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Smoking status in relation to obstructive sleep apnea severity (OSA) and cardiovascular comorbidity in patients with newly diagnosed OSA

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Abstract

Introduction: the relationship between smoking and sleep disturbance has been well documented. Smoking is a common risk factor for both obstructive sleep apnea (OSA) and cardiovascular diseases. The study aimed to: 1) evaluate the incidence of newly diagnosed OSA in patients presenting with symptoms suggestive of a sleep disorder, 2) assess the relation between smoking status and OSA severity; and 3) compare the prevalence of cardiovascular comorbidities in ever- and never smokers with newly diagnosed OSA.

Material and methods: a retrospective analysis of 5,353 patients suspected of OSA was performed. OSA was diagnosed on the basis of polysomnography. The influence of smoking status on indices of OSA severity was evaluated and the incidence of self-reported cardiovascular diseases and diabetes mellitus type 2 was analyzed in relation to smoking history.

Results: OSA was diagnosed in 3,613 patients (67.5%); of these, 21.6% were ever-smokers. Smokers with OSA had a higher apnea-hypopnea index [AHI; 31 (18.4–53.29) vs 29 (18.3–47.7), $p = 0.03$], lower mean oxygenation during sleep [90.9 ± 4.0 vs 91 ± 3.7 , $p < 0.001$] and a higher daytime sleepiness (Epworth Sleepiness Scale score 11.7 ± 5.5 vs 11.0 ± 5.5 , $p < 0.001$). The most frequent comorbidity was hypertension, followed by obesity, diabetes mellitus type 2 and coronary artery disease, with a statistically higher incidence of hypertension in non-smokers (59.2 vs 64.7 %, $p = 0.005$).

Conclusion: smoking is related with OSA severity and increased daytime sleepiness. Our study confirmed the elevated frequency of cardiovascular comorbidities in OSA patients in general but did not show an increased incidence of these comorbidities in smokers.

Key words: obstructive sleep apnea, smoking, cardiovascular comorbidity

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Introduction

Obstructive sleep apnea (OSA) is the most common sleep disorder and is characterized by recurrent nocturnal airflow limitation in the upper airways, resulting in blood oxygenation decrease and subsequent arousals. According to the classic study by Young *et al.*, OSA affects approximately 4% of men and 2% of women aged 30–60 [1], however, in many later studies, a higher incidence

of OSA was reported, and in some populations, it may reach as much as 23.4% in women and 49.7% in men aged 40–85 [2].

The relationship between the diagnosis of OSA and smoking has been well documented. Smoking is associated with a decreased quality of sleep [3], daytime sleepiness and problems with falling and staying asleep [4]. Lin *et al.* hypothesized that smoking contributes to OSA symptoms by inducing chronic inflammation of the

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upper airways [5]. Smoking is also a recognized risk factor for cardiovascular diseases [6, 7]. This risk depends not only on the cumulative exposure to cigarettes expressed in pack-years but also on smoking habits, as smoking fewer cigarettes per day for a longer time showed to be more harmful than smoking more cigarettes for a shorter period [8].

Cardiovascular diseases are a frequent comorbidity in OSA [9]. It is estimated that 38–65% of patients with coronary artery disease and 12–55% of subjects with heart failure suffer from OSA [10]. Among patients with arterial hypertension, the prevalence of OSA ranges between 30% and as much as 83% [10]. Furthermore, several studies have shown that people with OSA are not only at a higher risk of cardiovascular morbidity, but also have a higher risk of cardiovascular-related mortality, particularly in the group of OSA patients with the severe form of the disease [11, 12]. In individuals with hypertension, OSA severity was found to be related with myocardial injury and this was independent from blood pressure control [13]. The pathogenesis of cardiovascular diseases in patients with OSA is multifactorial. The postulated causative factors include endothelial dysfunction, oxidative stress, chronic inflammation, increased activity of the sympathetic nervous system, vascular stiffness and impaired glucose metabolism [14]. The contribution of each of these individual factors is difficult to determine because of the complex interaction between OSA and cardiovascular diseases.

This study was aimed to analyze the relation between smoking status and daytime sleepiness and the incidence of cardiovascular comorbidities in newly diagnosed patients with OSA. The specific aims of the study were the following: 1) to evaluate the incidence of newly diagnosed OSA in patients presenting with symptoms suggestive of a sleep disorder, 2) to assess the relation between smoking status and OSA severity; and finally: 3) to compare the prevalence of cardiovascular comorbidities in ever- and never smokers with newly diagnosed OSA.

