Obstructive sleep apnea: Awakening the hidden truth

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ABSTRACT
Obstructive sleep apnea (OSA) is a common type of sleep apnea and is caused by obstruction of upper airway. Sleep apnea is clinically defined as frequent episodes of apnea, hypopnea and symptoms of functional impairment, which could be life-threatening and associated with extreme daytime hyper somnolence, dysfunction, discemments in health-related quality of life, automobile accidents, and cardiovascular morbidity and mortality. Etiopathogenic factors that contribute to OSA include reduced upper-airway dilator muscle activity during sleep, upper-airway anatomical features, ventilatory control insufficiency, lung volume, and rostral fluid shifts. The presence of risk factors such as age, gender and obesity increases the incidence of OSA. The repetitive nocturnal hypoxemia experienced by patients with OSA is associated with activation of a number of neural, humoral, thrombotic, metabolic, and inflammatory disease mechanisms, all of which have also been implicated in the pathophysiology of various systemic diseases. This article summarizes the etiopathogenesis, epidemiology, associated systemic diseases such as cardiovascular diseases, diabetes, and dental diseases with OSA and the influence of tongue on oropharyngeal airway in OSA patients.

Key words: Apnea, breathlessness, snoring

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Introduction
“Sleep disorder breathing” (SDB) is a term, which includes simple snoring, upper-airway resistance syndrome, and sleep apnea.[1] Sleep apnea is clinically defined as frequent episodes of apnea (cessations) and hypopnea (discrete reductions) and symptoms of functional impairment, which could be life threatening and associated with extreme daytime hyper somnolence, dysfunction, discemments in health related quality of life, automobile accidents, and cardiovascular morbidity and mortality.[2] Sleep apnea is the most prevalent of all the upper-airway disorders and is classified as central, obstructive and mixed or mild, moderate and severe.[3] Obstructive sleep apnea (OSA) is a disorder characterized by repetitive collapse and reopening of the upper airway during sleep, which impairs ventilation and can result in intermittent hypoxemia and hypercapnia.[4]

Obstructive sleep apnea is insidious and patients are often unaware of the associated symptoms. Cardinal manifestations include loud snoring, witnessed breathing pauses during sleep, fitful sleep quality, fatigue, dry mouth, morning headache, and excessive daytime sleepiness (EDS). Early recognition and appropriate therapy can ameliorate the neurobehavioral consequences.[5]


Age,[12] gender,[13] and obesity[14] are interrelated in a complex manner and considered to be a risk factor for incidence of OSA. The cutoff value of body mass index (BMI) for obesity in the Caucasian populations is at 30 kg/m², but some Asian-Indian populations have redefined obesity at a lower BMI of 23 kg/m² for both the sexes.[15] The World
Health Organization (WHO) task force on obesity suggested that Asian-Indian populations have different associations between BMI, percentage of body fat, and health risks than do Caucasians (WHO, 2000). Clinically, neck circumference has been reported to be a useful predictor of OSA.\textsuperscript{[16]}

Several anatomic factors predispose to the development of OSA, which includes size of the tongue and craniofacial morphology.\textsuperscript{[15]} In adult snorers and OSA patients, there is a good correlation between clinical tonsil grade and objective tonsil volume.\textsuperscript{[18]} According to Nuckton et al. (2006), the Mallampati score is an independent predictor of OSA and its severity.\textsuperscript{[19]}

There is a robust association between OSA and systemic conditions such as cardiovascular diseases such as hypertension (HT) and diabetes mellitus (DM), which are the main health problems in both developed and developing countries. Patients with HT are nearly 2.5 times more likely to develop OSA.\textsuperscript{[20]} In patients with drug resistant HT an even higher OSA prevalence of 83\%\textsuperscript{[21]} is seen. HT is defined as blood pressure at least 140/90 mmHg.\textsuperscript{[22]}

Until date, four studies including a total number of nearly 900 type 2 diabetic patients have reported a striking overall prevalence of 73\%.\textsuperscript{[22-25]}

**Literature Review**

**Definitions and classification**

According to the American Academy of Sleep Medicine recommendations, OSA is defined with apnea-hypopnea index (AHI) > 5 or AHI ≥ 5 and associated with symptoms such as EDS, impaired cognition, mood disorders, insomnia, HT, ischemic heart disease, or history of stroke.\textsuperscript{[26,27]} OSA is a disturbance in normal sleep patterns; when combined with daytime symptoms, this condition is termed “OSA syndrome”.\textsuperscript{[28-30]}

Prevalence estimates of disturbed sleep range from 35\% to 41\% among adults, out of which the most common sleep disturbances is OSA, followed by the frequent snoring, difficulty initiating or maintaining sleep (insomnia symptoms), and EDS.\textsuperscript{[31]}

