**Original Research Article**

**Association between obstructive sleep apnea and comorbidities in adult patients**

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**ABSTRACT**

**Background:** With the emergence of lifestyle diseases in epidemic proportions in developing nations like India, Obstructive sleep apnea syndrome (OSAS) is increasing consistently. OSA brings many adverse consequences, such as systemic hypertension, cardiovascular diseases, obesity, diabetes mellitus, behavioral changes and many other comorbid conditions.

**Methods:** This is a prospective study of 46 polysomnography proven patients with OSA apnea hypopnea index (AHI) ≥5/h. The study period was from 1st October, 2017 to 31st March, 2019. Subjects were divided into three subgroups according to AHI: mild OSAS: 5<AHI<15, moderate OSAS: 15<AHI<30 and severe OSAS: AHI >30. The patients were thoroughly examined and evaluated for associated comorbidities.

**Results:** We evaluated 25 men and 21 women with OSA, mean age of 57.7 years (range 30–86). Average weight and body mass index (BMI) of the patients were 86.1 kg (range 65–132) and 33.1 kg/m² (range 25–46.9) respectively. On evaluation of comorbidities hypertension was on the top 30 (65%) followed by obesity 28 (61%), left ventricular hypertrophy 23 (50%), diabetes mellitus 21 (46%), dyslipidemia and chronic obstructive pulmonary disease in 12 (26%) each. Total no. of comorbidities and multiple comorbidities in a single patient were highest in severe OSA group.

**Conclusions:** OSA predominantly affects middle-aged (>55 years) individuals who are overweight with many having high neck circumference. There is statistically significant positive correlation between AHI and BMI and between number of comorbidities and severity of OSAS. Awareness regarding OSA among the general population and clinicians, wider availability of PSG studies will help in identifying and treating these patients.

**Keywords:** Obstructive sleep apnea, Apnea hypopnea index, Comorbidities, Obese

**INTRODUCTION**

Obstructive sleep apnea (OSA) is a potentially disabling chronic condition characterized by disruptive snoring, partial or complete recurrent upper airway obstruction during sleep. It results in periods of apnea, oxyhemoglobin desaturation and frequent night awakenings with excessive daytime sleepiness as a consequence, reducing performance at work and in social activities.

The epidemic of OSA is closely related to the obesity epidemic, an important public health related condition facing adults globally. The prevalence of OSA in India is on rise due to the increasing sedentary lifestyle in both urban and rural communities in the oriental population resulting in similar lifestyle-related diseases which till now were a burden of the economically developed nations only.
In fact, up to 80% of cases of moderate or severe OSA have gone undiagnosed despite adequate access to health care. A survey conducted in a semi-urban Indian population, it was found that around 6.2% among total sample were diagnosed with high-risk obstructive sleep apnea syndrome (OSAS) and 33.5% of the obese population was at high risk of OSAS. Even more striking is the number of health related conditions implicated with OSA like diminished neurocognitive function, increased risk of motor vehicle accidents, reduced quality of life, hypertension, insulin resistance, and cardiovascular diseases. Increasing awareness about the disease, improving diagnostic facilities will help to offer appropriate care to these patients.