Material and methods

Study design

This single-center retrospective observational study included patients referred to the institutional Sleep Laboratory due to symptoms suggestive of OSA. Patient evaluation included detailed medical history, basic anthropometric data and polysomnography to confirm or exclude

OSA diagnosis. Cardiovascular diseases (arterial hypertension, history of myocardial infarction, coronary artery disease, chronic heart failure and, additionally, diabetes mellitus type 2) were recognized when the patients reported such previous diagnoses or if any of these conditions had been mentioned in the patient's earlier medical reports. Clinical data and the parameters attained in polysomnography were analyzed in relation to smoking history and ever-smokers and non-smokers were compared.

According to our institutional policy, as this was a retrospective non-interventional study, the approval of the Review Board was not mandatory. However, it should be emphasized that every patient managed in the Sleep Laboratory in our institution is asked to give signed consent for the potential use of his/her clinical data for research purposes, and only those who gave such consent were included in the analysis.

Study population

The participants of the study were recruited from subjects referred to the institutional Sleep Laboratory due to the suspicion of OSA between January 2007 and December 2017. The specific inclusion criteria were as follows: 1) age \geq 18 years and 2) newly diagnosed OSA in accordance with the recommendations of the Polish Respiratory Society [15]. Patients who had been previously treated for snoring or OSA, as well as those with a previous history of central apnea syndromes or restless leg syndrome were excluded from the study.

OSA diagnosis

Daytime somnolence was assessed with the use of the Epworth Sleepiness Scale (ESS) [16]. An ESS score greater than 10 points was considered as excessive daytime sleepiness [15]. All participants underwent nocturnal polysomnography (Alice 4 camera, RESPIRONICS, Murrysville, Pennsylvania, USA and Embla S4000, Reykjavik, Iceland) to confirm or exclude the recognition of OSA. OSA diagnosis and severity were established in accordance with the recommendations of the American Academy of Sleep Medicine (AASM) and the Polish Respiratory Society. The diagnostic criteria were as follows: apnea-hypopnea index (AHI) $>$ 5/h coupled with typical symptoms or AHI $>$ 15/h regardless of the presence of symptoms of OSA. The range of AHI values for mild, moderate and severe OSA were 5–15/h, 16–30/h and $>$ 30/h, respectively [15, 16].

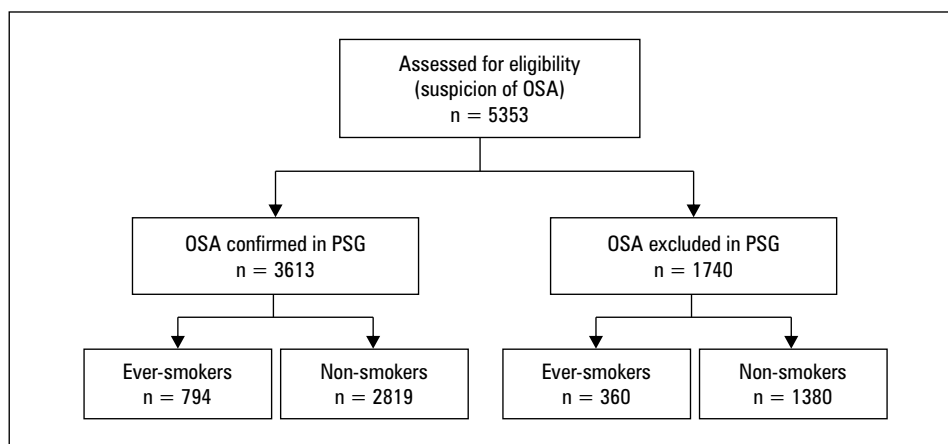


Figure 1. Flow chart of the participants of the study; OSA: obstructive sleep apnea; PSG: polysomnography

Statistical analysis

Normally distributed data were presented as mean with standard deviation. Variables with non-normal distribution were expressed as median and interquartile range (IQR). Correlations between variables were assessed using Spearman r coefficient. For comparison of continuous data between the two groups, Student t -test and Mann-Whitney test were applied. The analysis of covariance (ANCOVA) was used to determine effect of smoking status on sleepiness controlling for covariates. Discrete variables were expressed as percentages and were compared using Chi-square test with Yates's correction, when applicable. All performed tests were 2-tailed and differences between the compared groups were recognized as statistically significant with p -value < 0.05 .

