Original Article

Association of Metabolic Syndrome in Obstructive Sleep Apnea Patients: An Experience from Zonal Tertiary Care Hospital in Eastern India

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Abstract

Introduction: Even in a tertiary health-care setting, obstructive sleep apnea (OSA) patients often remain underdiagnosed. OSA and metabolic syndrome (MS) share many essential cardiovascular risk factors, including obesity, hypertension, and insulin resistance. Despite numerous studies, the relationship between OSA and MS still remains debatable. **Aim:** The purpose of our study was to see how frequently MS occurred in OSA patients and also if the presence of MS had any correlation with age, sex, or severity of OSA. **Methodology:** This cross-sectional study included 50 OSA patients being evaluated on outpatient department basis. All the patients were screened with detailed history; examination; hematological, biochemical parameters; and polysomnography. **Results:** In this study, out of 50 OSA patients, 41 were male and 9 were female; with age, body mass index (BMI), Apnea–Hypopnea Index (AHI), neck circumference, and waist circumference having mean of 42.5 years, 27.028 kg/m^2, 33.49/h, 39.7 cm, and 37.23 inch, respectively. Out of 28 obese patients, 22 had AHI >30 and 6 had AHI <30. 31 (62%) OSA patients were found to have MS, of which 27 were male and 4 were female. Pearson's bivariate correlation has also shown statistically significant association between AHI score and BMI value (P = 0.01). **Conclusion:** Our study has shown a positive association between OSA and MS and OSA may represent an important risk factor for development of MS. Therefore, it is prudent for clinicians to systematically evaluate the presence of metabolic abnormalities in OSA patients and vice versa.

Keywords: Insulin resistance, metabolic syndrome, obstructive sleep apnea, polysomnography, syndrome Z

Introduction

Obstructive sleep apnea (OSA) is a condition involving repetitive obstruction of upper airways during sleep, resulting in hypopnea or apnea. These include either symptoms of nocturnal breathing disturbances such as snoring, gasping or breathing pause while sleeping or daytime sleepiness, and fatigue despite ample sleep often unexplained by other medical problems.[1,2] OSA remains a difficult and underdiagnosed clinical condition, ultimately leading to health-care burden.[3] A community-based survey conducted in our country reported the prevalence of OSA around 9.3%.[4] OSA was observed to be prevalent in the range between 4% and 24% for men and 2%–16% for women.

People aged more than 40 years are more prone to OSA.[5] It is also approximated that 1 out of 5 adults has mild symptoms of OSA, while 1 out of 15 has moderate-to-severe symptoms. Studies even indicate twofold to threefold greater risk in men than in women.[3,6] The pathogenesis is multifactorial; however, anatomic defects play a major role.[7] These OSA patients tend to have coexisting risk factors such as obesity, hypertension, diabetes mellitus, and dyslipidemia.

It has been observed that OSA acts as an independent risk factor for hypertension and insulin resistance.[8,9] Both OSA

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and obesity were observed to have negative synergistic effect over glucose metabolism.[8,10] Further, it is detected that intermittent hypoxia leads to insulin resistance and beta-cell dysfunction.[10] OSA and metabolic syndrome (MS) are highlighted as syndrome Z which can increase the risk of cardiovascular disease[11] and insulin resistance. The possible mechanistic interactions between OSA, MS, and insulin resistance are highlighted in Figure 1. It has been observed that in India, the prevalence of syndrome Z ranges from 4.5% in population-based study to 79% among patients in hospital-based study.[12,13]

The National Cholesterol Education Program Adult Treatment Panel III report gives the definition of MS in view of considering the five parameters that include hypertension, insulin resistance or glucose tolerance, low-serum high-density lipoprotein cholesterol, elevated serum triglyceride levels, and abdominal obesity.[14] The above five set variables provide for easy identification of MS. These pose a serious threat of atherosclerotic cardiovascular disease and need to be diagnosed at an early stage in order to prevent further complications. Therefore, increased awareness is the need of the hour in order to screen the patients for Syndrome Z and its further threatening outcomes. This study aimed at studying the patients diagnosed with OSA and its association with MS.

