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Original Research Article

ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNOEA AND METABOLIC SYNDROME: A CORRELATION STUDY

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ABSTRACT

Background: Obstructive sleep apnea (OSA), also known as sleep disordered breathing (SDB), is a highly prevalent though under-recognized public health problem. It is characterized by repetitive episodes of upper airway collapse and consequent hypoxemia during sleep and associated with recurrent oxygen desaturation and arousals from sleep. The coexistence of OSA and MS, heightens cardio-metabolic risks. OSA prevalence is higher among patients with MS as reported by many studies.

Material and Methods: This prospective cohort study aimed to assess the association between obstructive sleep apnea (OSA) and metabolic syndrome (MS). The study was Conducted in the neurology department of a tertiary care medical college and included 50 patients diagnosed with OSA (Apnea-Hypopnea Index >5/h and daytime symptoms). MS was defined using International Diabetes Federation criteria. Body composition, metabolic parameters, and sleep apnea severity were evaluated. Statistical analysis was performed using SPSS 23.0 with $p < 0.05$ considered as statistically significant.

Results: Out of 50 studied cases there were 34 (68%) males and 16 (32%) females. There was a male preponderance with M:F ratio of 1:0.47. The mean age was 51 +/- 12.34 years. Hypertension was significantly more prevalent in severe OSA cases ($p=0.020$). Dyslipidemia was notably associated with OSA severity and gender, with males showing higher prevalence ($p=0.041$). AHI $\geq$10 was significantly correlated with higher Epworth Sleepiness Scale (ESS) scores ($p=0.001$), and ESS >10 was linked to severe OSA ($p<0.01$). The STOP-BANG score positively correlated with AHI ($p=0.01$), indicating its utility in predicting OSA severity.

Conclusion: There was a significantly higher incidence of metabolic syndrome (MS) in obstructive sleep apnea (OSA) patients compared to the general population. There is a need for screening OSA patients for MS to enable early detection and intervention, thereby preventing complications associated with delayed diagnosis.

Key Words: Obstructive Sleep Apnea, Metabolic Syndrome, Hypertension, Dyslipidemia.

INTRODUCTION

Obstructive sleep apnea (OSA), also known as sleep disordered breathing (SDB), is a highly prevalent though under-recognized public health problem. It is characterized by repetitive episodes of upper airway collapse and consequent hypoxemia during sleep,[1] and associated with recurrent oxygen desaturation and arousals from sleep. OSA leads to symptoms such as snoring, witnessed apnea, excessive daytime sleepiness and road traffic accidents due to sleepiness. It is also associated with an increased risk of cardiovascular disease, hypertension, insulin resistance and cerebrovascular disease.[2]

Additionally, in patients with OSA syndrome (OSAS), quality of life may also be affected with

increased incidence of road traffic accidents, mood disorders and neurocognitive deficits. The prevalence of metabolic syndrome is approximately 24% of US men and 23.4% of US women.[3] However, very little literature is available about the prevalence of OSA in South Asian population; 28.8% among men and 31.8% among women. A study done in Delhi estimated the prevalence of OSA and OSAHS in an Indian study population to be 13.7% and 3.6% respectively.[4] Although loud snoring is seen in all patients with OSA, not all snorers have OSA. Understanding the differences between patients with OSA and simple snorers is important to explain the mechanisms responsible for upper airway obstruction rather than those between OSA and normal non-snorers.[5] Polysomnography is considered to be the gold standard for diagnosis of OSA, estimation of its severity and measurement of treatment response.

