Original Article

Apnea and Metabolic Syndrome

Obstructive Sleep Apnea and Metabolic Syndrome; Causal Association or Co-Existence?

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ABSTRACT

Objectives: To assess the association between Obstructive Sleep Apnea (OSA) and Metabolic Syndrome (MS).
Study Design: Case-Control study.
Place and Duration of Study: This study was conducted at Sleep Lab, Dow University Hospital, Karachi from February 2013 to November 2014.
Materials and Methods: The study was conducted on 100 individuals, 50 each of OSA subjects attending Sleep Lab in DUHS, Karachi and 50 controls. After informed consent and detailed history those having positive Epworth Sleep Scale (ESS) score went through full night polysomnographyto confirm their OSA and its severity. Appropriate correlations among components of MS and OSA were evaluated and analyzed applying SPSS version 20.
Results: The frequency of MS was 76% in OSA subjects compared to 48% in controls. Frequency of MS in mild, moderate and severe OSA was 50%, 82.4% and 85.7% respectively.
Conclusions: Our findings suggest that OSA is associated with a higher occurrence of MS; it was also associated with severity of OSA. Future research with larger sample size is advised to confirm these associations.
Key Words: Metabolic syndrome, Obstructive sleep apnea

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INTRODUCTION

Obstructive Sleep Apnea (OSA), the most prevalent of all Sleep Related Breathing Disorders (SRBD), is a serious condition which requires early diagnosis and medical intervention to prevent complications[1,2]. OSA is characterized by repeated events of complete or partial upper airway obstruction during sleep for at least 10 seconds, resulting in hypopnea or apnea and respiratory effort-related arousals (RERAs). Severity of the disorder is characterized by the frequency of apnea and hypopnea episodes per hour of sleep which is termed as Apnea-Hypopnea Index (AHI)[3]. OSA is an underestimated, serious and potentially life-threatening disorder whose prevalence varies considerably in different countries; for example, 3-28% in western countries and 7.5 - 9.3% in India.

However no information is available for Pakistani population. According to a study carried out in Agha Khan University Hospital Karachi, in 2008, predisposing factors for OSA are highly prevalent in our country and our at least 10% population is at high risk for OSA[4].

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Studies report the association of OSA with Metabolic Syndrome (MS) and point towards possible causal role of OSA in the development of MS[3]. A recent Indian study emphasizes that the increasing prevalence of MS with increasing severity of OSA suggests a strong association of OSA with MS[5]. A UK based study showed prevalence of MS in patients with OSA to be 87% compared with 35% in normal controls[6]. Another hospital based study from UK shows MS in OSA group was 74% and in control it was 24%[7]. A study carried out in Turkey in 2011 showed that the MS was 47.2% in OSA patients, whereas it was only 29.4% in control group without OSA[8]. In a Chinese study, it was 58% in the former and 21% in the latter group of subjects[9]. In a Japanese study, MS was 49.5% in OSA group as compared to 22.0% in controls for men and 32.0% vs. 6.7% for women[10]. The studies from North India showing MS in OSA and control were 77% vs. 40% in a hospital based study and 79 % vs. 48% in a population based study respectively[2]

These studies though show a consistent association between OSA and MS, doesn't imply causality and thus this can be just another co-morbid condition present with the wide spectrum of OSA. For instance, some studies have emphasized that OSA is not limited to the conditions associated with MS and as much as 40% of the people suffering from OSA are not obese and can strike anyone at any age even children with normal BMI[11].

In Pakistan, little has been published on OSA which either discusses the frequency of risk factors for sleep apnea in our population[16] or general characteristics of

these patients[13]. Most of these research studies are based on the symptoms addressed by the questionnaire. Frequency of metabolic abnormalities in OSA subjects has not been studied in Pakistan so far. This study was intended to find out the frequency of MS in patients with OSA in our community.

MATERIALS AND METHODS

A total of fifty cases (aged between 30-65 years) with OSA, diagnosed at Sleep Lab, Dow University Hospital, Ojha campus Karachi and fifty age, sex & BMI matched controls (without any sleep disturbance) were enrolled for this study. The controls were selected from the employees of DUHS. Epworth Sleepiness Scale (ESS) scores were assessed in both groups using ESS questionnaire to determine the level of daytime sleepiness. This scale was introduced by Dr Murray Johns of Epworth Hospital in Melbourne, Australia in 1991(14). A total score less than 9 was considered normal while more than 9 indicated day time sleepiness revealed the chances of sleep disorders and indicated the need of Polysomnography (PSG) for further confirmation.

Patient`s age between 30 and 65 years having snoring, witnessed apnea or day time sleepiness, after the primary evaluation were went through full night Polysomnography. PSG was performed with multichannel polysomnography machine under continuous monitoring from a sleep technician(15).OSA subjects were classified according to the Chicago criteria as recommended by the American Academy of Sleep Medicine(5)as follows:

AHI 5 to 15 as mild OSA

AHI 15-30 as moderate OSA

AHI greater than 30 as severe OSA

After full night PSG of OSA subjects, fasting blood sample was collected in the morning for required blood tests. Control subjects were requested to give fasting blood samples in morning after a comfortable sleep at night.

