Association of obstructive sleep apnea with co-morbidities in smokers versus non-smokers - An observational study

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Abstract

Obstructive Sleep Apnea (OSA) and smoking are important global health issues that are widely prevalent. Both are independently associated with cardiovascular, respiratory, metabolic, neurological, psychiatric, and endocrinological abnormalities and cancer, leading to premature death. Whether coexistent OSA and smoking worsen multisystem abnormalities is inconclusive. Therefore, this study was done to find the association between OSA and other morbidities among smokers and non-smokers. The objectives of this study were i) to evaluate the association of OSA with co-morbidities in smokers and non-smokers and ii) to compare the severity of OSA in smokers and non-smokers.

Introduction

Obstructive Sleep Apnea (OSA) and smoking are important global health issues that are widely prevalent. Both are independently associated with cardiovascular, respiratory, metabolic, neurological, psychiatric, and endocrinological abnormalities and cancer, leading to premature death.[1] Whether coexistent OSA and smoking worsen multisystem abnormalities is inconclusive. Therefore, this study was done to find the association between OSA and other morbidities among smokers and non-smokers. The objectives of this study were i) to evaluate the association of OSA with co-morbidities in smokers and non-smokers and ii) to compare the severity of OSA in smokers and non-smokers.

Materials and Methods

This was a retrospective observational study conducted in a tertiary care centre in South India, involving data from May 2015 to November 2019. Patient data was collected from the sleep data register maintained in the Department of Respiratory Medicine. The study was approved by the Institutional Ethical Committee.

Inclusion criteria were patients with obstructive sleep apnea aged over 18. Exclusion criteria were other sleep disorders like central sleep apnea, restless leg syndrome, Rapid Eye Movements (REM) sleep behaviour disorder, previous treatment of OSA by upper airway surgery or usage of positive airway ventilation, and patients who did not undergo in-laboratory overnight polysomnography.

Two hundred sixty-six patients were assessed in our sleep clinic over a period of 55 months, 188 of whom were included in the present study.

The following details were collected from our sleep data register: personal details, including name, age, gender, address, con-

tact details, occupation, and history of smoking. Smoking history included smoking status (current smoker, non-smoker, and former smoker) and smoking index (number of cigarettes or beedis smoked per day multiplied by the number of years of smoking). Non-smokers were the subjects who had never smoked or smoked less than 100 cigarettes till the date of our interview. Current smokers were the subjects who were currently smoking. Former smokers were defined in our study as the subjects who had given up smoking at least one year back as on the day of the interview.

The sleep data register also included a history of hypertension, type 2 diabetes mellitus, hypothyroidism, Chronic Obstructive Pulmonary Disease (COPD), bronchial asthma, pulmonary hypertension, and coronary artery disease, which were diagnosed as per standard definitions. History of intake of anti-hypertensives, oral hypoglycemics or insulin, lipid-lowering medications, and usage of other medications were also included. Anthropometric data and resting blood pressure were included in the sleep data register as well; a normal Body Mass Index (BMI) was defined as <25 kg/m^2, overweight between 25-29.9 kg/m^2, obese as >30 kg/m^2. Furthermore, the sleep data register included information on fasting, post-prandial and/or random blood sugar, glycosylated hemoglobin, fasting lipid profile and fasting thyroid profile (T3, T4, TSH), Epworth Sleepiness Scale (ESS) questionnaire scores as a measure of excessive daytime somnolence and spirometry (Hypair Compact, Medisoft, Belgium) parameters (pre- and post-bronchodilator values of FVC, Forced Vital Capacity, FEV_1, Forced Expiratory Volume in the First Second, FEV_1/FVC). Finally, the objective sleep status was evaluated by in-laboratory overnight Polysomnography (PSG) (Embla S4500, Canada). It consisted of the Electroencephalogram (EEG) channels, Electrocardiography (ECG), Electro-Oculography (EOG), Electromyography (EMG), nasal and oral airflow (using both a nasal-oral thermocouple and nasal pressure cannula), snoring sounds, thoracic/abdominal movements, finger pulse oxygen saturation, leg movements, and body position for measurement of various sleep parameters. The polysomnogram was interpreted by a certified sleep technician, followed by a pulmonologist independently. Apneas and hypopneas were defined using the American Academy of Sleep Medicine (AASM) criteria.[1] Apnea-Hypopnea Index (AHI) <5/hour was considered normal, AHI of 5.1-14.9/hour, 15-29.9/hour, and ≥30/hour were categorized as mild, moderate, and severe OSA, respectively.