Metabolic syndrome has become one of the major public health challenges worldwide. It was first described as a cluster of metabolic abnormalities, with insulin resistance as the central pathophysiological feature, and was labelled as 'Syndrome X'.[6] Metabolic syndrome is recognized as a constellation of obesity, glucose intolerance, dyslipidaemia and hypertension. The cause of the syndrome remains unknown. Insulin resistance and central obesity have been acknowledged as key driving forces for the metabolic syndrome, and they are, independently, also well-known cardiovascular risk factors. The prevalence of metabolic syndrome is increasing due to the obesity epidemic. It is associated with a three-fold and two-fold increase in type II diabetes mellitus and cardiovascular diseases respectively. It is also associated with cardiovascular mortality as it comprises established risk factors for cardio-metabolic diseases.[7] Whether the syndrome is an independent risk factor to cardiovascular disease is subject to debate. Recent data show a strong association between OSA and the metabolic syndrome, which is indicative of adverse cardiovascular outcomes.

Recently, there has been great interest in the interaction between OSA and metabolic dysfunction. In particular, OSA has been independently associated with insulin resistance, suggesting that OSA may be an important factor for the development of type 2 diabetes and the so called metabolic syndrome (MS).[8] Obstructive sleep apnea syndrome has been associated with an increased incidence of hypertension, stroke, and cardiovascular disease. Syndrome Z is defined as the co-occurrence of OSA and metabolic syndrome.[9] Although there is circumstantial evidence to implicate OSA in the development of MS, the causal relationship remains unproven. Recent community based study on prevalence of OSA, MS and Syndrome Z in urban population in New Delhi, shows that there is a high prevalence of OSA among the patients with MS.

MATERIALS AND METHODS

This was a prospective cohort study conducted in the department of neurology of a tertiary care medical college. 50 patients having obstructive sleep apnea diagnosed on the basis of Apnea hypoapnea score of more than 5 or more/h and having daytime symptoms such as daytime somnolence, fatigue, or cognitive disturbance) were included in this study on the basis of a predefined inclusion and exclusion criteria. Institutional ethics committee approved the study and informed and written consent was obtained from all the participants. Sample size calculation was done on the basis of pilot studies done on the topic of obstructive sleep apnea and metabolic syndrome. Keeping power (1-Beta error) at 80% and confidence interval (1-alpha error) at 95%, the minimum sample size required was 46 patients; therefore, we included 50 patients in our study.

Body composition and metabolic parameters were assessed in all participants. Body Mass Index (BMI) was calculated in all cases. Neck circumference was measured at the level of the laryngeal prominence, while waist circumference was measured midway between the lower rib margin and the iliac crest. Blood pressure was recorded as the average of three measurements taken at 1-minute intervals using a standard sphygmomanometer. Fasting blood glucose and fasting lipid profile were measured after an overnight fast with glucose analyzed using a hexokinase-based assay and lipid profile parameters assessed using the CHOD-PAP immune-colorimetric assay.

The severity of sleep apnoea was defined using the apnoea–hypopnoea index (AHI), which represents the number of apnoeas and hypopneas per hour of sleep. Severity of sleep apnoea was graded as

Mild sleep apnoea when AHI: 5 to 15 events per hour,

Moderate sleep apnoea when AHI: 15 to 30 events per hour,

Severe sleep apnoea, when AHI is greater than 30 events per hour.

Patients were diagnosed to be having metabolic syndrome on the basis of criteria as laid down by International Diabetic Federation (IDF) criteria10 if in any individual there was presence of Central obesity – defined as waist circumference >/= 90cm for men and >/= 80 cm for women (Indian population) Plus any two of the following four factors

1. Raised triglyceride (TG) level >/= 150mg/dl or specific treatment for this lipid abnormality
2. Reduced High Density Lipid (HDL) cholesterol <40mg/dl in males and <50mg/dl in females, or specific treatment for this lipid abnormality
3. Raised arterial blood pressure (B.P) systolic > 130mm of Hg, diastolic > 85mm of Hg or treatment for previously diagnosed hypertension.
4. Raised Fasting Blood Glucose (FBG) >100mg/dl or previously diagnosed type 2 diabetes.

Association between obstructive sleep apnoea and Metabolic Syndrome was analysed.

Statistical analysis was done using SPSS version 23.0 software. Quantitative data was shown as mean and standard deviation whereas qualitative data was represented by incidence and percentage tables. For quantitative data unpaired t-test was used and for qualitative data, Chi-square test was utilised. p value less than 0.05 was taken as statistically significant.