METHODS

A total of 46 adult patients of either sex, above 18 years of age, suffering from OSA or history suggestive of OSA were included in the study after getting approval from ethical committee. These patients attended the department of Respiratory Medicine IMS, BHU, Varanasi in between 1st October, 2017 to 31st March, 2019. Patients with unstable psychiatric conditions, unstable chronic respiratory insufficiency, recent myocardial infarction that would interfere in performing the study were excluded from the study. After thorough history, clinical examination and anthropometric measurements all patients underwent polysomnography (PSG). Breathing pattern analysis for the presence of apneas and hypopneas were determined according to definitions standardized by the American academy of sleep medicine (AASM). Obstructive apnea was considered as cessation of airflow for at least 10 seconds with persistent respiratory effort. Patients were categorized as mild OSAS: 5<AH<15, moderate OSAS: 15<AH<30 and severe OSAS: AH>30. Body mass index (BMI)>30 kg/m2 was considered as obese. Abdominal circumference (AC) in men: >102 cm, women: >88 cm, waist circumference (WC) men: ≥90 cm; women: ≥80 cm and waist height ratio (WHtR) 0.5 were taken as cutoff for central obesity. Neck circumference (NC)≥37 cm. in men and>34 cm. in women was set as the upper limit of overweight /obesity. Neck length (NL) or mentohyoid distance of less than 3 finger width was considered as strong association with OSA. Calculation of epworth sleepiness scale (ESS) and STOPBANG Score was done to measure daytime sleepiness/dozing. The higher the ESS score, the higher is person's average sleep propensity (ASP), or 'daytime sleepiness'. BP≥130/85 mm Hg. or normal BP in the patients on medical therapy was considered as hypertension. Patients with fasting blood glucose≥110 mg/dl or normal sugar values on medication were taken as diabetic. Blood Triglycerides ≥150 mg/dl, HDL cholesterol<40 mg/dl in men and <50 mg/dl in women were classified as patient of dyslipidaemia. Diagnosis of metabolic syndrome was made in the presence of at least 3 of the 5 significant clinical signs ie obesity, hypertension, diabetes mellitus, hypertriglyceridemia and hypercholesterolemia.

RESULTS

Forty-six patients including 21 (46%) females and 25 (54%) males completed the study. The average age of female and male patients was almost similar i.e. 58.8 vs. 58 years, ranging from 30 to 86 years (Figure 1).

![Figure 1: Age-sex distribution of the patients with OSA.](image1)

Majority of patients (63%) belonged to urban area followed by 28.3% and 8.3% from semi-urban and rural areas. Almost 24% males were smokers and 16% of males were alcoholic and/or tobacco chewer. No female patient was having history of smoking or tobacco chewing. History of exposure of biomass/kerosene fuel smoke during home cooking was found in 38% of females. Majority of patients were obese and having BMI more than cut off value of 30 kg/m² (Figure 2).

![Figure 2: Majority of patients having BMI more than cut off value of 30 kg/m².](image2)

Average weight and BMI of the patients were 86.1 kg (range 65-132 kg) and 33.1kg/m² (range 25-46.9) respectively. Other anthropometric measurement data ranged from 34 to 50 cm (mean 40.5) for neck circumference (NC), 2 to 6 fingers (mean 4f) for neck length (NL) 57 to 152 cm (mean 109.8) for waist circumference (AC) in men: >102 cm, women: >88 cm, waist circumference (WC) men: ≥90 cm; women: ≥80 cm and waist height ratio (WHtR) 0.5 were taken as cutoff for central obesity. Neck circumference (NC)≥37 cm. in men and>34 cm. in women was set as the upper limit of overweight /obesity. Neck length (NL) or mentohyoid distance of less than 3 finger width was considered as strong association with OSA. Calculation of epworth sleepiness scale (ESS) and STOPBANG Score was done to measure daytime sleepiness/dozing. The higher the ESS score, the higher is person's average sleep propensity (ASP), or 'daytime sleepiness'. BP≥130/85 mm Hg. or normal BP in the patients on medical therapy was considered as hypertension. Patients with fasting blood glucose≥110 mg/dl or normal sugar values on medication were taken as diabetic. Blood Triglycerides ≥150 mg/dl, HDL cholesterol<40 mg/dl in men and <50 mg/dl in women were classified as patient of dyslipidaemia. Diagnosis of metabolic syndrome was made in the presence of at least 3 of the 5 significant clinical signs ie obesity, hypertension, diabetes mellitus, hypertriglyceridemia and hypercholesterolemia.

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Circumference (WC) and 89 to 158 cm (mean 115.7) for AC (Table 1). Out of 46 patients 31 (67.39%) were having Severe OSA (AHI>30) followed by 9 (19.57%) with moderate (15<AHI<30) and 6 with (13.04%) mild OSA (5<AHI<15) (Table 2).

