REVIEW ARTICLE

Obstructive Sleep Apnea Syndrome : Genetic and Biochemical Perspective

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Abstract

Obstructive sleep apnoea syndrome (OSAS) is a disorder characterized by repetitive complete or partial upper airway collapse occurring during sleep with daytime sleepiness. The health impact of obstructive sleep apnoea is enormous. Chronic intermittent nature of the physiologic disturbances associated with this disorder is major cause of its related morbidity e.g. the accompanying intermittent hypoxia with ventilatory overshoot hyperoxia, sympathetic nervous system surges, and enhanced state of inflammation, oxidative stress and endothelial dysfunction are potential mechanistic pathways leading to conditions including hypertension, nocturnal cardiac arrhythmias, cardiovascular disease, stroke, insulin resistance and increased mortality.

Quality of life may also be affected in obstructive sleep apnoea syndrome with increased likelihood of drowsy driving/accidents, mood disorders and neurocognitive deficits. This study is an effort to identify potential perception for genetic and biochemical basis of risk factors of OSAS and related co-morbidities.

Keywords: Obstructive sleep apnoea syndrome (OSAS), inflammation, oxidative stress.

Obstructive sleep apnea syndrome (OSAS) is a disease, characterized by disruptive snoring, repeated episodes of complete or partial pharyngeal obstruction during sleep resulting in nocturnal hypoxemia, frequent arousals during sleep, and excessive daytime sleepiness (EDS).[1,2,3]

The prevalence of OSA syndrome defined as an apnoea hypopnoea index (AHI) of five or more. [4]Apnoea-hypopnoea index (AHI) is the number of apnoeas and hypopnoeas per hour of sleep. [5] Apnoea is defined as a pause of at least ten seconds in the oral-nasal flow of air, despite the movement of the chest or abdomen, which leads to a reduction in O_2 saturation ($\geq$2.5%) and awakening, while hypopnoea occurs when mild obstruction leads to a decrease in air flow by 50%.[6]

The American Sleep Disorders Association classifies OSA as:

Mild OSA	AHI 5-15
Moderate OSA	AHI 15-30
Severe OSA	AHI <30

Prevalence

According to Wisconsin Cohort Study in the US involving middle-aged adults 30 to 60 yr of age prevalence of OSAS is 2 per cent in females and 4 per cent in males[7] In the urban Indian population, OSA syndrome is estimated to be 7.5 per cent in males between 35-65 year of age[8] According to another study the estimated prevalence of OSAS is 2.4% in males and 1% in females and of OSA was 4.4% (95%Confidence Interval (CI)

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3.8%-5.1%) in males and 2.5 % (95% CI 2%-3%) in females & OSAS in 2.4% [95%CI 1.9%-2.9%] in males & 1% (95%CI 0.08%-1.1%) in females. [9] Sharma *et al* show the prevalence of OSA and OSA syndrome (OSAS) 13.74% and 3.57% respectively. The prevalences of OSA and OSAS in men were 19.7% and 4.9%, respectively. The prevalences of OSA and OSAS in women were 7.4% and 2.1%, respectively in Population of Delhi, India.[3]

Risk Factors

Anatomy

The human upper airway is a unique multipurpose structure involved in performing functional tasks such as speech, swallowing of food/liquids, and the passage of air for breathing. The cross-sectional area of the upper airway is reduced in patients with OSA compared with subjects without OSA.[10,11,12] The arrangement of the surrounding soft tissues also appears to be altered in patients with OSA, which makes the upper airway susceptible for risk to collapse.[10] There is high closing pressure (more collapsible) in OSA subjects under conditions of general anesthesia and muscle paralysis.[3] A number of craniofacial, orthodontic skeletal or soft tissue structural abnormalities like dysmorphisms associated to mandibular or maxillary size and position (*e.g.,* a posteriorly placed mandible, a narrow posterior airway space), an enlarged tongue and soft palate, inferiorly placed hyoid bone, and narrowed nasal cavities, can result in a smaller or more collapsible upper airway, and an increased predisposition for the development of OSA.[14] Adenotonsillar hypertrophy in childhood can lead to abnormal growth patterns of the lower face and jaw (adenoidal facies) and may predispose to OSA in later life.[15]