Methodology

The study was conducted in a tertiary care service hospital from February 2017 to March 2018. A total of 95 patients underwent 32 channel polysomnography (Alice 5) and 58 patients met the Apnea–Hypopnea Index (AHI) criteria of OSA. However, eight patients who were hemodynamically unstable were excluded. The remaining 50 patients were taken up for further investigations. After a thorough polysomnography study, the patients diagnosed with OSA were followed up on outpatient department basis monthly. They were further evaluated with detailed history about their personal details, history of habits, symptoms, and treatment history. History regarding the quality of sleep was given due importance.

The patients were screened for any comorbid illness with hematological and biochemical parameters, including the metabolic markers such as body mass index (BMI), thyroid profile, lipid profile, and blood glucose profile. The data were scored manually as per the recommendations of the American Academy of Sleep Medicine.[15] The number of apnea and hypopnea occurring per hour of sleep is termed as AHI. AHI of 5 or more is suggestive of OSA, while a score of 5–14 suggests mild OSA, 15–30 is moderate OSA, and severe OSA has AHI more than 30[16] [Table 1]. Excessive daytime somnolence was assessed based on Epworth sleepiness scale (ESS).[17] Considering the time

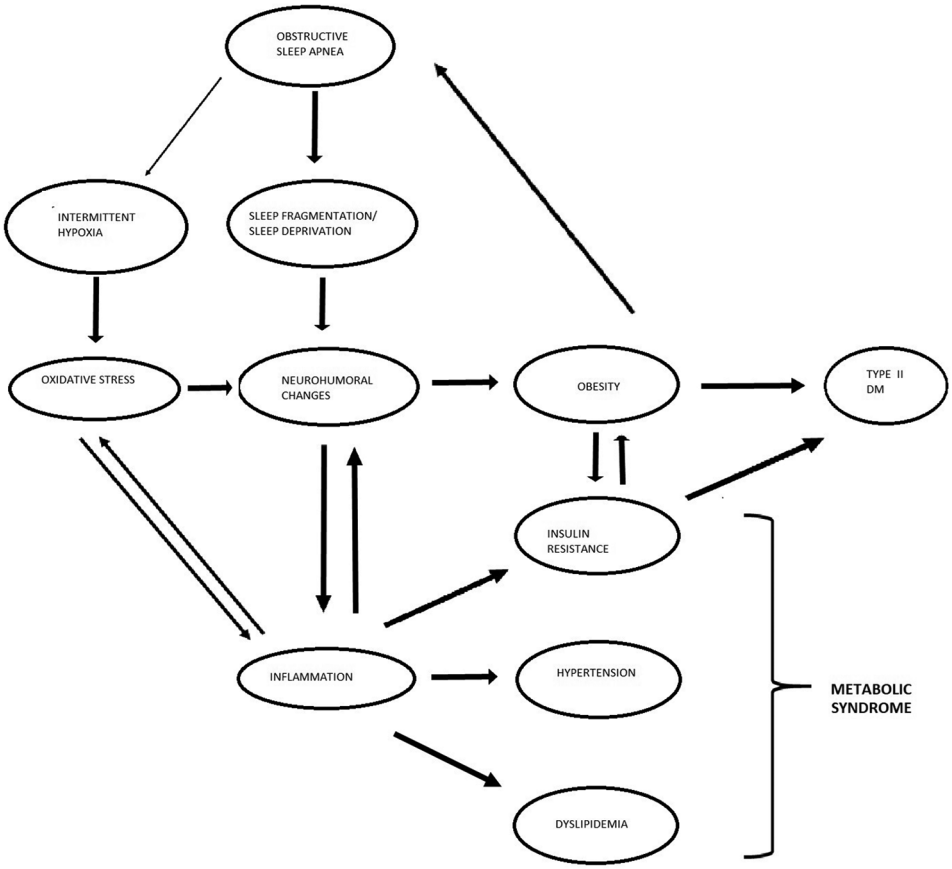

Figure 1: Possible mechanistic links between obstructive sleep apnea, metabolic syndrome, and insulin resistance

and feasibility, 50 patients diagnosed with OSA were investigated for the same and taken as the sample size for our descriptive study. Patients who were symptomatic but not meeting the AHI criteria and hemodynamically unstable were excluded from this study. The study was approved by the Institutional Ethics Committee and informed consent was obtained from the study participants.

