

Review Article

Obstructive Sleep Apnea and Related Disorders

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Abstract

Obstructive sleep apnea (OSA) is the most common type of sleep apnea. Certain risk factors may predispose susceptible individuals to develop OSA. Those risk factors include obesity, aging, male gender, and ethnicity, among others. Individuals with OSA may have increased comorbidity and mortality due to the presence of various medical conditions such as hypertension, cardiovascular diseases, diabetes mellitus, stroke, seizures and epilepsy. It is indispensable to understand the fact that those medical conditions may commutatively exacerbate the severity of OSA and interfere with the effective treatment for OSA. On the other hand, effective treatment of OSA may potentiate the efficacy of the treatment for OSA-related comorbidity. Therefore, earlier detection of OSA and appropriate treatment may significantly modify the outcomes of this potentially life-threatening condition and improve the quality of life for those susceptible populations.

Keywords: Obstructive sleep apnea; hypertension; cardiovascular diseases; diabetes mellitus; stroke; seizure.

Introduction

Obstructive sleep apnea (OSA) is a common medical condition that affects billions of people worldwide. The consequences of OSA may result in significantly increased mortality and morbidity including cardiovascular and neurological disorders. In this article, we reviewed the epidemiology, risk factors, clinical manifestations, and consequences of OSA.

What is OSA

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repeat brief interruptions of breathing during sleep. It is caused by relaxation of soft tissue in the back of the throat that blocks the passage of air. An apnea event is defined as the cessation of naso-buccal air flow for more than 10 seconds [1]. The indices commonly used to assess sleep apnea are the apnea-hypopnea index (AHI) and the respiratory disturbance index (RDI). The AHI is defined as the average number of episodes of apnea and hypopnea per hour. The RDI is defined as the average number of respiratory disturbances, such as obstructive apneas, hypopneas, and respiratory event-related arousals per hour. It is diagnosed based on an apnea-hypopnea index (AHI) value greater than five per hour of sleep [2], usually accompanied by a 4% decrease in oxygen saturation [2] on polysomnography (PSG). Individuals with OSA will partially awaken as they struggle to breathe, but in the morning they will not be aware of the disturbances in their sleep. According to the guideline for adult OSA [3], the diagnosis of OSA is confirmed if the number of RDI on PSG is greater than 15/hr or greater than 5/hr in a patient who reports any of the following: unintentional sleep episodes during wakefulness; daytime sleepiness; unrefreshing sleep; fatigue; insomnia; waking up breath holding, gasping, or choking; or the bed partner describing loud snoring, breathing interruptions, or both during the patient's sleep. OSA severity is defined as mild for RDI ≥ 5 and < 15 , moderate for RDI ≥ 15 and ≤ 30 , and severe for RDI > 30 /hr.

Clinical Manifestations of OSA

Common symptoms suggestive of OSA include snoring, restless sleep, daytime fatigue and sleepiness [4]. Common signs of OSA include unexplained daytime sleepiness, restless sleep, and loud snoring. Less common are arrhythmia, hypertension, decreased sex drive, unexplained weight gain, increased nocturia; gastroesophageal reflux; and heavy night sweats [4]. OSA is a relatively common disorder and the prevalence is approximate 16% among men and 5% among women between 30 and 65 years of age [5]. Five percent of adults have undiagnosed sleep apnea [6]. OSA is a widely underdiagnosed and is associated with significant morbidity and mortality [7-10] causing a broad variety of medical conditions [11]. Associations between OSA and arrhythmia [12], heart failure, hypertension [13-15], diabetes [16-21], insulin resistance [22] metabolic syndrome [23], and stroke [5,6,24-28] have been observed.

Epidemiology of OSA

In Canada, almost 26% of Canadians are at high risk of developing OSA. In China, similarly, 27.2 of adults have snore [29] and the overall rate of habitual snoring is 11.5 % (17.1% for men and 5.6% for women) [30]. It can be higher geographically, such as 33% in Brazil, particularly in men and obese individuals [31]. OSA poses a major public health concern due to its prevalence, severity and socioeconomic burden. It is estimated that 80% of obstructive sleep apnea cases remain undiagnosed [32], making it difficult to identify patients at risk of associated comorbidities [33]. Several risk factors are associated with development of OSA, including obesity, male gender [34-37], and aging [13,35-39].