Table 1: Prevalence in Indian Population

Study	Place	Pre-valence	Sex	Age group
Surendra Kumar Sharma *et al*	Delhi India	3.57%	Male- 4.9% Female- 2.1%	30-60 years
Udwadia and colleagues	Delhi India	7.5%	–	35-65 years
VK Vijayan *et al*	Delhi India	–	Male- 2.4% Female-1%	18 to 103 years

Sex

Male sex is a major risk factor for OSA and a 2-3-fold greater risk of OSA has been reported for men compared with women.[16] The prevalence of OSAS in men and women were found 4.9% and 2.1% respectively.[3] The gender related protective effect decreases in postmenopausal women who are not receiving hormone replacement therapy. Sex hormones, craniofacial morphology, pattern of fat deposition, differences in upper airway shape and genioglossal muscle activity during the awake state and control of ventilation, have been anticipated to account for a higher male risk of OSA. Though, reduction in the AHI on administration of estrogen and progesterone to men (or postmenopausal women) has not been established.[17]

Age

The frequency of apnea increases with aging, with a number of studies reporting a remarkable prevalence of sleep-disordered breathing in older individuals.[18,16] Only available prevalence study from India, Udwadia and colleagues [8] studied urban men between 35 and 65 years of age presenting to the hospital for routine checkup, and reported the estimated prevalence of OSA as 19.5% and that of OSAS as 7.5%.

Obesity

Among all the risk factors the most potent risk factor is obesity. Approximately 70% of patients with this disorder are obese and obesity is the only reversible risk factor of importance.[19]

Obesity and particularly central obesity may lead to increased pharyngeal collapsibility via mechanical effects on pharyngeal soft tissues and lung volume, and through central nervous system–acting signaling protein as leptin that may change airway neuromuscular control. Changes in the mechanical and neural control of upper airway collapsibility, which determine sleep apnea susceptibility, may be produced by the differences in the distribution and metabolic activity of adipose tissue by specific molecular signaling pathways encoding.[20]

The prevalence of OSA among obese patients exceeds 30%, reaching as high as 50–98% in the morbidly obese population.[21]

Genetic Predisposition, Biochemical status and Co-morbidities

The chronic intermittent nature of the physiologic

disturbances associated with this disorder is at the root cause of its associated morbidity. In results in state intermittent hypoxia with ventilatory overshoot hyperoxia, sympathetic nervous system surges, increased condition of inflammation, oxidative stress and endothelial dysfunction, which are potential pathways leading to adverse conditions including hypertension, cardiovascular disease, stroke, insulin resistance, nocturnal cardiac arrhythmias, and increased mortality. Quality of life may also be affected in patients of obstructive sleep apnoea syndrome with increased odds of drowsy driving/accidents, mood disorders and neurocognitive deficits.[4]

OSAS has strong genetic bases with variety of genes related to obesity, upper airway anatomy phenotype and physiological conditions like inflammation, oxidative stress and respiratory activity. These biochemical and genetic mediators of OSAS have raised expectations about the understanding the pathophysiology and development of a therapy for the disease and comorbidities in India population.

Following are the thrust areas to be investigated systematically to understand the molecular and genetic pathophysiology:

Familial Progression

There is a common familial basis to the development of OSA[39,40] This finding is true for both obese and non-obese patients with OSA.[40,41,42,] Studies using linkage analysis have provided initial insight into the potential link between specific areas of the genome and OSA pathogenesis.[43,44,45] Furthermore, traits such as the size of the upper airway soft tissue structures[46], ventilatory control abnormalities[47], and respiratory responses to resistive loading during sleep may also have a genetic basis.[48]