Inclusion Criteria

1. Patients with clinical history of snoring and excessive daytime sleepiness in patient.
2. OSA confirmed by limited polysomnography (RDI>/=5) using ALICE 5 and categorized to mild, moderate and severe OSA, based on AHI.
3. Age above 18 years.
4. Ready to give informed and written consent to be part of study.

Exclusion Criteria

1. Age less than 18 years.
2. Those who refused consent to be part of study,
3. Patients having history of chronic kidney disease, chronic liver parenchymal disease and congestive heart failure, viral hepatitis and chronic alcoholism.
4. Patients who are on CPAP at time of study.
5. Patients with significant psychiatric illnesses

RESULTS

Amongst the 50 studied cases there were 34 (68%) males and 16 (32%) females. There was a male preponderance with M:F ratio of 1:0.47. [Figure 1]

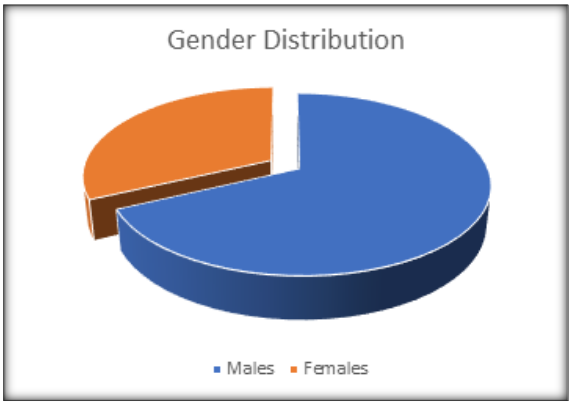

Figure 1: Gender Distribution of studied cases

The majority of patients in this study were middle-aged, with a mean age of 51 years and a mean BMI of 33.8 kg/m². The mean waist circumference was 118.9 cm, and the neck circumference ranged from 34 to 44 cm, with a mean of 39.36 cm. The mean systolic and diastolic blood pressures were 138 mmHg and 89 mmHg, respectively, while the mean fasting blood sugar, triglycerides, and HDL were 129 mg/dL, 158 mg/dL, and 40 mg/dL respectively. [Table 1]

The symptoms of OSA among subjects were excessive daytime sleepiness, snoring and witnessed apnoeas/awakening. Other symptoms reported in relation to nocturnal sleep were difficulty in falling asleep in 17 (34%), difficulty in maintaining sleep in 13 (26%), nightmares in 3(6%) and limb jerking in 3 (6%) patients. [Figure 2]

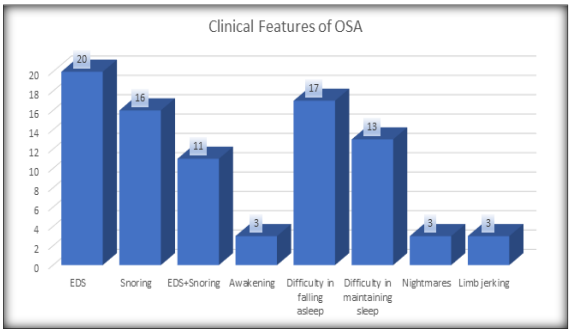

Figure 2: Clinical Features in studied cases.

Two or more components of the metabolic syndrome were present in all patients as the latter was the inclusion criteria for this study. Dyslipidaemia was the most prevalent disease among patients when compared with other components of the metabolic syndrome with 32 (64%) of patients. The other components constituting MS were Type 2 DM in 23 (46%) and hypertension in 20 (40%) patients. Other major co-morbidities present were Hypothyroidism in 2 (4%). Hypertension was significantly more common in patients with OSA and also showed statistical significance with the severity of OSA (p value-0.020). [Table 2]