Statistical analysis

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 17.0 (IBM, Armonk, New York, United States). The quantitative variables were expressed as mean ± Standard Deviation (SD), and qualitative variables were expressed as frequency and percentages. A p-value of <0.005 was considered significant in all analyses. The association between categorical data was calculated using the Chi-square test and Fischer's exact test. Association between continuous data was calculated using a t-test.

Results

There were 136 (72.34%) male and 52 (27.66%) female patients. There were 112 (59.57%) non-smokers (61 males, 51 females) and 76 (40.42%) smokers (75 males, one female). There were 75 current smokers (98.68%) and one former smoker (1.31%). In the non-smoker group, 62 patients (96.2 %) were aged >40 years compared to 50 patients (86.2%) who were <40 years (p=0.015). Similarly, in the smoker group, there were 53 patients (95.8%) aged >40 years compared to 23 patients (85.2%) <40 years (p=0.45). Demographic and anthropometric characteristics are shown in Table 1.

Positive correlation was seen with ESS and AHI, both among smokers (AHI 36.54±24.77, ESS 10.71±6.37, p<0.001) and non-smokers (AHI 28.79±23.08, ESS 8.84±6.04, p<0.001), *i.e.*, as the scoring of ESS increased, AHI also increased (Figure 1).

Mean AHI was higher among smokers (36.54±24.77/hour) than non-smokers (28.79±23.08/hour), which was statistically significant (p=0.029). Mild, moderate, and severe OSA was found in 63 (33.5%), 32 (17%), and 93 (49.5%) patients, respectively. The comparison of the severity of OSA in smokers and non-smokers is shown in Table 2.

The association of smoking and OSA with individual clinical variables (Table 3): 10 (90.9%) patients among smokers had COPD compared to 1 (9.1%) among non-smokers (p=0.001). Hypertension (18, 51.4% *vs* 17, 48.7%) and coronary artery disease (3, 100% *vs* 0) were found in higher frequency among smokers than non-smokers, though it was not statistically significant.

Table 1. Distribution of patients according to demographic, anthropometric characteristics, and Epworth Sleepiness Scale.

Smoker	Non-smoker	t	p	
Sex				
Male	75	61		
Female	1	51		
Mean age ± SD (years)	46.65±10.93	43.96±12.69	1.391	0.17
Mean AHI ± SD (n/hour)	36.54±24.77	28.79±23.08	2.195	0.029
Mean BMI ± SD (kg/m^2)	29.45±5.2	29.55±5.99	-0.105	0.92
Mean ESS ± SD	10.71±6.37	8.84±6.04	2.044	0.42

ESS, Epworth Sleepiness Scale; BMI, Body Mass Index; AHI, Apnea-Hypopnea Index; SD, Standard Deviation.

Table 2. Comparison of Apnea-Hypopnea Index (AHI) between smokers and non-smokers.

	AHI	Smoker (N/%)	Non-smoker (N/%)	t, p
<5	6(7.3)	10(8.2)	χ^2= 7.18	p= 0.07
5-14.9	17(20.7)	6(37.7)		
15-29.9	15(18.3)	17(39.9)		
≥30	44(53.7)	49(40.2)		
Total	82	122		

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The frequency of dyslipidemia (59.1% *vs* 40.9%, p=0.516), pulmonary hypertension (56.9% *vs* 43.1%, p=0.644), hypothyroidism (64.3% *vs* 35.7%, p=0.709), diabetes mellitus (65.3% *vs* 34.7%, p=0.342), bronchial asthma (66.7% *vs* 33.3%, p=0.191) and obesity (58.1% *vs* 41.9%, p=0.712) were higher in non-smokers compared to smokers, however, this was not statistically significant. The categorization of patients as per the severity of OSA among smokers and non-smoker groups in the diseases assessed is shown in Table 4.