**Etiopathogenesis of obstructive sleep apnea**

The most common factors that are known to contribute to the etiopathogenesis of OSA, are upper-airway dilator muscle activity during sleep, upper-airway anatomy, lung volume, ventilatory control instability, sleep state stability, and rostral fluid shifts.\textsuperscript{[11]}

**Upper-airway dilator muscle activity**

The largest of the pharyngeal dilator muscles is the genioglossus, the muscle that forms the majority of the body of the tongue\textsuperscript{[12]} and its function can be augmented in response to heightened airway resistance and hypercapnia through inputs from the sleep/awake centers of the brain, respiratory pattern generating neurons, chromoreceptors, and negative pressure receptors in the airway that can modify its activity.\textsuperscript{[6,34]}

**Upper-airway anatomy**

Anatomical factors, including increased airway length, lateral wall thickness, and tongue volume, are associated with the presence of OSA.\textsuperscript{[35]} A small maxilla or mandible can result in a reduced airway size.\textsuperscript{[7]}

**Lung volume**

Lower end-expiratory lung volume, increases the tendency of the upper-airway collapse.\textsuperscript{[16]} A continuous positive airway pressure (CPAP) level is necessary to maintain airway patency, and to reduce the severity of OSA.\textsuperscript{[8,37]}

**Ventilatory control instability**

Persons with OSA generally have greater instability of ventilatory control and higher loop gain than healthy individuals.\textsuperscript{[18]} Since upper-airway muscles receive input from respiratory control centers, unstable ventilatory control will cause greater fluctuation in the activity of the upper-airway muscles and promote upper-airway collapse.\textsuperscript{[8,33]}

**Fluid shifts**

Fluid shifts from the legs to the neck appear to play a role in pathogenesis of OSA. Overnight rostral fluid displacement from the legs correlates strongly with AHI, change in neck circumference.\textsuperscript{[15]} Furthermore, time spent in sitting was a significant risk factor even in non-obese, healthy men suspected of having OSA.\textsuperscript{[10,39,40]}

**Genetics**

Evidence from racial, familial, and twin studies indicates that OSA has a strong genetic basis.\textsuperscript{[41]} There is an evidence that the genetic determinants present for upper-airway muscles activity, skeletal structures, obesity, epidemiology of fat distribution and respiratory control may interact to cause OSA. The role of specific genes in the pathogenesis remains to be elucidated.\textsuperscript{[42]}

**Epidemiology of obstructive sleep apnea**

**Gender and age on obstructive sleep apnea**

Several investigators have reported gender differences in the abnormalities of nocturnal respiration. In the widely quoted Wisconsin Sleep Cohort Study, the prevalence of sleep disordered breathing in men (24\%) is almost three times higher than in the women (9\%).\textsuperscript{[13,43]} The reason for the gender differences in the prevalence and severity of sleep apnea are multifactorial, and is primarily attributed to
Obstructive sleep apnea and obesity

Obesity develops from an imbalance of energy over time, when energy intake exceeds energy expenditure, leading to accumulation of adipose tissue with a corresponding increase in lean body mass. Fat deposition in the tissues surrounding the upper airway appears to result in a smaller lumen and increased collapsibility, predisposing to OSA. Moreover, fat deposits around the thorax (truncal obesity) reduce chest compliance and functional residual capacity, and may increase oxygen demand. Factors such as reduced activity levels and increased appetite, particularly for refined carbohydrates, may conceivably contribute to weight gain in OSA patients. Current evidence based studies suggest that OSA may itself cause weight gain.

The cutoff value of BMI for obesity in the Caucasian populations is at 30 kg/m², but some Asian-Indian populations have redefined obesity at a lower BMI of 23 kg/m² for both the sexes. The WHO task force on obesity suggested that Asian-Indian populations have different associations between BMI, percentage of body fat, and health risks than do Caucasians (WHO, 2000). Clinically, neck circumference has been reported to be a useful predictor of OSA, however the exact role of neck circumference in the development of OSA has not been fully clarified.

Obesity is a major modifiable risk factor for OSA: weight loss is recommended for all overweight or obese patients with sleep apnea, as its beneficial effects embrace other obesity related health problems, notably cardiometabolic diseases.

Obstructive sleep apnea and craniofacial morphology

Craniofacial characteristics associated with OSA include aspects of skeletal craniofacial morphology pertaining to the mandible, maxilla, cranial base, hyoid, and head position, as well as soft tissue morphology relating to size of upper-airway soft tissues. Aspects of skeletal craniofacial morphology relating to OSA have been explored primarily using cephalometric analysis. Most common predictors include differences in maxillary mandibular morphology and its relationship. In terms of the maxilla, a shorter length and also narrower maxillary arch and mandibular deficiency has also been associated with OSA patients. Three-dimensional imaging techniques have also confirmed, a smaller mandibular enclosure areas seen in OSA subjects.