In our study, 23 (46%) patients had Diabetes Mellitus, out of which 7 (30.4%) had mild OSA, 3 (13%) had moderate OSA and 13 (56.5%) had severe OSA. 20 (40%) patients had Hypertension out of which 2 (10%) had mild OSA, 2 (10%) had moderate OSA and 16 (80%) had severe OSA.32 (64%) patients had dyslipidaemia, out of which 4 (12.5%) had mild OSA, 9 (28.1%) moderate OSA and 19 (59.4) had severe OSA. The proportion of subjects with MS and its components were analyzed separately for both men and women stratified by the presence of OSA using AHI cut off of less than and more than 10. A diagnosis of OSA, by using AHI cut off of 10, Dyslipidaemia was significantly more common in patients with OSA and also showed statistical significance (p value-0.012). [Table 3]

Of the 50 patients, 48 patients were found to have Metabolic Syndrome. The prevalence of MS was correlated with severity of OSA. Of the 50 patients, 48 were found to have Metabolic Syndrome. Out of 10 patients with mild OSA, 8 had MS, all patients with moderate OSA (12) and severe OSA (28) had MS. The prevalence of MS was correlated with severity of OSA. Out of 34 male patients 13 (38.2%) had Diabetes mellitus, 13 (38.2%) hypertension, 25 (73.5%) had Dyslipidaemia. Out of 15 female patients, 10 (62.5%) had Diabetes Mellitus, 7 (43.8%) had hypertension and 7 (43.8%) had Dyslipidaemia. There was a statistically significant

relation of Dyslipidaemia with Gender (p value – 0.041).

All those patients with clinical features suggestive of OSA and ESS > 10 underwent an overnight sleep study (limited Polysomnography) to confirm the diagnosis. It was found that 20% had mild OSA, 24% moderate and 56% severe OSA. There were 42 patients with AHI ≥ 10 and 8 patients with AHI ≤ 10. The proportion of subjects with severity of OSA were analysed separately using AHI cut-offs of less than or more than 10, both being statistically significant (p value - <0.001). In our study Epworth Sleepiness Scale scoring (ESS) were used as screening tools in patients with symptoms suggestive of OSA. By using AHI ≥10, ESS was found to be statistically significant (p value- 0.001). [Table 4]

In our study, 14 patients had ESS score of less than 10. Out of these 14 patients 7 (70%) had mild OSA, 4(33.3%) moderate and 3 (10.7%) severe OSA whereas out of 36 patients with ESS score more than 10 - 3(30%) had mild OSA,8 (66.7%) moderate and 25 (89.3%)had severe OSA with the p value being <0.01 showing significant difference between the two groups. [Table 5]

When STOP BANG used as screening tool, there showed positive correlation between the AHI score and STOP BANG score, as STOP BANG increases AHI score too increases significantly, (P=0.01). [Table 6]

Table 1: Mean & standard deviation for the individual variables of study subjects

	N	Mean	SD	Min.	Max.
Age (years)	50	51.0	12.342	27	79
BMI (kg/m^2)	50	33.8	6.745	24.2	58.5
Neck Circumference (cms)	50	39.36	2.601	34	44
Waist Circumference (cms)	50	118.90	9.861	102	140
SBP (mm Hg)	50	138.20	8.497	120	150
DBP (mm Hg)	50	89.40	7.398	80	100
Fasting Blood Sugar (mg/dL)	50	129.98	32.426	78	190
Triglyceride (mg/dL)	50	158.58	53.777	55	414
HDL (mg/dL)	50	40.44	9.549	22	62

