OBSTRUCTIVE SLEEP APNEA SYNDROME: AN OVERVIEW

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ABSTRACT
Obstructive sleep apnea is a common disorder, generally under-recognized and hence under diagnosed. It is associated with potentially serious morbidity and increasing mortality which can be prevented by early diagnosis, modification of risk factors and proper treatment. In this review, basic and updated information of obstructive sleep apnea of interest to internists and general physicians will be discussed. This includes important definitions, epidemiology, risk factors, diagnosis, pathophysiology, complications, mortality, and modalities of treatment.

Keywords: Obstructive sleep apnea, Snoring, Daytime sleepiness, Polysomnography, CPAP

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DEFINITION
Obstructive Sleep Apnea (OSA) is a disorder defined as intermittent cessation of breathing during sleep due to periodic collapse of the pharyngeal airway.

- An apnea is defined as the cessation of airflow for at least 10 seconds\(^1\), and it is classified as obstructive or central on the basis of the presence or absence of respiratory effort (Fig. 1).
- Hypopnea (Fig. 2) is indicated by one of the following features:
  1. Substantial reduction in airflow (> 50%)\(^1\).
  2. Any reduction in airflow with oxygen desaturation of > 3%\(^1\).
  3. Any reduction in airflow with evidence of electroencephalography (EEG) arousal.
- The severity of OSA is measured by the number of apneic and hypopneic events per hour of sleep by using the apnea-hypopnea index (AHI). OSA exists when AHI is ≥ 5.
- OSA syndrome (OSAS) is restricted to patients with increased AHI (≥ 5) together with symptoms of excessive daytime sleepiness (EDS).

EPIDEMIOLOGY
Unfortunately, there is no local data available regarding the prevalence of OSA in Saudi Arabia or even in the Middle East.

Among the middle-aged North American population, the prevalence of OSA is 24% for men and 9% for women\(^2\). The prevalence of OSAS, however, is 4% among men and 2% among women\(^2,3\). For comparison, the prevalence of asthma, another common disorder is 4.5% among the population of the United States.

PREDISPOSING FACTORS
1. Obesity is the most important risk factor because it is present in approximately 70% of patients with OSA. It is one of the most important reversible factors. The underlying mechanisms are not well understood. However, increased fat deposits in tissues surrounding the upper airway may directly diminish the size of upper airway lumen. On the other hand, these fat deposits can also increase airway collapsibility by altering tissue compliance\(^3,4\).
2. Gender is also a risk factor for obstructive sleep apnea. As mentioned above, the results of community-based studies suggested a 2- or 3-fold increased risk of this disorder in men versus women\(^2\).
3. Aging is a factor in adults, with the prevalence of this disorder increasing with age. The percentage of subjects with AHI of ≥5 increases with increasing age in the case of both men and women (32% and 17%, respectively)\(^2\).
4. Menopausal status is a recently identified risk factor for OSA. In a prospective follow-up study of individuals in the Wisconsin Sleep Cohort Study, an important increase in the frequency of apnea in postmenopausal women compared with premenopausal women was reported\(^2\). This effect of menopause is not related to aging. These observations and the high prevalence of OSA in men suggest that sex hormones may influence upper airway collapsibility.
5. Structural abnormalities of upper airways indicate a predisposition for OSA and include: nasal polyps, grossly deviated nasal septum, adenoids, macroglossia (absolute or relative), low-lying soft palate, enlarged tonsils, micrognathia, retrognathia and laryngotracheal lesions (e.g. tumors).
6. Metabolic disorders such as hypothyroidism, acromegaly, and amyloidosis are the other risk factors.
7. Finally, behavioral habits have also been identified as risk factors for OSA:

- Current smokers are at a greater risk (OR 4.44) than former smokers (OR 2.29), and both are at a greater risk than never-smokers for developing moderately severe OSA. Heavy smokers (> 40 cigarettes per day) were at the highest risk of developing moderately to severe OSA (OR 40.47)[5]. This risk from smoking was found to be independent of sex, age, and body mass index (BMI). The presumed mechanism is the upper airway congestion and edema.

- Alcohol consumption suppresses pharyngeal muscle dilation activation.

**CLINICAL PRESENTATION**

The 2 cardinal symptoms of OSAS are habitual snoring and excessive sleepiness. However, both snoring and sleepiness may be denied or underreported by the patient. Snorers may be unaware of the sounds of their nightly battle to breathe, unless there is a listener to tell them. There are at least 2 problems with sleepiness as a symptom. One is that sleepiness may develop very gradually over years so that patients “forget” what normal alertness is like. The other is that sleep deprivation is so common in many societies that sleepiness is ubiquitous, and thus non-specific. Observations by someone who has seen the patient’s behavior and daytime alertness can be very helpful to the clinician.