The diagnosis of MS was based on an updated definition by NCEP-ATP III criteria in which the BMI is ethnic specific. According to this definition, to diagnose MS three out of these five metabolic abnormalities must be present, including obesity (Asian origin, BMI more than 25 or waist circumference ≥90 cm in males, ≥80 cm in females), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg), hypertrigly ceridemia (triglycerides ≥150 mg/dl), low HDL cholesterol (HDL cholesterol ≤40 mg/dl in males, ≤50 mg/dl in females), and high fasting blood sugar (≥100 mg/dl)[16].

Statistical Analysis was done on Statistical Package for Social Sciences (SPSS) version 20.0. Threshold for statistical significance was set at $p < 0.05$. Mean and standard deviation computed for numerical variables by applying independent sample t-test. Continuous variables were summarized as mean and corresponding 95% confidence intervals and categorical variables as proportions, n(%). Comparison between groups was done by independent Sample t-test. Chi-square test was used for categorical variables to examine prevalence of MS and its components in various categories of OSA and their comparison with non-OSA subjects. Spearman correlation was applied to check strength of association between OSA & MS.

RESULTS

The mean age of the cases was 49.4 years (95% CI 47.21-51.63) and of controls 47.04 years (95% CI 44.79-49.29) with no statistically significant difference (p-value 0.13). Male to female ratio were similar in both groups (3:2). Anthropometric parameters including height, weight and BMI, neck circumference, waist circumference, hip circumference waist hip ratio and others are shown in table 1.

Mean ESS score for OSA group was 12.84 with SD ± 4.20 and for control group it was 4.52 with ± SD of 1.82.

The mean of AHI for cases was 32.795 ± 22.70. The percentage of different OSA categories are shown in table 4.3, these are 24% (12) with mild apnea, 34% (17) with moderate apnea and 42% (21) with severe apnea (Table 2).

All the components of MS were analyzed in both cases and controls and frequency of MS was determined 76% of cases and 48% of controls. Presence of MS was further analyzed based on AHI/severity of OSA, using a definition of OSA with an AHI ≥ 5. It was found that 48% population of control group, 50% population of mild apnea group, 82.4% population of moderate apnea group and 85.7% population of severe apnea group had MS (Table: 4). No significant difference was found in control group and mild apnea group with respect to the presence of MS, which was 48% and 50% in both groups respectively. But significant difference was present in control and moderate/severe apnea group which indicated clear relationship between MS and severity of apnea, more the severity of apnea higher the % of MS.

In order to determine the strength of the linear relationship between OSA and MS, Spearman correlation was applied. It was observed that MS was significantly and directly related to severity of apnea. 34.3% positive correlation was present between severity of apnea and MS.

Table 1 Comparison of mean baseline characteristics with 95% confidence intervals among subjects with and without Obstructive Sleep Apnea

Baseline characteristics	Controls	Cases	p-value
Age (years)	47.04 (44.79-49.29)	49.42 (47.21-51.63)	0.133
Height (m)	1.65 (1.63-1.68)	1.67 (1.64-1.71)	0.405
Weight (Kg)	83.12 (78.37-87.87)	89.22 (84.20-94.24)	0.079
BMI	29.89 (28.37-31.47)	31.98 (30.13-33.83)	0.087
Neck circumference (m)	0.38 (0.37-0.39)	0.39 (0.38-0.41)	0.101
Waist circumference (m)	1.04 (0.99-1.08)	1.10 (1.04-1.16)	0.086
Hip circumference (m)	1.11 (1.07-1.15)	1.17 (1.12-1.21)	0.093
Waist to Hip ratio	0.92 (0.9-0.94)	0.94 (0.90-0.97)	0.343
Systolic Blood Pressure (mmHg)	129.40 (125.16-133.64)	138.60 (134.60-140.60)	0.002*
Diastolic Blood Pressure (mmHg)	80.90 (76.86-84.94)	85.84 (81.91-89.77)	0.081
Fasting Blood Glucose (mg/dL)	98.42 (89.63-107.21)	113.30 (106.92-119.68)	0.007*
Total Cholesterol (mg/dL)	180.76 (171.56-189.96)	199.44 (179.31-219.57)	0.093
Triglycerides (mg/dL)	173.06 (151.12-195.00)	185.18 (159.20-211.16)	0.476
LDL (mg/dL)	112.26 (103.39-121.13)	128.30 (113.10-143.50)	0.070
HDL (mg/dL)	41.68 (38.92-44.43)	37.38 (35.08-39.69)	0.018*

*Statistically significant difference, p-values generated by t-test

Table No. 2 Distribution of Metabolic Syndrome with severity of Apnea (n=100)

Metabolic Syndrome	Control n(%)	Cases		
		MildApnea n(%)	ModerateApnea n(%)	Severe Apnea n(%)
Absent	26(52%)	6(50%)	3(17.6%)	3(14.3%)
Present	24(48%)	6(50%)	14(82.4%)	18(85.7%)
Total	50(100%)	12(100%)	17(100%)	21(100%)