Table 1: Representing mean, mode, standard deviation values of anthropometric variables.

| Variables         | Mean   | Median | Mode  | Standard deviation | Minimum | Maximum |
|-------------------|--------|--------|-------|--------------------|---------|---------|
| Age (yrs.)        | 57.7   | 56.0   | 55.0  | 12.4               | 30.0    | 86.0    |
| Wt. (kg)          | 86.1   | 82.0   | 100.0 | 15.7               | 65.0    | 132.0   |
| BMI (kg/m²)       | 33.1   | 31.7   | 29.8  | 5.7                | 25.0    | 46.9    |
| Neck Circum. (cm) | 40.5   | 40.0   | 38.0  | 3.9                | 34.0    | 50.0    |
| Neck Length (finger) | 4.0   | 4.0    | 3.0   | 1.1                | 2.0     | 6.0     |
| Waist Circum. (cm)| 109.8  | 108.0  | 122.0 | 18.6               | 57.0    | 152.0   |
| Abd. Circum. (cm) | 115.7  | 114.0  | 130.0 | 16.8               | 89.0    | 158.0   |

Table 2: Severity of OSA (AHI grades) and mean, mode and standard deviation of AHI.

| AHI Grades       | Grand Total | Mean | Median | Mode  | Standard deviation | Minimum | Maximum |
|------------------|-------------|------|--------|-------|--------------------|---------|---------|
| Mild (5≤AHI<15)  | 9           | 19.57% | 44.3   | 41.3  | 80.4               | 90      | 95      |
| Moderate (15≤AHI<30) | 6          | 13.04% | 19.57% | 44.3  | 41.3               | 90      | 95      |
| Severe (AHI≥30)  | 31          | 67.39% | 19.57% | 44.3  | 41.3               | 90      | 95      |
| Grand Total      | 46          | 100%  | 44.3   | 41.3  | 80.4               | 90      | 95      |

Average ESS for mild, moderate and severe OSA were 14.44, 17.00 and 17.77 and average STOPBANG score for mild, moderate and severe OSA were 4.89, 5.33 and 5.48 respectively. On evaluation of comorbidities hypertension was on the top 30 (65%) followed by obesity 28 (61%), left ventricular hypertrophy 23 (50%), diabetes mellitus 21 (46%), dyslipidemia and COPD in 12 (26%) each. Other comorbidities were less common like depression 9 (20%), metabolic syndrome 6 (13%), hypothyroid 4 (9%) allergic rhinitis 2 (4%), PAH and chronic kidney disease in 5 (11%) each and CAD and asthma was present in 3 (7%) each. GERD was present only in one patient (Table 3).

Another observation was that only 59% of patients with Hypertension, 46% of patients of type-2 diabetes mellitus and 2% of patients with psychiatric illnesses were taking treatment regularly. Four or more than four comorbidities were highest (30.43%) in patients with severe OSA followed by mild (15.22%) and moderate (8.70%) OSA. No patient with mild OSA had more than four comorbidities (Figure 3, 4).

We calculated correlation values (CV) between AHI and BMI, NC, NL, AC, WC, ESS, STOPBANG, TG, LDL, HDL and VLDL as shown in (Table 4).

Table 3: Prevalence of comorbidities vs. OSA severity.

| Comorbidities  | Mild (n=9) | Moderate (n=6) | Severe (n=31) | Grand Total (n=46) |
|----------------|------------|---------------|----------------|--------------------|
| Hypertension   | No         | Yes           | Yes            | Yes                |
| Obesity        | No         | Yes           | Yes            | Yes                |
| LVH            | No         | Yes           | Yes            | Yes                |
| DM             | No         | Yes           | Yes            | Yes                |
| Dyslipidaemia  | No         | Yes           | Yes            | Yes                |
| COPD           | No         | Yes           | Yes            | Yes                |
| Depression     | No         | Yes           | Yes            | Yes                |

Continued.
Table 4: Correlation between AHI and BMI, NC, NL, AC, WC, ESS, STOPBANG, TG, LDL, HDL and VLDL.

