factor for hypertension, while DM and HL are thought to be in close relationship with BMI.

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Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, which is characterized by complete or partial cessation of breathing due to the obstruction of the upper airways. As a result of this disorder, intermittent hypoxemia and hypercapnia periods occur and these periods lead to fragmentation of sleep, increased sympathetic

activity, oxidative stress, systemic inflammation, and activated hypothalamic-pituitary-adrenal axis, and altered circulating adipokines. Obesity is also accompanied as a result of sleep deprivation and all these factors are responsible especially for increased systemic blood pressure and type 2 diabetes [1]. The patients, especially those who have severe OSA, are usually obese and have systemic hypertension (HT), hyperlipidemia (HL), and type 2 diabetes mellitus (DM) due to this underlying pathophysiology [2].

Systemic hypertension is one of the most studied comorbidities of OSA patients and shows a correlation with the

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severity of OSA [3,4]. Studies show a ratio of HT prevalence in OSA patients between 35-80% and 60% of severe OSA patients (Apnea hypopnea index (AHI) ≥ 30) were found to have HT. Likewise, patients with HT show a 40% prevalence of OSA [5,6]. Type 2 DM has a prevalence between 15-30% in OSA patients and its prevalence is higher in severe OSA [7-10]. OSA is now being suggested as an additional manifestation of the metabolic syndrome because metabolic syndrome is highly prevalent in OSA patients [11-12]. These comorbidities differ between males and females. DM is more prevalent in men with OSA; whereas HT is more prevalent in women with OSA compared with non-OSA subjects [13]. Age is another factor affecting the relationship between comorbidities and OSA. Hypertension and OSA association were found to be stronger in adults under 50 years old [14,15].

These studies show that OSA is associated with the comorbidities such as metabolic diseases and HT, but due to the presence of strong confounders, especially obesity and age, it is controversial if OSA is an independent risk factor or not. There are examples in the literature showing that although sleep-disordered breathing is positively associated with the incidence of HT when the adjustments for BMI, gender, and neck circumference are made the significance of the association is lost [15,16]. The same controversy is also present for diabetes mellitus. Studies showed a correlation between type 2 DM and OSA patients but when the adjustments for BMI and other confounders were done, this correlation became attenuated [1,7,8].

As mentioned above, the main problem in the literature is, due to the presence of some confounders, especially BMI, it is still not clear if OSA is an independent risk factor for these comorbidities or not. This issue may be shown more clearly with BMI and age-matched groups since these two factors are strongly related to metabolic diseases and HT [17,18]. In this study, it is hypothesized that the metabolic diseases (DM and HL) and HT between body mass index (BMI) and age-matched groups of normal/mild OSA (apnea-hypopnea index < 15) and moderate/severe OSA (apnea-hypopnea index ≥ 15) subjects will show a significant difference if OSA is an independent risk factor. Comparison of the ratios of the presence of DM, HL, and HT between the groups is primarily aimed in the present study. The groups are planned to be matched by mean age and mean BMI values.

Materials and Methods

Probable - stratified sampling method was used in this case-control study. The patient group and the control group were matched by the individual-matching method, regarding their body mass indexes and ages. Patients who were admitted to the Acibadem Taksim Hospital neurology and check-up outpatient clinics for sleep problems between March 2020 and September 2021 were retrospectively scanned from the patient files. The Sample size for quantitative analysis was aimed to have a 95% of confidence level with a 15% margin of error. Patients who had been evaluated by polysomnography and by routine blood tests were included in the study. In order to make a study group with homogeneous age patients over 40 years old were included. Sleep studies were performed by Neu-

rosoft Neuron-Spectrum-4/P[®] 21 channel EEG System and scored by the same physician (MET) according to the criteria defined by American Sleep Medicine Academy (AASM) [19].

Patients having sleep breathing disorders other than obstructive apnea/hypopnea were excluded. Patients were then grouped into two groups according to their apnea/hypopnea indexes (AHI), which is an index used to show the number of apnea and hypopneas per hour. Group 1 consisted of patients with AHI lower than 15 (normal subjects and cases with mild obstructive sleep apnea) and Group 2 consisted of patients with AHI equal to or above 15 (cases with moderate and severe obstructive sleep apnea). Age, gender, AHI, fasting glucose level, Hba1c level, total cholesterol level, medical histories of diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), body weight and height, and blood pressure during the examination were scanned from the patient files. Cases on anti-hypertensive treatment or having systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90mmHg during their physical examination were accepted as hypertension positive cases. Patients on insulin or oral anti-diabetic drugs or having an Hba1c value over 6.5% or fasting glucose level over 125 mg/dl were accepted as diabetes mellitus positive cases. Patients on statine and/or fibrate treatment or having total cholesterol level over 200 mg/dl were accepted as positive for the presence of hyperlipidemia. Body mass indexes (BMI) were calculated by the formula body weight (kg)/body height² (m²) and outlier cases were excluded in order to make both groups homogeneous.