Discussion

Obstructive sleep apnea is a sleep-related breathing disorder where there is a reduction or cessation of airflow despite a continuous effort to breathe. Obstructive sleep apnea is an underdiagnosed condition.[2] The prevalence of OSA in India is 7.5%-13.5%.[3,4] The prevalence of OSA is 4-24% in men and 2-16% in women in India.[2] The prevalence of OSA has been rising with a proportional increase in obesity and tobacco smoking.[5] As a consequence of repeated upper respiratory obstruction during sleep, there is repetitive hypoxemia, disturbances in heart rate, blood pressure, and intrathoracic pressure associated with poor sleep.[6] These effects lead to the risk of developing cardiovascular, respiratory, metabolic, neurological, psychiatric, and endocrinological abnormalities, including the possibility of cancer leading to premature death.[7] Thus, there is a significant impact on morbidity and mortality if OSA is untreated. Motor vehicle and industrial accidents have resulted due to excessive daytime sleepiness caused by OSA.[7] Cigarette smoking affects every organ in the body. The mortality rate is three times higher in smokers compared to non-smokers.[8] Five to six million people die due to adverse effects of smoking annually.[9] As the country with the second-highest level of tobacco consumption worldwide,[9-11] India faces a particularly large health challenge. Cigarette smoking is one of the preventable causes of morbidity and mortality.

A bidirectional relationship has been noted between smoking and OSA. Cigarette smoking may increase the severity of OSA. Mechanisms postulated are chronic inflammation of upper airways leading to narrowing of oropharynx, upper airway neuromuscular dysfunction, changes in sleep architecture and increasing the arousal threshold of sleep.[10] Conversely, smoking addiction has been caused by untreated OSA, as per some evidence.[11] The increase in the number of nicotine binding sites caused by chronic hypoxia in OSAS (Obstructive Sleep Apnea Syndrome) is seen in smokers due to adaptation, which leads to increased frequency of

Table 3. Association of co-morbidities among smokers and non-smokers.

Disease	Smoker (%)	Non-smoker (%)	Total	t, p
COPD	10 (90.9)	1 (9.1)	11	χ^2=10.24 p=0.001
Hypertension	18 (51.4)	17 (48.7)	35	χ^2=2.162 p=0.141
Pulmonary hypertension	22 (43.1)	29 (56.9)	51	χ^2=0.213 p=0.644
Dyslipidemia	76 (40.9)	110 (59.1)	186	Fischer's exact p=0.516
Hypothyroidism	5 (35.7)	9 (64.3)	14	χ^2=139 p=0.709
Diabetes mellitus	17 (34.7)	32 (65.3)	49	χ^2=0.904 p=0.342
Bronchial asthma	19 (33.3)	38 (66.7)	57	χ^2=1.708 p=0.191
Coronary artery disease	3 (100)	0	3	Fischer's exact p=0.516
Obesity (BMI>30 kg/m^2)	36 (41.9)	50 (58.1)	86	2=0.136 p=0.712

COPD, Chronic Obstructive Pulmonary Disease; BMI, Body Mass Index.

Table 4. Categorization as per severity of OSA among smokers and non-smokers.

	Non-smokers AHI			Smokers AHI		
Co-morbidity	Mild (n/%)	Moderate (n/%)	Severe (n/%)	Mild (n/%)	Moderate (n/%)	Severe (n/%)
COPD	0	1(100)	0	1(10)	2(20)	7(70)
Hypertension	0	5(29.41)	12(70.59)	1(5.55)	3(16.66)	14(77.77)
Pulmonary hypertension	0	2(6.9)	27(93.1)	0	1(4.5)	21(95.5)
Dyslipidemia	45 (40.90)	16 (14.54)	49 (44.54)	17 (22.36)	15 (19.73)	44 (57.8)
Diabetes mellitus	5 (15.65)	8 (25)	19 (59.35)	2 (11.76)	4 (23.59)	11 (64.7)
Hypothyroidism	2 (22.22)	2 (22.22)	5 (55.55)	0	3 (60.0)	2 (40.0)
Bronchial asthma	25 (65.78)	6 (15.78)	7 (18.42)	12 (63.15)	4 (21.05)	3 (15.78)
Coronary artery disease	0	0	0	0	1(33.3)	2(66.7)
	72	40	119	33	33	104