| Variables             | Mild (n=9) | Moderate (n=6) | Severe (n=31) | Grand total (n=46) |
|-----------------------|------------|----------------|---------------|--------------------|
| **AHI**               | 1.00       |                |               |                    |
| **BMI**               | 0.284      | 1.000          |               |                    |
| **NC**                | 0.487      | 0.546          | 1.000         |                    |
| **NL**                | -0.245     | -0.458         | -0.587        | 1.000              |
| **AC**                | 0.389      | 0.666          | 0.493         | -0.546             |
| **WC**                | 0.245      | 0.643          | 0.415         | -0.397             |
| **ESS**               | 0.349      | 0.387          | 0.280         | -0.363             |
| **STOPBANG**          | 0.060      | 0.434          | 0.348         | -0.393             |
| **TG**                | 0.061      | 0.175          | -0.009        | -0.243             |
| **LDL**               | 0.075      | 0.249          | -0.076        | -0.046             |
| **HDL**               | -0.003     | 0.158          | -0.045        | 0.060              |
| **VLDL**              | -0.041     | 0.094          | 0.064         | -0.112             |

Table 4: Correlation between AHI and BMI, NC, NL, AC, WC, ESS, STOPBANG, TG, LDL, HDL and VLDL.
Figure 5: Scatter charting of correlation between AHI and BMI, neck, girth (circumference), neck length, abdominal and waist circumference.

Positive correlation value of +0.28 between AHI and BMI indicates that an increase in value of AHI will also increase the value of BMI and vice versa i.e. the patients who were having severe OSA were having high BMI. Similarly, the correlation of AHI vs. Neck Circumference was positive (CV±0.48) but AHI vs. Neck Length was negative (CV-0.24). AHI vs. Abdominal Circumference was positive (CV±0.38) and so was AHI vs. Waist Circumference (CV±0.24) (Figure 5).

The correlation of AHI vs. ESS (CV±0.34), AHI vs. STOPBANG (CV±0.06), AHI vs. TG (CV±0.06), AHI vs. LDL (CV±0.07) was positive.

Correlation of AHI vs. HDL (CV±0.002) and AHI vs. VLDL (CV±0.04) was negative (Figure 6).

DISCUSSION

Recurrent partial or complete collapse of upper airways during sleep brings many adverse consequences, such as obesity, hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, cardiac and cephalic alterations and behavioral changes. In India, obese individuals have nearly four times higher risk of OSA as compared to non-obese individuals independent of age and gender. In a population-based survey from north India, the prevalence of OSAS was estimated as 3.6 percent and separately for males and females was 4.9 and 2.1% respectively.6

In this study we included 21 (46%) female and 25 (54%) male patients who were clinically and polysomnographically confirmed for OSA. These patients were studied for the prevalence of associated comorbidities and correlation of comorbidities with severity of OSA. Association of obesity with OSA is likely to be bidirectional. That is, obesity worsens the symptoms and severity of sleep apnea and OSA promotes weight gain and obesity.7

In a study by Himanshu et al. 2019, approximately 30% of patients with a BMI greater than 30 and 50% of those with a BMI greater than 40 kg/m² had OSA8. In our study out of 46 patients 36 (78 %) were obese and having BMI more than cut off value of 30 kg/m². The average AHI of 44.3 was well in correlation with average weight (86 kg) and BMI (33.1 kg/m²). There were 67% (31) patients in severe OSA group followed by 13.4% (6) in moderate and 19.5% (9) in mild OSA. The average neck circumference (NC) was 40.5 cm and all the patients excluding two were having neck circumference above the cut-off value (>37 cm. in men and >34 cm. in women).

A study by Lara et al suggested that the external neck circumference and the degree of obesity determined through BMI measurement may be important predictors of sleep apnea in adult Filipino males suspected to have OSA. Given the high probability of having true OSA in symptomatic male adults with a collar size ≥40 cm.9
In another study subjects with OSA had a neck circumference 4 cm larger than subjects without OSA and neck circumference of 40 cm or greater had a sensitivity of 61% and a specificity of 93% for OSA, regardless of the person’s sex. A large neck circumference has been associated with an increased risk of OSA. NC correlates better with OSA than the BMI. Majority of patients were having AC and WHt.R above the normal cut off values. Only six male patient were having AC within normal limit and one female patient having WHt.R below 0.5. On evaluation of correlation it was observed positive correlation of AHI with BMI (CV±0.284), Neck Circumference (CV±0.486), WC (CV±0.244) and AC. (CV±0.389). It means that the patients who were having more neck, waist, abdominal circumference and obese were having more severe OSA and vice-versa in proportion of their correlation values. The patients who were having shorter neck length had more severe OSA (negative correlation with neck length, CV±0.245). (Table 4 and Figure 5)