Excessive daytime sleepiness can be subjectively evaluated using the Epworth Sleepiness Scale (ESS)[6]. This scale has been validated in several studies and is currently the most utilized subjective test of daytime sleepiness in clinical practice. A normal score is < 10[2]. Witnessed obstructive events during sleep for a habitual snorer are strong predictors of clinically important sleep apnea.

Other reported manifestations of OSA include:

- Physically restless sleep
- Night sweats
- Morning dry mouth or sore throat
- Personality change
- Morning confusion
- Cognitive impairment
- Impotence
- Morning headaches

**PHYSICAL EXAMINATION**

Examination of a middle-aged man with OSA showed that he was hypertensive, obese, had a large neck, and a structurally abnormal or “crowded” upper airway. The abnormal airway is the critical factor, so the disease is not really age or gender specific. The loci of obstruction in the upper airway are not easily accessed by the clinician while the patient is awake. Instead the clinician examines the patient for severe nasal obstruction, a low hanging soft palate and large uvula, enlarged tonsils, and/or adenoids and retrognathia. In general, men with a neck circumference of 17 inches and women with a neck circumference of 16 inches are at a higher risk of sleep apnea[3,4]. Therefore, it is important to note the patient’s neck circumference. Neck size appears to be a stronger predictor of sleep apnea than BMI, presumably because that is where additional tissue can influence the size or compliance of the upper airway. Nasopharyngeal tumors are rare but must be ruled out. Other uncommon contributory disorders include hypothyroidism, acromegaly, amyloidosis, neuromuscular disease, and vocal cord paralysis.

**PATHOPHYSIOLOGY**

This is a complex process and not completely understood; however, a simple explanation of the principles follows.

In OSA patients, the pharynx is smaller in size and more collapsible than in healthy individuals. This information is based on MRI and CT scan findings in awakened individuals. However, according to a study in which the pharyngeal airway size was assessed in patients with apnea, versus healthy controls under paralyzed, anaesthetized conditions[7,8], these findings seem to persist during sleep. Thus, patients with OSA clearly have smaller and more collapsible pharyngeal systems than those without apnea.

In addition to the difference in size and collapsibility of the upper airway, there are 2 opposing forces that normally control the patency of the pharynx (Fig. 3).

1. **Collapsing forces:**
   a) Negative intraluminal pressure created during inspiration.
   b) Positive extraluminal pressure due to fat deposition and/or a small mandible, for example.

2. **Dilator forces:**
   a) Pharyngeal dilator muscle contraction, for example, genioglossus contraction.
   b) Lung volume: increases in lung volume with inspiration tend to keep the airway open by longitudinal traction.

![Figure 3. A diagram demonstrating the two opposing forces that normally control the patency of the upper airway (collapsing and dilator).](image)
The balance between these 2 forces controls the patency of the upper airway.

In OSA patients, in whom the pharynx is smaller than that in normal individuals, as mentioned previously, it was found, using a special electromyography (EMG) technique, that the activity of dilator muscles during sleep and while awake is higher than that in normal individuals. For example, the dilator forces for OSA patients are stretched to the maximum to keep the airway patent.

During inhalation, the pressure within the pharynx becomes negative and the airway tends to be sucked closed. However, this is prevented when awake, by the action of the dilator muscles.

What happens during sleep? During sleep, muscle tone decreases throughout the body, including the dilator muscles, causing relaxation. For individuals with normal pharyngeal size, sleep relaxation would not lead to significant airway narrowing.

However, for many individuals, sleep relaxation results in considerable, but not critical upper airway narrowing during inspiration, causing turbulent flow and vibration of soft tissues (mainly the soft palate and uvula), which are the sources of the snoring noise.

In individuals with OSA in whom the pharynx is already small, the upper airway may occlude (resulting in apneas) or almost occlude (resulting in hypopneas).

The apneas will continue until the subject is woken up, probably by the struggle to breathe against the blocked pharynx.

This awakening, called an arousal, is so brief that the subject is not aware of it, but it is recorded and identified by EEG. However, sleep during a single night may contain hundreds of such arousals, which results in sleep fragmentation, and hence, day time sleepiness.