Ethical approval from the local ethical committee is present for the study (Acibadem University-ATADEK, Approval No: 2022-02/12).

Statistical analysis

Statistical Package for the Social Sciences (SPSS)[®] 15.0 for Windows was used for the data analysis. Numerical variables were given as mean \pm standard deviation. Categorical variables were shown as numbers. The Chi-Square test or Fisher's exact test was used to show any difference between the categorical variables of the groups. An Independent T-test was used to show any numerical difference between two independent groups. Four assumptions for the chi-square test were established: both variables were categorical (status of smoking, alcohol use, having diabetes, hypertension or hyperlipidemia was either positive or negative), all observations were independent, ie. not affecting each other, all the individuals in the contingency table were belonging to only one cell and the expected values of the cells were greater than five in at least 80% of the cells. Four assumptions of the independent t-test were established: Normality is checked with the Shapiro-Wilk test and normal distribution was seen in age and BMI variables (Sig. 0.259 and 0.877 respectively); equal variances were checked with Levene's test (Sig. for age is 0.442 and sig. for BMI is 0.229), observations in each group are independent of observations in every other group and there were no outliers. Statistical significance was accepted as $p < 0.05$.

Results

Fourteen female and 25 male patients were included in the study. The mean age of the study group was 51.84 ± 8.37 years (between 40-67 years). Group 1 included 22 cases (13 females, 9 males) with an $AHI < 15$, and Group 2 included 17 cases (1 female, 16 males) with an $AHI \geq 15$. The mean body mass indexes (BMI) of Group 1 and 2 were 27.08 and 28.9 respectively which were statistically similar ($p=0.206$). Group 1 had a mean age of 49.59 years and Group 2 had a mean age of 54.76 years where there was no statistically significant difference ($p=0.054$). There was male dominance in Group 2, and the odds ratio showed that males are 23 times more likely to have obstructive sleep apnea ($p=0.001$) (Table 1).

The frequencies of the positivity of DM, HT, and HL between the groups were compared. It is found that Group 2 has a significantly higher ratio of HT positive patients than Group 1. (47% vs 5%; $p=0.005$). Diabetes was found in 64% of the cases in Group 1 and 76% of the cases in Group 2. The ratios did not show statistical significance ($p=0.49$). The ratios of HL were also similar between Group 1 and 2 (55% and 59% respectively, $p=1.0$) (Table 2).

Although the ratio of smoking was found to be twice of Group 1 in Group 2 (19% vs 43.8%) there was no statistical significance. ($p=0.15$). Alcohol use was reported similar in both groups (33.3% vs 41.2%) ($p=0.74$) (Table 2).

Discussion

In the present study, the comparison of the ratios of the metabolic diseases and HT was done between the normal/mild OSA patients and the moderate/severe OSA patients. The results showed that the ratio of the patients having HT was significantly higher in the moderate/severe OSA group. The relationship between OSA and HT is an important study subject since they have a strong association and OSA has potential prognostic importance [5,20]. The results of the studies are controversial. Some of them support an independent role of OSA in the pathogenesis of HT, but on the other hand, co-existing factors, especially obesity, mediate this association. This issue is still not clear in the literature [5].

In a prospective cohort study, consisting of 5681 subjects, it is found that sleep-disordered breathing at baseline was positively associated with the incidence of HT. Hypertension had been detected during the follow-ups. After the adjustment for BMI, this association became statistically insignificant [15]. Another study was designed to follow up the patients for 8 years, with the adjustments done for gender, BMI, cigarette, and alcohol use. It was found that even cases with low AHI (0.1-4.9) had an increased odds of having HT than the cases with 0 AHI . This risk was shown to be increased with higher $AHIs$ and $AHI > 15$ was related to a two- or three-times increased risk of having HT when compared with AHI 0 cases. However, no threshold of AHI was found, below which HT was not related to OSA [21]. An increased risk of HT with higher respiratory distress was also reported in a longitudinal study of 2148 subjects, but when adjustments for gender, BMI, and neck circumference were applied, the correlation became insignificant [16]. As seen in these studies, there are variable results on

OSA as an independent risk factor for OSA.