The lowered hyoid position is also considered as confounding factors for OSA patients.

Obstructive sleep apnea and cardiovascular diseases

The strong association between OSA and HT has attracted considerable attention in recent years. HT is defined as taking antihypertensive without regard to the actual measurement of blood pressure, or having a systolic blood pressure reading greater than 140 mm Hg or a diastolic blood pressure reading greater than 90 mm Hg.

Pathophysiology

Three key pathophysiological features of OSA that give rise to these abnormal cardiovascular oscillations are:

a. Generation of exaggerated negative intrathoracic pressure against the occluded pharynx
b. Hypoxia and
c. Arousals from sleep.

a. Negative intrathoracic pressure against the occluded pharynx: Ineffective inspiratory efforts are a hallmark of obstructive apneas. The resulting exaggerated negative intrathoracic pressure swings increase left ventricular (LV) transmural pressure by increasing the difference between extra cardiac and intracardiac pressures, and hence after load, but without increasing Blood Pressure (BP). It also increases venous return to the right ventricle, leading to its distention. The resulting leftward shift of the interventricular septum can impede LV diastolic filling. There is also evidence that exaggerated negative intrathoracic pressure during apnea can impair LV relaxation, which could further impede LV filling. The combination of increased LV after load and reduced LV preload leads to a reduction in stroke volume during obstructive apneas that is proportional to the negative intrathoracic pressure generated.

b. Hypoxia: During obstructive apneas, the sympathoexcitatory effect of hypoxia is amplified by apnea and CO₂ retention. This result in increased sympathetic vasoconstrictor tones however; these sympathoexcitatory effects are not engaged until several seconds into the apnea. Intermittent hypoxia during obstructive apneas may directly depress cardiac contractility, or
reduce cardiac performance indirectly by causing pulmonary vasoconstriction and increasing pulmonary arterial pressure. The degree of desaturation during each obstructive apnea has been directly related to the magnitude of the increase in BP following the apnea. Arousal is a critical defense mechanism that makes active upper-airway dilator muscles and prevents asphyxiation in OSA. Arousals causes only a small further increment in heart rate (HR) and blood pressure (BP). One confounding factor is that arousals are accompanied by an abrupt increase in ventilation that precedes increases in HR and BP. This suggests that the increased ventilatory drive at termination of apnea coactivates cardiovascular sympathetic neurons that are closely linked with respiratory neurons in the brainstem.

c. Arousals: Arousal is a critical defense mechanism that makes active upper-airway dilator muscles and prevents asphyxiation in OSA. Arousals causes only a small further increment in heart rate (HR) and blood pressure (BP). One confounding factor is that arousals are accompanied by an abrupt increase in ventilation that precedes increases in HR and BP. This suggests that the increased ventilatory drive at termination of apnea coactivates cardiovascular sympathetic neurons that are closely linked with respiratory neurons in the brainstem.

d. Correlation of HT and OSA: Patients with HT are nearly 2.5 times more likely to develop OSA. In patients with drug resistant HT an even higher OSA prevalence of 83% is seen and has been reported that SDB and HT is seen in both sexes and all ethnic groups and are slightly stronger among those who are overweight or obese. The hypothesis of a causal association between sleep apnea and HT is supported by evidence from intervention trials, showing that successful treatment of sleep apnea by means of weight loss; CPAP is accompanied by significant decreases in both daytime and nighttime blood pressure. SDB is more prevalent in men with HT than in normal individuals without HT. Several studies have proposed hemodynamic disturbances due to OSA resulting in abnormal activation of arterial chemoreceptors and increased sympathetic activity, followed by arousals during sleep.

Metabolic syndrome and obstructive sleep apnea
Metabolic syndrome (MS) is strongly linked to obesity and comprises of multiple metabolic abnormalities, such as HT, insulin resistance, central obesity, and dyslipidemia. Current data suggest that there is an increased prevalence of MS in subjects with OSA.

The MS is also known as insulin resistance syndrome. The constellation of metabolic derangement includes insulin resistance/glucose intolerance, central obesity, HT, and dyslipidemia, which are well-known risk factors for cardiometabolic diseases. Several studies has been indicated that MS predicts future diabetes as well as an increased risk of cardiovascular disease and all causes of mortality.

Pathophysiology of MS is still a subject of debate, and both visceral obesity and insulin resistance appear to be the predominant drivers of this syndrome. It has been proposed that visceral fat probably plays a role in the hepatic manifestations of central obesity and systemic free fatty acid concentrations are found to affect muscle, pancreatic β cells, and vascular functions at molecular level. The current status stated that visceral fat is particularly damaging and is of greater risk for DM, cardiovascular disease and certain cancers.