Statistical analysis

Data were collected and analyzed using SPSS Inc. PASW Statistics for Windows, Version 18.0. Chicago: USA. All continuous variables were summarized in terms of mean ± standard variation and other categorical variables were calculated as percentage. Pearson's bivariate correlation method was used to find the association. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Out of the total 50 studied OSA patients, 41 (82%) were male and 9 (18%) were female. The baseline characteristics are mentioned in Table 2. Out of 50 patients analyzed in the study, 28 (56%) were obese having BMI of more than 27 kg/m^2 and 22 (44%) were found to be nonobese with BMI <27 kg/m^2. Out of the 50 patients, 4 (8%), 17 (34%), and 29 (58%) were detected to be suffering from mild, moderate, and severe OSA, respectively. 60% of the study population had a positive history of regular and occasional use of alcohol, while 32% had positive history of smoking.

Based on the symptomatology, 88% had daytime sleepiness, 56% had frequent night awakenings, 28% with nonrestorative sleep, 35% with difficulty falling asleep, 56% had morning headache, 40% had nasal congestion, 2% with personality changes, 72% with history of snoring, and 14% with nocturia. Occasional episodes of breathing pause (16%) and choking, aspiration, gasping, and body movements were seen in 4% each, respectively [Table 3]. On further examination, 56% had hypertension and 14% were hypothyroid, 68% had impaired glucose tolerance, and 54% had dyslipidemia [Table 4].

Apnea–Hypopnea Index and its association with various clinical variables

Severity of AHI with BMI: Out of 28 obese patients, 22 (78.57%) had AHI >30. Of the 22 nonobese patients, 7 (31.81%) had AHI >30 [Table 5].

AHI with smoking: 16 of the 50 patients studied were found to be smokers of which 11 (22%) had AHI >30 [Table 5].

AHI with treatment history and comorbidities: 17 of the patients studied were on antihypertensives only, of which 12 had AHI >30. All the 4 patients on Oral hypoglycemic agents (OHAs), only had AHI >30. 11 of the 50 patients were on both OHAs and antihypertensive therapy, of these 4 had AHI >30. Two patients who were on other medications (1 for coronary artery disease and 1 for old cerebro Vascular accident (CVA)) had AHI >30. Seven of these 50 patients were coincidentally found to have hypothyroidism of which 2 had AHI <30 [Table 5].

31 patients were detected to have MS [as per the criteria in Table 1] out of which 27 (65% of all males) were males.

Table 1: Current criteria for the diagnosis of metabolic syndrome and sleep apnea severity classification

Factor	Criteria
Hypertension	Current antihypertensive therapy or BP ≥130/85 (mmHg)
Dyslipidemia-elevated triglycerides	Plasma triglycerides ≥150 (mg/dl) or specific treatment for high triglycerides
Dyslipidemia-depressed HDL	HDL <40 (mg/dl) in men or <50 (mg/dl) in women or specific treatment for low HDL
Obesity	Waist circumference >37 inches in men or >31.5 inches in women
Glucose	Fasting glucose ≥100 (mg/dl) or previously diagnosed type 2 diabetes
Requirements for diagnosis	Waist circumference criteria plus any two of other criteria
No OSA	AHI <5/h
Mild	AHI 5–14/h
Moderate	AHI 15–30/h
Severe	AHI >30/h

OSA: Obstructive sleep apnea, HDL: High-density lipoprotein, BP: Blood pressure, AHI: Apnea-Hypopnea Index, IDF: International diabetes federation

Table 2: Baseline characteristics

Variable	Subjects (n=50)
Age (years) mean±SD	42.54±11.242
Sex (male/female)	41/9
Hypothyroidism (%)	7/50 (14)
BMI (in kg/m^2), mean±SD	27.028±2.338
AHI (per hour), mean±SD	33.494±17.653
Waist circumference (inch) mean±SD	37.23±2.8
Neck circumference (cm), mean±SD	39.7±2.3