Risk factor of OSA**Obesity**

Obesity is a recognized risk factor for OSA. In the United States, over two-thirds of adults are overweight, and one-third of the adult

population suffers from obesity [40]. There are two most common measures in classifying obesity: body mass index (BMI) and waist-to-hip ratio. BMI is a calculated ratio of body weight in kilograms divided by height in meters squared and is widely used for estimating body fat for adults. An adult who has a BMI of 25-29.9 is considered overweight and over 30 obese. BMI of 35-40 is classified as severe obesity, 40-44.9 morbid obesity, and greater than 45 is described as super obesity [41,42]. Considering ethnic factors, some nations have redefined obesity as BMI greater than 25 in Japan [43] and greater than 28 in China [44]. Because the pattern of the body fat distribution differs in men and women, the waist-to-hip ratio (in inches) is obtained by measuring the waist at its narrowest point and the hips at the widest point and is used to estimate not only how much fat a person has but also where the fat is deposited. Women usually deposit fat in their hips and buttocks, displaying a “pear” shape, while men deposit fat in abdomen, making an “apple” appearance. Waist-to-hip ratios of greater than 0.8 in women and more than 1.0 in men are “apples”. Apple-shaped individuals are more likely to suffer from medical problems related to obesity [42]. A longitudinal study showed that a 1 standard deviation increase in BMI is associated with a 4.5-fold increased risk of OSA, and a 10% weight gain associated with a six fold greater risk for OSA at 4-year follow-up [9]. Neck circumference, like BMI, is also positively associated with OSA [45]. Obese patients, especially those with a central distribution of fat or “apples”, have an increased risk of various medical disorders including OSA [41,42].

Aging, gender, and ethnicity

Aging also plays a role as OSA is more common in the elderly than among middle-aged population. Approximately 20% of people aged 65 or older have OSA compared to approximately 10% in the 39-49 year-old age group [46]. The prevalence ratio for adult OSA is approximate 2-3:1 in men to women [45]. The decrease in gender prevalence differences after menopause in women suggests a pathogenetic basis for sex hormones. Additionally, OSA tends to aggregate in families. Having a first-degree relative with OSA increases one's risk for OSA substantially. Estimated heritability of AHI is 30-40%. There is a higher prevalence in certain ethnic populations, for example, Asians have approximately two times the risk of OSA compared to Caucasians. African-Americans and Mexican-Americans are also at higher risk of OSA [41,47]. Smokers are more likely to have OSA than nonsmokers [9] because smoking may cause upper airway inflammation and edema or sleep instability from nicotine withdrawal.

Comorbidity of OSA

Hypertension

Clinical studies showed that patients with OSA have an increased blood pressure. Hypertension is a common chronic medical condition affecting approximate 1 billion individuals worldwide [48]. It is defined as blood pressure higher than 140mmHg systolic over 90mmHg diastolic [48]. Hypertension is an established major risk factor for stroke and cardiovascular disorders, which significantly shorten life expectancy. Notably, the risk of hypertension increases with increasing OSA severity [46,49]. There is a dose-response manner of association between OSA and hypertension with AHI as a significant factor influencing odd ratios for hypertension prevalence.

The risk for the development of hypertension was nearly threefold higher in moderate-to-severe OSA as compared to controls [9]. OSA may be prevalent in over 80% middle-aged adults with drug-resistant hypertension. Approximately 70% to 90% of patients with OSA have hypertension [10]. Administration of continuous positive airway pressure (CPAP) or treatment with surgery showed improvement of blood pressure control, in addition to reduction of daytime somnolence, improvement of quality of life, and also a decrease of OSA-related cardiovascular morbidity in OSA patients, which supports the hypothesis of a causative role of OSA in hypertension development.

Cardiovascular disorders

OSA is a recognized independent risk factor for heart failure, and the link may be via hypertension [46,50]. CPAP has been shown to improve left ventricular ejection fraction in heart failure patients with OSA. Bradycardia is caused by vagal activation in OSA, while tachycardia is due to vagal withdrawal. A higher incidence of atrial fibrillation (AF), nonsustained ventricular tachycardia, and complex ventricular ectopy in patients with OSA has been shown [46]. Obesity, along with OSA, is also an independent risk factor for development of AF. The risk of AF increases by 4% for every one-unit increase in BMI [51-53]. This association is stronger for patients aged < 65 years [50]. Sleep apnea is more common in patients with congestive heart failure (CHF), and CHF itself is associated with high risk of AF [54-57]. Notably, OSA is more prevalent among younger AF patients with normal left ventricular function [58]. Four times higher occurrence of AF has been observed in patients with OSA than those without (4.8% vs 0.9%) [46]. CPAP treatment for OSA is beneficial in mitigating the burden of AF and improving the effectiveness of AF treatments. Additionally, poor efficacy of electrical cardioversion and radiofrequency ablation on AF has been evident in untreated OSA patients. The rate of postoperative AF appears significantly higher (32% vs 18%) among patients with OSA (AHI \geq 5). AF patients with OSA respond poorly to both pharmacological and non-pharmacological therapy (cardioversion or ablation) with high rate of recurrence [59-61]. Patients with OSA who were treated appropriately with CPAP had 82% lower rate of recurrence than patients who did not received treatment [62].