All calculations were done in R version 3.4.0 — environment for statistical computing. Standard and “car” packages were used [17, 18].

Results

In the analyzed period, 5,353 subjects (3,556 men and 1,797 women, mean age 57.3 ± 9.5 years) were referred and diagnosed in our department. The diagnosis of OSA was confirmed in 3,613 (67.5%) patients, with the majority of cases (49.0%) being in the severe form. As expected, the mean ESS score was higher in patients with OSA when compared to the non-OSA group. There was a marked predominance of men in both groups, however, the proportion of men was significantly higher in patients with OSA. OSA subjects were older and had a higher body mass index (BMI). The number of ever-smokers and non-smokers in both groups was comparable (Fig. 1).

The prevalence of arterial hypertension, myocardial infarction and diabetes mellitus type 2 was higher in patients with OSA when compared to the non-OSA group, while the prevalence of coronary artery disease and chronic heart failure did not differ significantly between the groups (Table 1).

OSA in smokers and in non-smokers

Ever-smokers comprised 22.0% of the analyzed patients with OSA, and the median number of pack-years in this group was 20 (15–30). There was no difference in the relative distribution of OSA severity between the two groups, but smoking patients with OSA had a significantly higher AHI, lower mean oxygen saturation and declared a higher daytime sleepiness than those who did not smoke, and this applied both to men and women (Tables 2, 3).

One-way ANCOVA revealed that smoking status did not have a significant effect on sleepiness after controlling for age, AHI, mean saturation during polysomnography both in men ($F 2.352$, $p < 0.05$) and in women ($F 0.552$, $p > 0.05$). The number of pack-years was not correlated with AHI ($r = -0.093$, $p > 0.05$), ODI ($r = -0.024$, $p > 0.05$), SpO_2 mean ($r = -0.035$, $p > 0.05$) and SpO_2 min ($r = 0.027$, $p > 0.05$).

OSA comorbidities in relation to smoking status

The most frequent comorbidity in the whole investigated group of patients with OSA was hypertension, followed by obesity, diabetes mellitus type 2 and coronary artery disease. With the exception of hypertension, which was significantly more frequent in non-smoking OSA patients, the frequency of the analyzed comorbidities did not differ between the two groups (Table 3).

Table 1. Clinical characteristics of the studied population and the comparison between patients with obstructive sleep apnea (OSA) and those in whom OSA was not confirmed (OSA and non-OSA groups, respectively)

Parameter	All subjects (n = 5353)	Subjects with OSA (n = 3613)	Non-OSA subjects (n = 1740)	p-value
Age [years]	57.3 ± 9.5	57.5 ± 9.4	56.9 ± 9.6	< 0.05
BMI [kg/m ²]	30.7 ± 5.7	31.5 ± 5.9	29.2 ± 4.9	< 0.001
Obesity*, n (%)	2623 (49)	1973 (54.6)	650 (37.3)	< 0.001
Men, n (%)	3554 (66.4)	2597 (71.9)	957 (55.0)	< 0.001
Epworth Sleepiness Scale score (ESS)	10.1 ± 5.5	11.1 ± 5.5	7.8 ± 4.7	< 0.001
Ever-smokers, n (%)	1154 (21.6)	794 (22.0)	360 (20.6)	> 0.05
AHI [n per hour]	18.7 (7.5–38.4)	29.3 (18.3–48.9)	4.7 (2.1–9.0)	< 0.001
ODI [n per hour]	11.0 (3.6–26.4)	18 (8.4–34.2)	3.1 (1.1–7.3)	< 0.001
SpO ₂ mean [%]	91.9 ± 3.5	91.4 ± 3.8	93 ± 2.6	< 0.001
SpO ₂ min [%]	82 (75–86)	79 (73–84)	86 (82–89)	< 0.001
OSA severity mild/moderate/ /severe (%)	–	16.1/34.9/49.0	–	–
Hypertension, n (%)	3239 (60.5)	2293 (63.5)	946 (54.4)	< 0.001
Diabetes mellitus type 2, n (%)	792 (14.8)	567 (15.7)	225 (12.9)	< 0.01
Coronary artery disease, n (%)	920 (17.2)	637 (17.6)	285 (16.3)	> 0.05
Myocardial infarction, n (%)	75 (1.4)	60 (1.7)	15 (0.9)	< 0.05
Chronic heart failure, n (%)	21 (0.4)	18 (0.5)	3 (0.2)	> 0.05