Mild Apnea: (AHI=5-15), Moderate Apnea: (AHI=15-30), Severe Apnea: (AHI >30)

Table No.3: Factors associated with Obstructive Sleep Apnea

	OSA patients	Controls	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
MS absent	12	26	1.00		1.00	
MS present	38	24	3.43(1.46-8.06)	0.005	1.24 (0.25-6.01)	0.78
Normal BMI	13	12	1.00		1.00	
Obesity level I	11	19	1.87 (0.63-5.51)	0.25	0.72(0.20-2.55)	0.61
Obesity level II	26	19	0.79 (0.29-2.11)	0.64	0.78(0.24-2.50)	0.68
Hypertension absent	13	35	1.00		1.00	
Hypertension present	37	15	6.64(2.77-15.92)	<0.0001	7.85(2.51-24.51)	<0.0001
Diabetes absent	19	34	1.00		1.00	
Diabetes present	31	16	3.46 (1.52-7.90)	0.003	3.60(1.21-10.70)	0.02
Triglycerides Normal	21	25	1.00		1.00	
Triglycerides High	29	25	1.38(0.62-3.04)	0.42	0.52(0.14-1.87)	0.31

DISCUSSION

Close relationships between sleep regulatory mechanisms and autonomic nervous system, makes it clear that OSA can lead to alterations in sympathetic activity and metabolic abnormalities which have been linked to increase cardio-vascular risk[17]. There is paucity of information about this syndrome in Pakistani population. Continuous increase in its prevalence reported in western and some Asian countries, with no report from Pakistan, in the present era of changes in life style demands conduction of research in our population. Likewise, the contribution of MS in OSA subjects as reported in previous studies[5,17] have not yet been tested in our population.

The loss of statistical significance at the multivariable analysis might be due to the higher prevalence of MS in the healthy controls which diluted the association after controlling for BMI. In both groups mean BMI was not significantly different suggesting that mechanisms other than obesity may play a bigger role in the patho-physiology of the MS in OSA subjects.

Difference in both groups with respect to the frequency of MS was slightly lower than represented by Coughlin at el and gruber at el in their UK based study[6,9] as well as in a Chinese study conducted by Lam et al[9] while it is higher than Turkish research study conducted by

Basoglu OK et al[8]. Coughlin et al` study showed higher BMI in OSA subjects as compared to controls, which raised the possibility that obesity could be a co-factor for those results. The finding in the present study was in line with one conducted in north Indian hospital based population[5] although mean BMI was higher in OSA subjects as compare to controls in their study. But in the present study where BMI was matched in control selection, possibility of biasness due to this confounder was eliminated. The present study showed frequency of MS in controls almost comparable with a community based study (n=500) of Pakistani individuals showed MS prevalence 49% in urban population of Karachi[18].

The findings on Japanese OSA subjects also produced similar results, which were independent of obesity. Likewise Zgierska et al[19] reported an independent association between OSA and MS. Thus the present findings based on individual components of MS with respect to the degree of severity of OSA support the suggestion showing OSA to be associated with higher BP, high FBS and deranged lipid profile. These findings are in concordance with previous studies showing OSA to be associated with higher BP[20,21], insulin resistance[22] and deranged lipid profile[3,22, 23].

Like many other previous studies, OSA patients were selected from a hospital-based sleep clinic and compared with controls recruited from the community, such designs could be a reason of selection biasness because seeking medical advice that results in referral to an outpatient clinic may select a group with higher risk of metabolic abnormalities relative to that found in the general community.

Many of our controls had association with health care profession (doctors or hospital related persons). They had better health related knowledge, and might be more conscious for their cardio-vascular health and had better metabolic profile than general population. This would have served to increase the difference found between groups. Number of female patients was less as compare to male, although it is according to previous international studies which showed higher prevalence of OSA in male, but prevalence of OSA in both genders should be further ruled out in our community, to eliminate the chances of underestimation in females. Temporal relationship of OSA and MS is not clear yet, therefore a cohort study with larger sample size is needed here which would be able to definitely prove whether OSA precedes and causes MS or vice versa.

Although at univariate level, MS was found to be strongly associated with OSA however, the association diminished when the effect was controlled for other factors. The inability of MS to sustain the association might be due to overall high prevalence of MS in the Pakistani population. Almost of the controls had MS which is extremely high prevalence. Furthermore the findings of this study support that MS is co-morbidly present with OSA and further investigation is necessary before MS can be labelled as the cause of OSA.

CONCLUSION

A great Strength of Study is that suspected cases and control subjects were selected by their ESS Score and then we confirmed their OSA and AHI score by supervised, full night, hospital based polysomnography in contrast to some other Pakistani studies which investigated OSA risk just on the bases of day time sleepiness, symptoms and questioners .A great strength of present study is that the mean BMI was not significantly different in both groups making it less likely that any dissimilarity could be present only on the basis of obesity. Despite this, multiple metabolic disturbances were found in OSA subjects as compared to the controls.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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