Diabetes Mellitus

There are strong associations between OSA and insulin resistance, glucose intolerance, and type 2 diabetes mellitus [16-23]. Up to 60-80% of type 2 diabetic patients may have OSA. Increased OSA severity is often seen in poor glycemic control. However, administration of CPAP showed inconsistent effects on glycemic control. OSA may adversely lead to worsening of obesity secondary to sleep deprivation with daytime sleepiness and decreased physical activity.

Stroke

OSA is also an independent risk factor for stroke and for stroke recurrence [46]. Moderately severe OSA in men is associated with an approximately threefold increase in ischemic stroke [46]. OSA worsens functional outcomes and increases mortality rates in stroke patients, possibly due to the fact that OSA promotes hypertension, transiently decreases cerebral blood flow, impairs cerebral autoregulation, facilitates atherosclerosis, increases endothelial dysfunction, hypercoagulability, and oxidative stress. It is estimated

that the increase of each unit in the obstructive AHI index increased stroke risk by 6%.

Seizure and Epilepsy

OSA is common in epilepsy, affecting more than 30% of patients with intractable seizures [36,37,63-72]. Presence of OSA may facilitate seizures in susceptible individuals [63,66,68]. The hypoxia caused by OSA may cause structural and functional alteration of neurons in the central nervous system (CNS). The processes of repeated OSA may promote epileptic seizures via increased sleep stage transitions, arousals from sleep, and re-entries into sleep. Notably, epileptic seizures are more common in lighter stages of sleep [73], including non-rapid eye movement (NREM) stage 1 sleep [74]. OSA is postulated as a cause of sudden unexpected death in epileptics [75,76]. On the other hand, sleep can influence interictal epileptiform discharges by facilitating abnormal neuronal synchronization and recruiting a critical sum of neurons to initiate and sustain epileptic discharges during NREM sleep [77]. Seizures prolong REM where OSA becomes worse due to atonia of respiratory musculature. Sleep fragmentation in OSA causes increased sleep stage transitions which, in turn, promotes the occurrence of seizures [63,78]. Moreover, epileptic seizures can cause apneas, therefore, epilepsy and OSA can profoundly exacerbate each other [79]. Neuro-imaging revealed evidence of hippocampal atrophy in OSA. Treatment with CPAP has demonstrated a direct effect of reducing interictal spikes, suggesting a potential for reducing epileptogenicity [80] and improving seizure control [63,66,68,81-84], particularly in obese patients [85].

Management of OSA

There are a variety of treatments for OSA, depending on an individual's medical history and the severity of the disorder. Most treatment regimens begin with non-pharmacologic measures, such as lifestyle changes, avoiding alcohol consumption, reducing weight, quitting smoking; and pharmacologic measures, such as sedatives and muscle relaxants. Some individuals may be benefited by special pillows or devices, or oral appliances to keep the airway open during sleep; or combination of therapies. CPAP is the treatment of choice for OSA, and has been consistently shown to lower the AHI, decrease subjective and objective sleepiness, and lower blood pressure. Effective treatments of OSA help to better control many of the associated diseases and chronic conditions [6,86,87].

Summary

OSA is a common sleep disorder and is a widely under diagnosed. OSA is more commonly seen in elderly, men, and obese individuals. It is associated with significant morbidity and mortality causing a broad variety of medical conditions. By inducing pathophysiological changes through repeatedly intermittent hypoxia, OSA causes multi-system and organ damage. Various medical conditions have been recognized to be linked with OSA including cardiovascular disorders, e.g. arrhythmia, heart failure; hypertension; metabolic syndromes, e.g. diabetes, insulin resistance; and neurological comorbidities, e.g. stroke, seizures and epilepsy. Those OSA-related medical conditions significantly impact on the human health in those susceptible individuals. On the other hand, those medical conditions are considered as risk factors not only for promoting the development of OSA but also exacerbating the severity and interfering with the treatment of OSA as well. Clinical evidence shows that effective

treatment of OSA may potentiate the efficacy of the treatment for OSA-related comorbidity. Early recognizing and diagnosing OSA and treating risk factors are crucial in effective management of OSA and OSA-related disorders.

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