BMI: body mass index; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; SpO₂ mean: mean oxygen saturation during polysomnography; SpO₂ min: minimal oxygen saturation during polysomnography; COPD: chronic obstructive pulmonary disease

*BMI > 30 kg/m²

Table 2. Comparison between smokers and non-smokers with obstructive sleep apnea (OSA)

Parameter	Ever-smokers with OSA (n = 796)	Non-smokers with OSA (n = 2817)	p-value
Age [years]	53.8 ± 8.0	58.6 ± 9.5	< 0.001
BMI [kg/m ²]	31.5 ± 6.3	31.5 ± 5.8	> 0.05
Obesity*, n (%)	435 (54.6)	1538 (54.6)	> 0.05
Men, n (%)	620 (77.9)	1977 (70.2)	< 0.001
Epworth Sleepiness Scale score	11.7 ± 5.5	11.0 ± 5.5	< 0.001
AHI [n per hour]	31 (18.4–53.2)	29 (18.3–47.7)	< 0.05
ODI [n per hour]	17.4 (8.0–37.0)	18.3 (8.5–33.5)	> 0.05
SpO ₂ mean [%]	90.9 ± 4.0	91.5 ± 3.7	< 0.001
SpO ₂ min [%]	79 (72–84)	80 (73–84)	> 0.05
OSA severity mild/moderate/severe (%)	15.3/32.9/51.8	16.4/35.4/48.2	> 0.05
Hypertension, n (%)	471 (59.2)	1822 (64.7)	< 0.01
Diabetes mellitus type 2, n (%)	121 (15.2)	446 (15.8)	> 0.05
Coronary artery disease, n (%)	127 (16.0)	510 (18.1)	> 0.05
Myocardial infarction, n (%)	11 (1.4)	49 (1.7)	> 0.05
Chronic heart failure, n (%)	3 (0.4)	15 (0.5)	> 0.05

BMI: body mass index; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; SpO₂ mean: mean oxygen saturation during polysomnography; SpO₂ min: minimal oxygen saturation during polysomnography; COPD: chronic obstructive pulmonary disease

*BMI > 30 kg/m²

Table 3. Comparison of smokers and non-smokers in women and men with OSA

Parameter	Women with OSA (n = 1016)		p-value	Men with OSA (n = 2597)		p-value
	Smokers (n = 176)	Non-smokers (n = 840)		Smokers (n = 620)	Non smokers (n = 1977)	
Age [years]	55.3 ± 7.5	61.2 ± 8.7	< 0.001	53.4 ± 8.1	57.4 ± 9.6	< 0.001
BMI [kg/m ²]	30.8 ± 7.3	31.3 ± 6.7	> 0.05	31.7 ± 5.9	31.5 ± 5.6	> 0.05
Obesity*, n (%)	81 (46 %)	442 (53%)	> 0.05	350 (56%)	1084 (55%)	> 0.05
Epworth Sleepiness Scale score	11.5±5.5	10.4±5.5	< 0.05	11.8 ± 5.5	11.2 ± 5.4	< 0.05
AHI [n per hour]	24.8 (5–123.9)	23.8 (5–118.7)	> 0.05	33.0 (5–118.3)	31.2 (5–134.5)	> 0.05
ODI [n per hour]	14.8 (0–107.5)	15.1 (0–102.7)	> 0.05	22.9 (0–110.8)	20.0 (0–187.8)	> 0.05
SpO ₂ mean [%]	91.2 ± 4.2	91.8 ± 3.5	< 0.05	90.8 ± 3.9	91.4 ± 3.8	< 0.01
SpO ₂ min [%]	78.8 (50–93)	80 (50–94)	> 0.05	79 (49–94)	79 (41–96)	> 0.05
OSA severity mild/ /moderate/severe [%]	16.7/30.1/43.2	21.2/33.6/38.8	< 0.05	12.1/33.7/54.2	14.3/33.5/52.2	> 0.05

BMI: body mass index; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; SpO₂ mean: mean oxygen saturation during polysomnography; SpO₂ min: minimal oxygen saturation during polysomnography