Table 2 : Risk factors for OSAS in Indian Population (Sharma *et al)*

Age	>45 years
Sex	Male gender
Body Mass Index	>25 kg/m^2
Waist Hip Ratio	> 0.80 in women > 0.95 in men
Socioeconomic Status	Upper Socioeconomic Status

Oxidative Stress and Inflammation

OSAS is associated with significant oxidative stress (related to increased reactive oxygen species (ROS) production, decreased scavenging power) that may eventually lead to the sympathetic activation[22] and endothelial dysfunction[23] in the OSAS patients. ROS are also associated with pathogenesis of atherosclerosis.[24]

Both oxidative stress and endothelial dysfunction might develop from chronic inflammation. A proinflammatory status has been accounted at both systemic and local (upper airways) levels in patients with OSAS. Increased circulating levels of proinflammatory cytokines such as interleukin 6, tumor necrosis factor α (TNF alpha)[25], and C-reactive protein[26,27] appear as common findings to all studies. Tumor necrosis factor (TNF)-alpha and interleukin-6 levels are elevated in patients with OSAS when compared with patients with hypersomnia[28] and subjects with non-apneic obesity.[29]

Another sensitive marker for systemic inflammation, C-reactive protein (CRP) is also increased in obstructive sleep apnea syndrome subjects in comparison to age and body mass index (BMI) matched control subjects.[30] The presence of systemic inflammation, characterized by elevated levels of these pro-inflammatory mediators and reactive oxygen species may predispose to the development of cardiovascular complications in OSAS.[54]

Fat distribution, hyperleptinemia and leptin resistance

BMI and Waist-hip-ratio (WHR) were found to be independent predictors of OSA. Parameters of obesity such as BMI of >25 kg/m^2, Waist Circumference (WC) of >102 cm in men and >88 in women, WHR of >0.95 in men and >0.8 in women were shown significant correlation with AHI in Indian population. Leptin levels were found in correlation with visceral fat accumulation, and both leptin and visceral fat accumulation decreased in patients with OSA following the nasal continuous positive airway pressure treatment[49].

Human studies indicate that leptin and the leptin receptor have important and powerful roles in the mechanism of obesity. Circulating leptin is significantly increased in OSAS patients and correlates with the severity of OSAS.[50] Both OSAS and obesity are thought to be leptin resistant states. It has been found that serum leptin concentration is proportional to body mass, but

Table 3 : Genes Related with Predisposing Factors and Associated Co-morbidities in OSAS

Leptin	Obesity and hypoventilation	Tansu Ulukavak Ciftci et al
Leptin Receptors	Obesity and dyslipidemia	Popko K et al
Beta3-Adrenergic receptor	Obesity	Piérola J et al
Angiotensin converting enzyme	Hypertension	Patel SR
GABA(B)R1 receptor gene	Neurotransmission	Bayazit YA et al
Tumor necrosis factor-alpha promoter gene	Inflammation	Liu HG et al Riha RL et al
Insulin receptor substrate	Insulin resistance	Bayazit YA et al
HT2A receptor	Serotonin dependent respiratory activity	Bayazit YA et al

may be lowered rapidly by fasting or inflammatory reaction[51,52,53] Leptin is increased in patients with OSAS when compared with control subjects matched for age and body mass index.

Leptin is an adipocyte-derived hormone regulating energy homeostasis and body weight. Leptin receptor (LEPR) is a single transmembrane protein for leptin signaling. The presence of Arg allele (LEPR Gln223Arg) is linked to a higher risk of obesity and higher lipid levels in OSAS patients[31]

Other genes which are found to be associated with OSAS occurrence, severity and related co-morbidities are beta3-Adrenergic receptor[32] angiotensin converting enzyme (ACE)[33], GABA(B)R1 receptor gene[34], tumor necrosis factor-alpha promoter gene [35,36] Insulin receptor substrate[37] 5-HT2A receptor[38] related with obesity, hypertension, neurotransmission, inflammation, insulin resistance and serotonin dependent respiratory activity respectively.

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