COPD, Chronic Obstructive Pulmonary Disease; AHI, Apnea-Hypopnea Index.

smoking.[11] It has been hypothesized that smoking and OSA may adversely affect each other, leading to greater co-morbidity and altering the effects of ongoing treatment.[11]

Though there is a possible association between smoking and OSA, the evidence is not conclusive. As per our literature search, the studies that have assessed the combined effects of OSA and smoking on other morbidities are scarce. We conducted this study to evaluate the association of OSA with co-morbid diseases in smokers versus non-smokers. Understanding this would shed more light on treatment strategies and better patient care.

We found that the prevalence of OSA increased with age. Similar results were found in other studies where people over 40 years were more prone to OSA.[2,12,13]

The present study showed male predominance in cases of OSA similar to that in other studies.[12-15] Trenchea *et al.* found a significant association of smoking as a risk factor for OSA in males ($p<0.0007$).[12] Martinez Rivera *et al.* proposed female hormones as a protective factor against OSA. Although females had higher BMI than men, they had lesser AHI when compared to men in their study.[16] Smokers had higher ESS scores than non-smokers, according to studies conducted by Wen Hyu Hsu *et al*., Conway *et al*., and Bielicki *et al*., similar to the present study.[17-19] In the present study, we found that smokers had higher mean AHI than non-smokers ($p=0.032$). Wetter *et al.* investigated a total of 811 active smokers and former smokers by polysomnography. They found that active smokers had more chance of snoring and heavy smokers had a greater risk of developing OSA compared to non-smokers.[20] Hoflstein's study showed greater prevalence of active and heavy smokers (>30 pack years) in subjects with AHI>50/hour, but the relationship was not statistically significant.[21] Macy Lui *et al.* found moderate to severe OSA was seen in active and former smokers compared to non- smokers ($p=0.035$).[5] On the contrary, in a study done by Wen Hu Ysu, the authors did not find any significant association between cigarette smoking and OSA after adjusting for age, sex, and BMI. Cigarette smoking and OSA showed a significant association in the unadjusted model (OR-1.51), but this association was not seen when it was adjusted for age, sex, and BMI (OR-1.02).[17]

In the present study, we found that both smokers and non-smokers had a mean BMI in the range of overweight ($p=0.817$). BMI was higher in non-smokers than smokers, but it was not statistically significant. This could be explained by the effect of nicotine in smokers, which decreases body weight by increasing the basal metabolic rate, sympathomimetic action, and increasing lipolysis. Smokers weigh 4-5 kg less than non-smokers.[22] High BMI has been found to be a risk factor for OSA.[10,14-16] Mass load effect by obesity on the upper airway increases its collapsibility, leading to OSA.[16] Higher rates of smoking and more severe OSA were seen in obese patients.[16]

In the present study, smokers with OSA had a higher frequency of hypertension and coronary artery disease. Elevated sympathetic activity, systemic inflammation, oxidative stress, endothelial dysfunction, and sleep fragmentation may lead to the occurrence of cardiovascular disorders in patients with concomitant smoking and OSA.[12] Cigarette smoking in patients with sleep apnea has been known to enhance vascular inflammation, formation of atheroma and dyslipidemia.[5,10] Arterial hypertension was more common among non-smokers compared to smokers in a study done by Bielicki et al.[19] Similarly, no significant difference was found in the incidence of coronary artery disease among smokers and non-smokers in their study. Trenchea *et al*. and Lavie *et al.* found smokers with severe OSA had higher cardiovascular risk compared to non-smokers with OSAS.[12,23] We found smokers with OSA had an increased frequency of COPD than non-smokers with significant association. Increased neutrophils, TNF-α, and IL-8 were found in bronchoalveolar lavage fluid in adults with OSA and COPD (overlap syndrome) compared to patients with only COPD, indicating OSA may lead to airway inflammation. Smoking history was a predictor of overlap syndrome as per a study done by Steveling E.H. *et al*.[24]