Excessive day time sleepiness (EDS) that is, how frequently the patient is likely to doze off in 8 frequently encountered situations was assessed by using the epworth sleepiness scale (ESS) Questionnaire, although patients did not always accurately describe their sleepiness on this scale compared with objective measures. An ESS score greater than 10 was considered sleepy. However, a study by Punjabi et al showed that an ESS score of 12 was associated with a greater propensity to fall asleep on the multiple sleep latency test (MSLT), suggesting that 12 would be a better cut-off. Due to subjective variation we also included STOPBANG scoring for better prediction and correlation with OSA. A study by Chung et al supports that the screening in pre-surgical patients using the STOP BANG score has a high probability of OSA detection. If the criteria from both the ESS and STOP BANG mnemonics are met, the sensitivity of the patient having an AHI of greater than 5 is 93% and an AHI of greater than 15 is 83%. In our study average ESS for mild, moderate and severe OSA were 14.44, 17.00 and 17.77 and for STOPBANG scores for mild, moderate and severe OSA were 4.89, 5.33 and 5.48 respectively. In contrast to the above study we found better positive correlation value (CV) for ESS (CV±0.349) than STOPBANG scores (CV±0.060) when both were correlated with AHI. The prevalence of comorbidities associated with OSA increases with age and the peak occurs at 55 years. In our study maximum no. of males (15%) and females (22%) were present in the age group ranging from 50 to 69 years with an average age of 57.7 years. The average age of females was almost similar to that of males (58.8 vs. 58 yrs.). The highest average AHI (51.4) was observed in 50 to 59 years of age group. OSA is closely associated with a greater propensity to fall asleep on the STOP BANG mnemonics are met, the sensitivity of the patient having an AHI of greater than 5 is 93% and an AHI of greater than 15 is 83%. In our study, 65% (30) of obese patients were having hypertension out of which highest 43% (20) belonged to patients with severe OSA followed by moderate OSA 11% (5) each. OSA has not been established as a cause of heart failure, and whether it hastens death in patients with heart failure is uncertain. However, a 2007 study examining untreated OSA in patients with heart failure reported that those with an AHI higher than 15 had increased mortality compared with those with an AHI below fifteen. In our study LVH was observed in as much as 50% of patients which may proceed to development of heart failure, if OSA is not be treated properly. The link between diabetes mellitus and obstructive sleep apnea is confounded by common risk factors. Increased activity in the sympathetic nervous system due to sleep deprivation and fragmented sleep are suggested as a possible mechanism linking obstructive sleep apnea with diabetes mellitus.
Growing evidence suggests that OSA may contribute to the metabolic derangements that characterize the metabolic syndrome. Multiple studies have shown that patients with OSA have increased glucose levels and increased insulin resistance.\textsuperscript{20,21} Cross-sectional studies suggest that up to 30% of patients with OSA have type II DM and up to 86% of obese patients with type II DM have OSA.\textsuperscript{22,23}

In the present study we observed Diabetes mellitus in 21 (46%), Dyslipidemia in 12 (26%) and Metabolic syndrome in 6 (13%) patients with OSA. All these comorbidities increased with severity of OSA. Data from sleep heart health study indicates that total cholesterol levels are associated with AHI values, after correlation with age and BMI.\textsuperscript{24} Most of the studies on dyslipidemia had shown an increase in lipid abnormalities in patients with OSA. The AHI was the main determinant for cholesterol dysfunction. These observations suggested that cholesterol tends to be altered in patients with OSA and partly contributes to increase the cardiovascular risk.\textsuperscript{25-27} In our study, 12% (12) out of all patients had dyslipidemia and all of them belonged to moderate or severe AHI and had shown positive correlation with AHI. Correlation values for AHI Vs Triglyceride was +0.06 and AHI vs. LDL was +0.07. The correlation values of AHI with HDL and VLDL were negative. Obesity is in itself associated with mood, anxiety, and somatof orm disorders as well as elevations in psychological distress.\textsuperscript{28-30}