In the present study, the subjects who have high blood pressure on their physical examinations, and the subjects who were on antihypertensive treatments were accepted as HT positive patients. The cases having $AHI \geq 15$ had a very significant high ratio of HT (8 cases out of 17 cases), while there was only one HT positive case out of 22 cases in $AHI < 15$ group ($p=0.005$). The single HT positive case of the first group was a 56-year-old male, with an AHI of 4.5. His BMI was 25.3 and he had no medical history of HT. He had no DM but had a high cholesterol level (Total cholesterol level 230 mg/dl). If he had an AHI close to 15, it might be considered as he was in the border zone of mild/moderate sleep apnea and HT could be attributed to sleep apnea. But his polysomnography is within the normal limits, so it is concluded that, finding this single HT positive case in the first group was by chance.

It is also worth mentioning that although the hypertensive effect of smoking acutely is much clear, no definite evidence of a direct causal relationship between chronic smoking and blood pressure could be supported by the studies [22-24]. According to this data, the high ratio of HT in Group 2 was concluded to be due to the presence of OSA and could not be attributed to the smoking habit. Excessive alcohol consumption also has an association with high blood pressure due to its effects on the vasoconstrictor 20-HETE and oxidative stress [25]. In the present study, the effect of drinking habit on HT is accepted as limited, since both groups reported similar ratios of alcohol use. Gender may be another reason for the high ratio of HT in Group 2 since only one female case was present in that group. But after 40 years of age, the difference in the prevalence of HT between the genders starts to become similar [26]. This study included cases over 40 year-old; so the effect of the gender on HT is considered to be limited. Since the groups of this study have similar BMIs, cigarette and alcohol habits and the role of the gender is limited; sleep apnea is considered to be the main risk factor for high blood pressure in the second group of this study. It is concluded that the result of the present study supports the possible independent role of moderate and severe OSA in the pathogenesis of HT and is in line with the supporting studies in the literature.

Diabetes mellitus, type 2 is another comorbidity that can be seen especially in moderate and severe OSA patients [1,10,27-30]. Although the studies show a prevalence of type 2 DM between 15-30% in OSA patients; adjustments for BMI and other confounders attenuate these findings [1,7,8]. It seems that OSA is not an independent risk factor for type 2 DM according to this data.

In the present study DM was checked by the criteria: being on insulin or oral antidiabetic treatment and/or having a blood fasting glucose level over 125 mg/dl and/or blood HbA1c level over 6.5%. Patients, who were accepted as DM positive according to these criteria had similar ratios between the groups ($p=0.49$). This finding is concluded as OSA is not an independent risk factor and BMI could play a major role in diabetes mellitus type 2 and is in line with the literature.

In the present study, the positivity of hyperlipidemia showed no significant difference between the groups. This

Table 1. Demographics.

Total study group	Group 1 (AHI<15)	Group 2 (AHI≥15)	OR	CI	p
n=39	n=22	n=17	23.11	2.58-206.86	0.001
Female= 14 Male= 25	Female=13 Male= 9	Female= 1 Male= 16	(male/female)		
Mean Age= 51.84±8.37	49.59±7.48	54.76±8.77			0.054
Mean body mass index	27.08±4.96	28.9±0.4			0.206

Table 2. Comparison of the groups.

Positive cases of	Group 1 (AHI<15)	Group 2 (AHI≥15)	OR	CI	p
Diabetes Mellitus	14 (64%)	13 (76%)	1.85	0.45-7.66	0.494
Hypertension	1 (5%)	8 (47%)	18.66	2.02-171.98	0.005
Hyperlipidemia	12 (55%)	10 (59%)	1.19	0.33-4.28	1.0
Smoking	n= 4 (19%) (1 missed)	n= 7 (43.8%) (1 missed)	3.3	0.76-14.38	0.15
Alcohol use	n= 7 (33.3%) (1 missed)	n= 7 (41.2%)	1.4	0.37-5.26	0.74

result is also considered to be due to the similar BMIs of the groups; since dyslipidemia is strongly related to body weight [17].

Conclusion

In conclusion, obstructive sleep apnea seems to be an independent risk factor of HT, whereas DM and HL are thought to be in close relationship with BMI rather than sleep apnea.

Limitations

This study's main limitations are having a small size of subjects and not involving control examination and laboratory tests of the cases after the convenient treatment of OSA. Also, the amount of alcohol and cigarette which had been used by the subjects could not be found in the files. However, the strong side of this study is providing homogenous groups of cases in terms of age and BMI, two main factors taking a role in HT and metabolic diseases.

Ethics approval

Local Ethical Committee (Acibadem University-ATADEK) has approved the present study. Approval No: 2022-02/12.

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