Pulmonary hypertension associated with OSA is caused by a remarkable hypoxic vascular response, which is usually mild to moderate and could be reverted by positive pressure airway therapy, as demonstrated by Sajkov *et al*.[25] Changes in vascular tone and faster cell aging occur as components of pulmonary arterial remodeling caused by smoking. Therefore, smoking directly leads to pulmonary hypertension. However, the present study shows pulmonary hypertension was more common in non-smokers than smokers, though statistically insignificant.[26] Dyslipidemia occurred with higher frequency in non-smokers than smokers in the present study, but a significant association was not found. Smokers with sleep apnea have been found to have dyslipidemia, as per Zhu *et al.* and Pinto *et al.*[10,27] Low-density lipoprotein cholesterol level was found to be independently associated with OSAS.[8] Lavie *et al.* studied a total of 70 smokers and non-smokers with sleep apnea and found smokers with sleep apnea had lower levels of HDL and higher levels of triglycerides compared to non-smokers.[23] Diabetes mellitus was more common among non-smok-

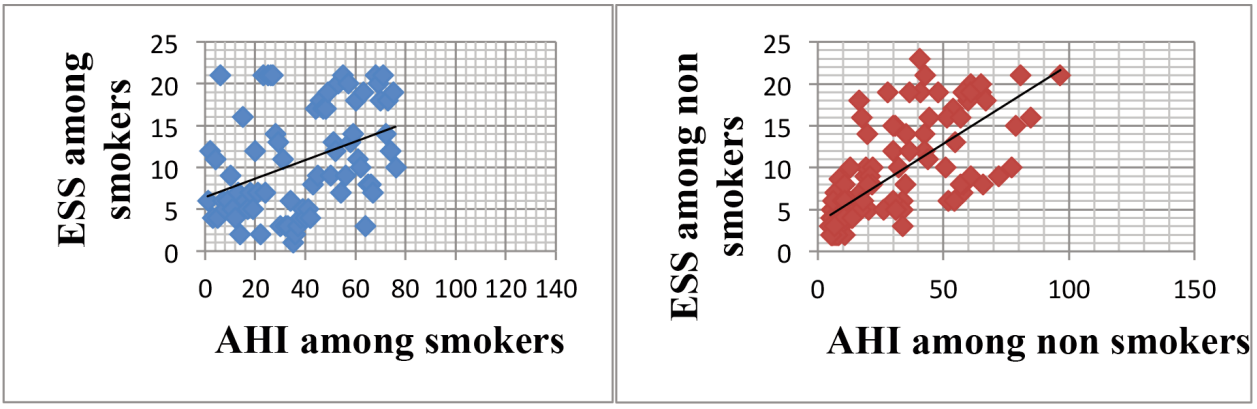

Figure 1. Scatter plots showing the correlation between AHI and ESS among smokers (n=82) and non-smokers (n=122). AHI, Apnea-Hypopnea Index, ESS, Epworth Sleepiness Scale.

ers than smokers in our study, though it was not statistically significant. This was dissimilar to results found by Zhu *et al., where they confirmed derangement of glucose metabolism is a result of the* combined effect of smoking and OSAS.[10] Shi Y. *et al.* found the progression of OSA may lead to an increase in thyroid hormone levels due to oxidative stress and inflammation caused by OSA in the non-elderly population, whereas in the non-elderly population, they speculated that hypoxia for long duration leads to damage of thyroid cells rather than hyperfunction leading to negative impact of thyroid hormone levels.[28] Smoke exposure may affect various metabolic and biological processes, including hormone biosynthesis and secretion; interfere with thyroid hormone release, binding, transport, storage, and clearance; and be associated with adverse effects on the thyroid, resulting in changes in circulating hormone concentrations.[29] Soldin *et al.* measured serum cotinine levels and categorized subjects into active smokers/passive smokers/non-smokers in a population of 237 non-pregnant women. Active smokers showed decreased TSH and T4 levels.[29] Though certain diseases were found in higher frequency among non-smokers than among smokers, the association was statistically insignificant. This could have been possibly due to a greater number of non-smoker subjects compared to smokers.

Limitations

The present study includes a small sample size.

Conclusions

In smokers with OSA, co-morbidities such as coronary artery disease, systemic hypertension, and COPD were present significantly in comparison to non-smokers with OSA.

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