Psychiatric symptoms or associated disorders with OSA include depression, anxiety and stress disorder. They seem to be more common and more severe in females with OSA than in males. Symptoms of depression, though prevalent in OSA do not correlate with severity of OSA.\textsuperscript{31}

In our study, we found 20% (9) patients with depressive symptoms but only one female patient was on medication. The depression was more in female patients. Out of 9 patients 6 were females with no significant differences between the AHI values i.e. 4 in mild, 2 in moderate and 3 in severe group. Three patients (2 male and 1 female) were suffering from anxiety disorder. Several publications have discussed the relationship between asthma and OSA. Salles et al, reported that OSA is prevalent in patients with asthma and is associated with disease severity. Asthma is associated with acute and chronic inflammation that affects the respiratory muscles, including upper airway dilators.\textsuperscript{32}

The biological mechanism that correlates asthma to OSA would be the fact that the inflammation of the upper airways caused by asthma would facilitate the collapse of the muscles favoring OSA. National Asthma Education and Prevention Program recommend screening of OSA in patients with asthma because treatment of OSA has proven to be effective in improving symptoms of asthma.\textsuperscript{33} In our study, only 7% (3) of patients had asthma associated with OSA, although it has not presented expressive values; only three patients with severe AHI had associated asthma.

There is possible association between GERD and OSA. However, only a single study confirmed the direct relationship between the two diseases.\textsuperscript{34} In our study, 7% (3) of OSA patients were diagnosed with GERD. One patient each in mild, moderate and severe OSA irrespective of severity of OSA.

Patients with OSAS are always exposed to sustained intermittent hypoxia and reoxygenation deriving from the cycles of apnea/arousals leading to oxidative stress and activation of a systemic inflammatory response with increases in general blood antioxidant activity and in production of proinflammatory cytokines, including tumour necrosis factor TNF-\(\alpha\) and interleukin-6.\textsuperscript{35} PSG is poor predictor of OSA-associated morbidities.

In other words, two patients with similar OSA severity may present with markedly different clinical phenotypes, whereby one will manifest substantial end-organ morbidities related to the presence of OSA, while all such features are absent in the other. The phenotypic variance in the clinical morbidity of OSA has therefore prompted exploration of biomarkers that would enable the identification of the more “vulnerable” patients, who would more likely benefit from timely and targeted therapeutic interventions. Ideal biomarkers should be highly sensitive and specific for OSA-induced end-organ dysfunction and should be involved in an important causal pathway, so that changes in the biomarker levels in the context of OSA treatment reliably predict improvements in the specific end-organ outcome. Blood-based biomarkers were accounted in the majority of the studies, and most of the explored approaches did not identify definitive biomarkers of OSA morbidity. Many biomarkers like hs-CRP, IL-6 are associated with AHI in the majority of the studies, but most of the explored approaches were not able to identify definitive biomarkers of OSA morbidity. In a study done by Sharma Deepanjali et al IL-6 appeared to exhibit a favourable profile for a biomarker aiming to discriminate OSA in adult patients.\textsuperscript{35}

Limitations

The first is small sample size, second, we did not rely on a control group without OSA to correlate with associated morbidities. Based on current literature, data and the values found in our work, we can correlate significance of obesity values with OSA and their AHI values. Research with control group and a higher number of cases are necessary for further investigations and correlations.

CONCLUSION

Considering the strong correlation between OSA and cardiovascular disease, endocrine/ metabolic comorbidities shown in this study, and supported by
several previous ones, we suggest that early diagnosis and treatment of OSA may change the course of both diseases. Therefore, we encourage physicians to address the issue of sleep disordered breathing in a patient with cardiovascular diseases. The routine follow-up of patients with cardiovascular diseases should include a detailed history and a validated quality-of-life questionnaire such as the Epworth sleepiness scale, followed by definitive Polysomnography in highly suspect cases. Blood-based biomarkers accounted for the majority of the studies, and most of the explored approaches did not identify definitive biomarkers of OSA morbidity. IL-6 appeared to exhibit a favourable profile for a biomarker aiming to discriminate OSA patients with and without morbidity in adults.

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