*BMI > 30 kg/m²

Discussion

Our study showed that OSA may be confirmed in approximately two thirds of patients presenting with symptoms of a sleep disorder and that the majority of persons with newly diagnosed OSA suffer from the severe form of the disease. We found that smoking had an impact on OSA severity and daytime symptoms. In the analyzed group, smokers had a significantly higher AHI, lower mean oxygen saturation during sleep and declared a higher daytime sleepiness than those who did not smoke. Arterial hypertension was the most frequent comorbidity in both groups and, interestingly, it was more frequent in non-smokers than in smokers. To our knowledge, this is the first study to show the impact of smoking status on the course of OSA and the incidence of cardiovascular comorbidities in a Polish cohort of OSA patients.

The detrimental effect of smoking on sleep has been well documented. Smokers have greater difficulty with falling asleep and maintaining sleep continuity, and report more sleepiness during the day [4]. This may be related not only to the stimulant properties of nicotine *per se* but, even more importantly, to the degree of nicotine addiction [19]. On the other hand, inhalation of cigarette smoke contents causes irritation of the throat and subsequent local edema of the mucosa

of the upper airways, which may be one of the contributing factors to upper airway obstruction and an increased risk of OSA. Smokers are several times more likely to experience respiratory sleep disorders than non-smokers [20], and have been reported to increase daytime sleepiness [21]. Our results are in line with these observations. We have shown that smokers with OSA have a significantly higher ESS score than non-smokers. Smoking patients with OSA also had a remarkably higher AHI compared to non-smokers, despite a younger age and a comparable BMI. However, increased daytime sleepiness in smokers found in our cohort was not confirmed in the analysis performed after controlling for age, AHI and BMI. In view of the above, we may assume that a higher ESS score in smokers with OSA may rather be attributed to the increased probability of respiratory disorders in response to smoking than to the direct impact of nicotine on sleepiness during day.

Arterial hypertension is one of the most frequent comorbidities in OSA. Hypertension is diagnosed in 30% to even 83% of patients with OSA, while 30–35% of hypertensive patients suffer from OSA [10, 22–24]. These observations were confirmed in our study. Hypertension was the most frequent self-reported cardiovascular comorbidity and was present in the vast majority of the investigated patients. Interestingly, it was more frequently reported by non-smokers than by smo-

kers. One of the possible explanations for this finding may be related to the younger age of smokers in the investigated cohort. According to the guidelines of the Polish Society of Hypertension and the European Society of Cardiology (ESC) on the diagnosis and management of hypertension [25], age over 55 years has a more predictive value in the diagnosis of hypertension than smoking and the occurrence of OSA.

Coronary artery disease was the second most frequent cardiovascular comorbidity in our patients. This is in line with the results of previous studies which showed that OSA is an independent factor of coronary heart disease and myocardial infarction [26, 27]. Although we did not show significant differences in the incidence of coronary artery disease in ever-smokers and non-smokers with OSA, the proportion of patients with a history of myocardial infarction was significantly higher in subjects with confirmed OSA when compared to persons in whom OSA was excluded. Our results also confirmed the increased likelihood of diabetes mellitus type 2 in individuals with OSA [28]. In the investigated group, self-reported diagnosis of diabetes was significantly more frequent in patients with OSA compared to those in whom OSA was not confirmed. We did not, however, find differences in the incidence of diabetes in smoking and non-smoking OSA patients.

The major limitation of our study is that the diagnosis of cardiovascular diseases and diabetes mellitus type 2 was based on patient self-reported data. Considering the retrospective nature of the study, this could not have been avoided. However, we made full effort to verify these data in the patients' available earlier medical documentation. On the other hand, epidemiological research based on self-reported patient data is frequently encountered in the literature [29, 30].

Conclusions

To summarize, we showed that OSA may be diagnosed in the majority of patients presenting with symptoms suggestive of sleep disorders and referred for polysomnography. Almost half of newly diagnosed subjects with OSA suffer from the severe form of the disease. Our study confirmed the increased frequency of hypertension, diabetes mellitus type 2 and past myocardial infarction in patients with OSA. Smoking was related with OSA severity and more pronounced abnormalities during sleep and increased daytime sleepiness. Our findings on the impact of smoking status on

the course of OSA and OSA cardiovascular comorbidities need to be confirmed in large population prospective studies.

Conflict of interest

The authors declare no conflict of interest.

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