Table 2: Association of components and OSA among the study subjects

Components		OSA			Total	χ^2 value*	P value
		Mild	Moderate	Severe			
Fasting Blood Sugar	<=100	1	5	7	13	2.876	0.237
		7.7%	38.5%	53.8%	100.0%		
	>100	9	7	21	37		
		24.3%	18.9%	56.8%	100.0%		
Diabetes Mellitus	Present	7	3	13	23	4.451	1.08
		30.4%	13.0%	56.5%	100.0%		
	Absent	3	9	15	27		
		11.1%	33.3%	55.6%	100.0%		
Blood pressure	<130/85	4	5	8	17	0.842	0.656
		23.5%	29.4%	47.1%	100.0%		
	>130/85	6	7	20	33		
		18.2%	21.2%	60.6%	100.0%		
Hypertension	Present	2	2	16	20	7.817	***0.020***
		10.0%	10.0%	80.0%	100.0%		
	Absent	8	10	12	30		
		26.7%	33.3%	40.0%	100.0%		
Dyslipidemia	Present	4	9	19	32	3.311	0.191
		12.5%	28.1%	59.4%	100.0%		
	Absent	6	3	9	18		
		33.3%	16.7%	50.0%	100.0%		

Table 3: Distribution of study subjects according to individual variables and AHI score by gender, BMI & co-morbidities

		AHI				P value
		<=10 (N=42)		>10 (N=8)		
		n	%	n	%	
Gender	Male	29	69.0%	5	62.5%	0.716
	Female	13	31.0%	3	37.5%	
BMI	<35	29	69.0%	4	50.0%	0.297
	>=35	13	31.0%	4	50.0%	
Diabetic Mellitus	Present	18	42.9%	5	62.5%	0.307
Hypertension	Present	18	42.9%	2	25.0%	0.345
Hypothyroidism	Present	1	2.4%	1	12.5%	0.181
Dyslipidemia	Present	30	71.4%	2	25.0%	**0.012**

Table 4: Correlation of AHI and Epworth Sleepiness Scale and Stop-Bang Sleep Apnoea score

	AHI	N	Mean	SD	Min.	Max.	't' value	P value
Epworth Sleepiness Scale scoring	>=10	42	14.21	4.535	4	22	13.646	0.001*
	<10	8	7.88	3.907	3	14		
Stop-Bang Sleep Apnoea Score	>=10	42	4.93	1.314	5.00	2	1.257	0.268
	<10	8	4.38	1.061	5.00	2		

Table 5: Correlation of OSA severity with Epworth Sleepiness Scale scoring

OSA severity and Epworth Sleepiness Scale scoring			ESS Score		Total
			<10	>10	
OSA	MILD	Count	7	3	10
		% within OSA	70.0%	30.0%	100.0%
	MODERATE	Count	4	8	12
		% within OSA	33.3%	66.7%	100.0%
	SEVERE	Count	3	25	28
		% within OSA	10.7%	89.3%	100.0%
Total		Count	14	36	50
		% within OSA	28.0%	72.0%	100.0%
Chi square test df=2, p<0.01 *					

Table 6: Correlation between STOP BANG and AHI score

		STOPBANG	Sleep Study AHI
STOPBANG	Pearson Correlation Sig. (2-tailed) N	1 50	.460** .001 50
SLEEP STUDY AHI	Pearson Correlation Sig. (2-tailed) N	.460** .001 50	1 50
**. Correlation is significant at the 0.01 level (2-tailed)			

DISCUSSION

Our study has demonstrated that there is a high prevalence of MS in patients with OSA. This is in concurrence with the statistics reported in the literature. Many studies have proved the association of OSA with various components of the MS. However, literature linking MS as a whole with OSA is scarce. It has also been proven that the prevalence of Metabolic syndrome is higher in patients with OSA than in the general population or in obese non-OSA subjects.[11] It has been hypothesized that OSA itself may be a part of the spectrum of metabolic syndrome (Syndrome Z).[12]

Although the literature abounds with studies on the association between OSA and different individual components of the metabolic syndrome, not many studies have addressed the relationship between OSA and metabolic syndrome. A case control study in Caucasian men reported a nine-fold and six-fold risk respectively, for independent association between OSA and metabolic syndrome.[13] Similarly, a study of community-based Chinese subjects showed a very high association between the two entities, with OSA subjects at a five-fold risk of having the metabolic syndrome,[14] and a positive correlation between AHI and the number of metabolic components present. A case-controlled study in Japan found an independent association between OSA and metabolic syndrome in men, but not in women.[15] Other studies identified associations between sleep-disordered breathing and multiple metabolic factors within the metabolic syndrome, independent of obesity.[16] A study by Jha A al in 2006 reported that obesity, and not OSA, was the determinant of derangements in MS.[17] The same authors conducted a community based study in South Delhi in 2010 and reported that MS and OSA (syndrome Z) in 19.9% of the population studied.[18]