SD: Standard deviation, BMI: Body mass index, AHI: Apnea-Hypopnea Index

Table 3: Symptomatology of obstructive sleep apnea

Symptoms	Frequency (%)
Excessive daytime sleepiness	44 (88)
Frequent night awakenings	28 (56)
Nonrestorative sleep	14 (28)
Difficulty falling asleep	18 (36)
Morning headache	28 (56)
Nasal congestion	20 (40)
Personality changes	1 (2)
Snoring	36 (72)
Nocturia	7 (14)
Breathing pauses	8 (16)
Choking	2 (4)
Aspiration	2 (4)
Gasping	2 (4)
Abnormal body movements	2 (4)

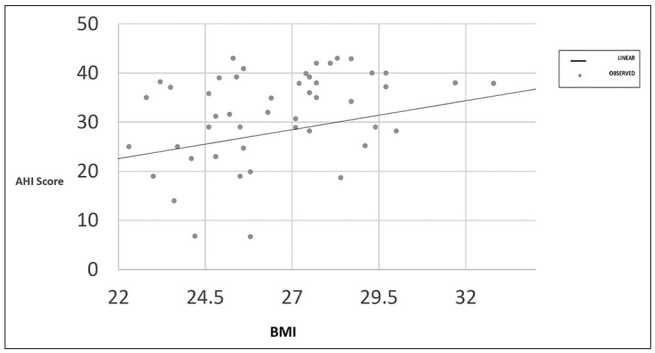

Figure 2: Scatter plot diagram showing the relationship between Apnea–Hypopnea Index score and body mass index

Table 4: Comorbidities associated with obstructive sleep apnea (Apnea-Hypopnea Index >30)

S.No	Comorbidities	Frequency	*P*
1	Hypertension	17	0.45
2	Hypothyroidism	5	0.27
3	IGT	20	0.05
4	Dyslipidemia	14	0.03

IGT: Impaired glucose tolerance

Table 5: Severity of Apnea-Hypopnea Index with various clinical variables

	AHI	
	≤30	>30
BMI		
<27	15	7
>27	6	22
Smoking history		
Positive	5	11
Negative	16	18
Treatment history		
Nil	9	7
Antihypertensives only	5	12
Oral hypoglycemic agents only	0	4
Antihypertensives + oral hypoglycemic agents	7	4
Others	0	2

AHI: Apnea-Hypopnea Index, BMI: Body mass index

Using Pearson's bivariate correlation method, a highly significant association ($P = 0.01$) was observed between AHI score and BMI value.

Discussion

In this study, a total of 50 patients (41 males and 9 females) were between the age group of 28 and 84 years who were diagnosed as OSA patients by standard polysomnography. They were studied for their clinical profile and were assessed for further relationship between OSA and MS. The mean age of the population was 42.5 years. The mean BMI, AHI, waist circumference, and neck circumference were 27.02 kg/m^2, 33.49/h, 94.5 cm, and 39.7 cm, respectively. Our study revealed males and those people with higher neck circumference, BMI and who are aged above 40 years are found to have association with development of OSA. Similar findings were reported in a recent Indian study.[18]

The common symptoms were excessive daytime sleepiness, snoring, frequent night awakenings, morning headache followed by others. Cases in this study had severe symptoms with many among them having associated comorbidities. This implies that a large number of patients of OSA with mild-to-moderate disease who are generally asymptomatic would remain undetected unless screened for the same. Impaired glucose tolerance (IGT)/dyslipidemia has shown an association with severity of OSA with MS; although this study was not designed to establish a cause-effect relationship.