Prevalence of obstructive sleep apnea in type 2 diabetics
The prevalence of OSA in patients with type 2 diabetes was assessed by methods other than the gold standard full polysomnography (PSG) (e.g., limited PSG or overnight oximetry), should variable estimate ranging from 2 to 70%.

Until date, four studies including a total number of nearly 900 type 2 diabetic patients have reported a striking overall prevalence of 73%, reported an OSA prevalence of 77% in 60 type 2 diabetics (Mean Age: 57 years) using a less stringent cutoff of 3% for oxygen desaturations, and when the dataset was reanalyzed using a stricter 4% criteria, this estimate decreased to 58%. Considering that the prevalence of OSA by full-night PSG in patients with type 2 diabetes averages 73%, this would then suggest that nearly 17 million diabetics currently suffer from this unrecognized comorbidity.

Prevalence of type 2 diabetes in obstructive sleep apnea
In cross-sectional analyses, it has been demonstrated that there is a significantly higher prevalence of DM in patients with OSA as compared to those without OSA. The Bussleton health study found a significant independent association between moderate to severe OSA and incident DM over a 4-year follow-up period, but the sample size was small and there were only few incident cases of diabetes, which resulted in a wide confidence interval. The prevalence of undiagnosed obstructive OSA is high among patients with poorly controlled type 2 diabetes and that it is mainly related to visceral obesity. Furthermore, we have found that the presence of obstructive OSA cannot be predicted by clinical data, which suggests that OSA should be systematically screened for in such a patient population.

In summary, future studies from large longitudinal cohorts are clearly needed to assess the role of OSA as a potential risk factor for diabetes.

Dental predisposing factors and obstructive sleep apnea
Influence of tongue on oropharyngeal airway in obstructive sleep apnea patients
Cephalometric analysis in patients with OSA and healthy controls, reported that the non-obese patients with OSA showed enlarged tongue and inferior shift of the tongue volume, in comparison with their BMI matched healthy controls.
The upper-airway soft tissue structures were three-dimensionally analyzed with an advanced analysis technique through magnetic resonance imaging and Shigeta et al. stated that the volume of the tongue and lateral walls independently increases the risk of sleep apnea. There is a significant positive correlation between BMI and tongue volume, and a significant negative correlation between BMI and airway volume and there also is a negative correlation between airway volume and tongue and mandible (T/M) ratio. As tongue volume increases with BMI, the T/M ratio is affected, and thus is likely to be involved in the development of OSA.

**Influence of tonsil volume and uvula size on obstructive sleep apnea patients**

The role of thickened and exceedingly collapsible lateral pharyngeal walls in the pathophysiology of OSA is well recognized in adults.

According to Force et al. (2009); tonsils are subjectively measured using a grading system in which grade I represents; tonsils are hidden in the tonsillar fossa and barely visible behind the anterior pillars. In grade II, the tonsils are visible behind the anterior pillars and occupied up to 50% of the pharyngeal space (the distance between the medial borders of the anterior pillars). In grade III, the tonsils occupied between 50 and 75% of the pharyngeal space. In grade IV, the tonsils occupied more than 75% of the pharyngeal space.

In Mallampati’s technique, with the tongue kept in place without the use of a tongue depressor, grade I, represents the tonsils, pillars, pharynx, and soft palate are clearly visible; grade 2, the uvula and the only part of the pillars and tonsils are visible between the palate and the tongue; grade 3, only the soft and hard palate are visible, whereas the tonsils, pillars, pharynx and base of the uvula are hidden behind the tongue. In grade 4, only the hard palate is visible. The Mallampati score is an independent predictor of OSA and its severity.

In adult snorers and OSA patients, there is a good correlation between clinical tonsil grade and objective tonsil volume. The clinical ability to infer tonsil volume is not impaired by possible changes in pharyngeal geometry that are related to OSA. Although tonsil volume correlates with AHII, from a clinical perspective, only tonsil grade IV predicts severe OSA. Pharyngeal tissue volume likely reflects BMI rather than OSA.

**Conclusion**

Obstructive sleep apnea is gaining lots of importance in the recent years due to its impact on various systems of our body. It has been considered as a Pandemic disease. We conclude that snoring and sleep apnea are common among Indian adults. Recognition of the importance of OSA among general public would be a valuable step toward implementing population-based strategies to reduce OSA prevalence. Various studies have showed sex, higher BMI, and presence of HT is considered as risk factors for OSA. Therefore, early detection and treatment of OSA may be essential with intervention to reduce risk of associated medical problems.

**References**

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