In our study, the age range of patients with MS and OSA was 27-79 years. 68% of patients were aged between 40-60 years and the remaining 32% were more than 60 years of age. A study by Bixler EO et al found that most of the age-related increase in prevalence of OSA occurs before age 45 and that there is a plateau in prevalence rate thereafter.[19] Our study has demonstrated a similar trend in prevalence of OSA even in patients with MS, thus strengthening the hypothesis that OSA is part of the spectrum of MS.

In our study there was a male preponderance in the incidence of OSA. In many studies it has been reported that OSA is 2 to 3 times more prevalent in men particularly in middle-aged obese men.[20] This sex-protective effect for females is diminished in premenopausal overweight women, menopausal women not receiving hormone replacement therapy and overweight women receiving hormone replacement therapy.[21]

In a community-based cohort of middle-aged subjects, Young et al,[22] showed that a 1-SD increase in BMI was associated with a four-fold increased risk for prevalent sleep apnoea, and they demonstrated a sleep apnoea prevalence of approximately 40% in moderately overweight men from the community who were otherwise healthy. In severe obesity (BMI > 40 kg/m2), the prevalence of sleep apnoea was estimated to vary between 40 and 90%, and the severity of sleep apnoea was generally greater than that found in leaner clinical populations. Peppard et al,[23] have provided further evidence for a link

between sleep apnoea and obesity by demonstrating that a 10% change in body weight was associated with a parallel change of approximately 30% in the apnoea–hypopnea index (AHI), the major index of sleep apnoea severity. Markers of OSA severity, such as the apnoea-hypopnoea index or the degree of oxygen desaturation correlated with the amount of visceral fat in a study by Vgontzas et al.[24]

In our study, Epworth sleepiness scale (ESS) and STOP BANG was used as a screening tool in patients presenting with symptoms suggestive of OSA. In patients with obstructive sleep apnoea syndrome ESS scores were significantly higher.25 In our study, 50 (100%) patients had ESS score >10 and with other symptoms suggestive of OSA they underwent overnight sleep study and were proven to have OSA. Thus, the usefulness of ESS as a screening tool for OSA with almost no false positivity and good specificity has been reiterated in our study. Thus, symptoms of a high index of clinical suspicion and associated risk factors of OSA, along with an ESS score of >10 should guide further workup. Similar results were shown with statistical significance with STOP BANG as the scoring increases the severity of OSA increased.

This study has demonstrated that there is a very high prevalence of MS among patients with OSA compared to that in the general population and also correlated with the severity of the OSA. Analysis of the metabolic syndrome component variables shows that hypertension and dyslipidaemia is the primary variable component with a diagnosis of OSA. Although a bigger study would have enabled derivation of the odds of developing MS with OSA or vice versa, there is convincing evidence from the present study to mandate screening for undiagnosed MS in all patients with OSA.

Our study is unique and different from other studies for being a hospital based prevalence study of metabolic syndrome in patients with OSA. The prevalence of metabolic syndrome was found to be as high as 96%, which is very high when compared with that reported in the general population in Indian as well as Western literature.

CONCLUSION

Incidence of MS (Metabolic Syndrome) was significantly higher in Obstructive Sleep Apnea (OSA) patients in comparison to general population. There was a significant association between OSA and components of MS, OSA in combination with MS. Early detection and treatment of MS in OSA patients can prevent development of complications in them due to the combined effects of both diseases. Thus, need for screening OSA patients for undiagnosed MS has been reinforced by this study.

Conflict of Interest: None

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