Asian Indians have higher body fat, visceral fat and waist circumference, lower skeletal mass, thinner hips, higher rates of insulin resistance, diabetes, dyslipidemia, hypoadiponectinemia, and increased cardiovascular risk.[19,20] In our study, 78.6% of the obese patients were found to have severe OSA, while only 31% of nonobese individuals had severe OSA. There has been an escalating rise in obesity and MS and its subsequent cardiovascular risk in South Asian population.[21]

The obstructive sleep apnea syndrome (OSAS) affects 2%–4% of the adult population. It is a grossly underdiagnosed and undertreated condition. It is observed that OSA is also an important risk factor for the development of systemic hypertension, arrhythmias,[7] and cerebrovascular events.[22] The number of cardinal features of MS increases with increased severity of OSA. Out of the 50 OSA patients included in our study, 28 were known hypertensives. Apart from hypertension, 15 were known diabetic patients, 1 was an old case of CVA, and 3 had a history of ischemic heart disease. Several studies have reported high incidence of OSAS in patients of congestive heart failure. There was also significant association of OSA with MS leading to cardiovascular morbidity.[23]

In our study, 29 (58%) patients were found to have severe OSA and 17 (34%) patients with moderate OSA. Similar observations were made by Peled *et al*. in their study, in which out of 98 patients 53 (54%) were found to have severe OSA and 27 (28%) had moderate OSA.[24] OSA is said to augment sympathetic nervous system activity and alter renin-angiotensin aldosterone system to cause BP derangements. A study by Sharma *et al*. concluded that in patients with moderate-to-severe obstructive sleep apnea–hypopnea syndrome, 3 months of continuous positive airway pressure (CPAP) lowers BP and partially reverses metabolic abnormalities.[25]

34 of our study patients were found to have impaired glucose tolerance. This is supported by various other cross-sectional studies that have reported a connecting link between the presence and severity of OSA and glucose tolerance, insulin resistance, and diabetes.[24,26-35] Eventhough some studies have

not reported positive findings in favor of this,[36-38] a study by Meslier *et al*. reports diabetes in one-third of suspected OSA patients, with increasing severity of OSA associated with IGT and insulin resistance, independently of age and BMI.[32]

Obesity is strongly associated with MS and well-known risk factor for OSA. Now with increasing epidemic of obesity, the prevalence of OSA among adults is is further on the rise. In our study, 32% patients had BMI <25, 64% had BMI ranging from 25 to 29.9 and 4% had BMI of 30 and above. Our study showed significant association between AHI score and BMI value with a $P = 0.043$ ($P < 0.05$) and was depicted in Figure 2. The shared relationship of OSA and MS with obesity should be taken into account because it is contributing airway narrowing during sleep. Obesity, especially central obesity, is a significant risk factor which is linked to increased leptin production further leading to insulin resistance and increased development of OSA. Hence, central obesity significantly causes upper airway functional abnormality as compared to peripheral obesity with raised fat deposition around the neck.[39-42] There are also other studies which have shown that 3% reduction in AHI with every percent of weight reduction in the individual.[8,43] Some studies have shown that OSA is associated with carotid intimal thickening, increased levels of a variety of oxidants such as C-reactive protein, interleukin-6, tumor necrosis factor-α, and pentraxin including oxidized low-density lipoprotein which are thought to play a key role in promoting atherosclerosis.[44,45] In our study, 54% of the patients were found to have dyslipidemia and 14% patients were found to have hypothyroidism who showed increased propensity toward development of MS, similar observations were made by other workers.[46-48]

The salient finding in our study revealed MS in 31 (62%) patients with coexistence of OSA. Similar findings were reported by Parish *et al*.[49]

Limitation

The study results had certain limitations, as it was done in a single hospital. Hence, results of the study cannot be applied to the general population. Second, this study had a small sample size.

Conclusion

The relationship between OSA and MS still remains controversial despite substantial evidence from both clinical and population studies suggesting their link. CPAP which still remains the mainstay of OSA management, also forms the backbone of various research works trying to establish a link between the two conditions.

However, in a resource-limited setting like India, the paucity of health-care facilities with polysomnography equipment and CPAP machine, pose a major hurdle to diagnosis, evaluation, and management of OSA, thus further hindering the researchers. Identification of syndrome Z may bring out opportunities to interrupt pathophysiology of OSA and prevent manifestations of MS.

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Conflicts of interest

There are no conflicts of interest.

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