EDITORIAL

Obstructive Sleep Apnea, Metabolic Syndrome, and Implications For Cardio-Vascular Diseases

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Obstructive sleep apnea (OSA) affects about 4% of men and 2% women of middle aged population, as defined by an apnea-hypopnea index (AHI) ≥5 and daytime excessive sleepiness (1). It has been frequently associated with increased cardio-vascular morbidity and mortality from both ischemic heart disease and stroke (2,3). Data from many studies have identified a number of risk factors, such as hypertension, glucose intolerance, hypercholesterolemia (4) and increased neck circumference (5), which are independently associated with increased cardiovascular morbidity and mortality. Epidemiological studies have identified clustering of many such risk factors in individual patients and one such cluster which includes systemic hypertension, insulin resistance, hyperlipidemia and central obesity has been defined as "Syndrome X" (6). More recently, "The National Cholesterol Education Program (NCEP)" adult treatment Panel III (ATP III) (2001) has identified a "constellation of lipid and non lipid risk factors of metabolic origin" and they have designated this cluster of abnormalities as the "metabolic syndrome" and also suggested that this syndrome is closely linked to insulin resistance (7). According to the recommendations of this panel, the diagnosis of metabolic syndrome should be made when an individual has three of the following five risk factors: increased waist circumference (> 102 cm in men & >88 cms in women), hypertension (≥ 130/≥ 85 mm Hg), fasting glucose of ≥ 110 mg/dL, decreased high density lipoproteins (HDL) cholesterol (<40 mg/dL in men & < 50 mg/dL in women) and triglycerides ≥ 150 mg/dL. Besides these other abnormalities such as increased sympathetic activity, hypercoagulability, endothelial dysfunctions, increased markers of inflammation e.g. C-reactive protein (CRP) and sedentary life- style are also important features of metabolic syndrome (8). A number of positive adverse interactions between these risk factors further increase the cardio vascular risk to the individual.

Patients with OSA have many cardiovascular risk factors commonly seen in individuals with metabolic syndrome. OSA is commonly associated with systemic hypertension independent of age, obesity, or other confounding factors as shown by various population based epidemiological studies (9,10,11). Laboratory studies of animal models of OSA in dogs and rats strongly support the evidence that sustained hypertension can be caused by exposure to repeated episodes of obstructive apneas during sleep (12,13). OSA is commonly observed in patients with difficult to control hypertension (14,15). Moreover, treatment of OSA with nasal CPAP or tracheostomy has been associated with reduction in blood pressure (16). Obesity is common in OSA patients (17,18) and the reverse is also true i.e. the prevalence of OSA increases with increasing body mass index (BMI). The distribution of fat is mainly central resulting in an increase in waist and neck circumference. Whether OSA is caused by or results in central obesity is not fully understood. This is particularly important because central obesity is commonly seen in patients with insulin resistant diabetes. OSA is usually associated with conditions known to increase insulin-resistance and cardio-vascular risk, such as hypertension, obesity and

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diabetes. Previously it was thought that increased insulin resistance in OSA patients is due to these co-existing conditions. Recently, a number of studies have demonstrated abnormal glucose-tolerance and hyper insulinemia in patients with OSA (19,20) and, significantly increased insulin resistance in obese patients with OSA than patients with simple obesity (21,22). Treatment of OSA with nasal continuous positive airway pressure (nCPAP) has been shown to significantly improve insulin sensitivity in these patients (23,24,25). These data suggest that OSA causes insulin resistance independent of the effects of co-existent of central obesity. Patients with OSA have also been independently found to have other important features of metabolic syndrome including increased sympathetic activity (26,27) which improves after treatment with CPAP (28); endothelial dysfunction (32,33), hyper coagulability (29,30,31) and increased inflammation (34,35). The latter abnormalities have also been shown to improve after treatment with nasal CPAP. Keeping in view the frequent occurrence of various components of metabolic syndrome in patients with OSA, it has been suggested that metabolic syndrome (previously named 'Syndrome X') should include OSA as its integral component ('Syndrome Z') (36).

Although the previous studies have shown increased prevalence of individual components of metabolic syndrome, a recent study by Coughlin and colleagues (37) have demonstrated 40% increase in prevalence of metabolic syndrome in patients with OSA. This may help explain the increased cardio-vascular morbidity and mortality associated with OSA (38,39). In a recent study by Shiina and colleagues (40), there was a significantly greater increase in pulse wave velocity (PWV) and C-reactive proteins (CRP), both of which are known markers of cardiovascular risk, in patients with OSA and metabolic syndrome. Thus the concurrent presence of metabolic syndrome ('Syndrome Z') may increase the cardiovascular risk in subjects with OSA (40). This leads to an important question: whether treatment of OSA patients with nasal CPAP would lower the overall prevalence of the metabolic syndrome and the consequent cardiovascular risk? A significant insight has been provided by Milleron and colleagues (41) who have demonstrated that the treatment of OSA in coronary artery disease (CAD) patients is associated with a decrease in the occurrence of new cardiovascular events, and an increase in the time to such events. Although the study had limitations in methodology (sleep was not recorded), the number of patients and cardiovascular outcome variables used, nevertheless the findings have potentially important implications for cardiovascular disease prevention. The mechanisms by which CPAP acts to reduce the cardiovascular morbidity could be due to its cumulative effects on blood pressure, sympathetic activity and insulin resistance as already mentioned.

Conclusion

Obstructive sleep apnea is independently associated with increased prevalence of various cardiovascular risk factors and as a cluster of abnormalities in the form of metabolic syndrome. Because of these risk factors, there is evidence that untreated OSA is associated with increased cardiovascular morbidity and mortality and poor long term prognosis. There is also evidence that treatment of OSA with nasal CPAP in CAD patients is associated with decreased hospitalization for heart failure, acute coronary syndrome and cardio vascular deaths. At this point of time, the majority of patients with OSA are treated because of symptoms such as excessive daytime sleepiness, snoring and poor quality of life. With the linking of OSA independently with metabolic syndrome and its consequent cardiovascular implications, the indications for treatment of OSA in future may need to be changed from symptomatic to prognostic reasons. Given the magnitude of obesity increasing to epidemic proportions, the prevalence of metabolic syndrome and OSA could also rise in future. This would have a tremendous impact on future cardiovascular morbidity and mortality and is likely to pose a great challenge for sleep specialists in the developing countries like India.

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