The narrowest point of the upper airway in awaked normal subjects is behind the soft palate (oropharynx). During sleep, about half of healthy individuals experience the largest increase in resistance at the level of the palate, and the other half, at the hypopharynx. Similarly, half of OSA patients have obstruction at the soft palate level, and the other half, at the hypopharyngeal level.

**COMPLICATIONS**

**Cardiovascular**

Repetitive obstructive apneas cause progressive asphyxia and a large amount of intrathoracic negative pressure, which is generated by inspiratory efforts made against a closed upper airway (Muller’s maneuver). Oxygen desaturation may stimulate the sympathetic nervous system, leading to catecholamine secretion and consequent acute systemic and pulmonary hypertension.

During apneas, bradycardia occurs initially owing to increased vegal tone during Muller’s maneuvers. At the termination of the apnea and with the decline in oxygen saturation, tachycardia result because of catecholamine release, and cyclic brady-tachy arrhythmias are common. A significant relationship between oxygen desaturation and ventricular ectopy has been reported, with a 3-fold increase in premature ventricular contractions at saturations < 60%.

Negative intra-pleural pressures are as low as -60 cm H2O during obstructed breaths increase venous return to the right side of the heart. Then, by the mechanism of ventricular interdependence, an increased right ventricular volume causes a leftward shift in the inter-ventricular septum that reduces the left ventricular compliance, volume, and stroke output. Furthermore, reductions in the intra-thoracic pressures increase ventricular after-load by increasing transmural pressure gradients for both, the right and left ventricles. These deleterious effects would be maximal at apnea termination when desaturation is greatest and heart rate begins to speed up.

It is not surprising that arhythmias occur at this point and that nocturnal angina pectoris has been reported in patients with OSAS. Effective treatment with tracheotomy or constant positive nasal airway pressure will eliminate these acute hemodynamic changes.

Chronic cardiovascular consequences of OSAS (Fig. 4) include systemic hypertension, which cannot be completely explained by the concomitant presence of obesity. Reports of decreases in systemic blood pressure after treatment of OSAS, suggest that repetitive nocturnal oxygen desaturation may eventually cause sustained diurnal systemic hypertension. Approximately 30% of patients with systemic hypertension have sleep apnea, whereas 50% or more of patients with OSA have systemic hypertension.

There is increasing evidence of the causal role of sleep-disordered breathing in the development of hypertension. The data from the longitudinal Wisconsin Sleep Cohort Study with over 700 patients were evaluated at baseline, and 4 years later with full polysomnography. Hypertension status and blood pressure were also monitored. The investigators found that baseline elevations of AHI were associated with blood pressure elevation at follow-up. This relationship persisted even after correcting for confounding variables, such as age, sex, neck circumference and BMI measurements for obesity, alcohol and cigarette use, and the presence of hypertension at baseline. There was a dose response relationship were those with the highest AHI at baseline had the greatest odds ratio of having hypertension 4 years later. Subjects with an AHI > 15 were nearly 3 times as likely to have hypertension at follow-up as those without sleep-disordered breathing.

Pulmonary hypertension in patients with OSA, if present, is usually mild. Right ventricular hypertrophy and mild pulmonary hypertension, as observed on echocardiography, may result from the repetitive effects of oxygen desaturation on the pulmonary vasculature. Right-sided heart failure and cor-pulmonale is usually not related to OSAS and requires the additional presence of daytime hypoxemia, hypercarbia, or moderately severe COPD (Overlap Syndrome).
Severe OSA has been associated with increased incidence of fatal and non-fatal coronary artery events. Sleep apnea has also been implicated in the development of other manifestations of cardiovascular disease (CVD). The Sleep Heart Health Study (SHHS) is a community-based multicenter that studies the relationship between sleep-disordered breathing and CVD in 6,424 individuals. Participants underwent overnight, unattended, polysomnography at home and were interviewed to evaluate for self-reported CVD. The population was divided into quartiles according to apnea severity, depending on AHI. The OR for the presence of any CVD was significantly elevated for the third and fourth quartiles (AHI 4.5-11, and AHI > 11, respectively). The ORs for coronary artery disease (CAD), heart failure (HF), and stroke were 1.27, 2.23, and 1.58, respectively. The increased risk persisted even after correction of age, sex, race, and obesity, presence of hypertension or hypercholesterolemia, and cigarette use. These findings are consistent with a modest to moderate effect of sleep-disordered breathing on multiple manifestations of CVD. Of note, this increased risk of CVD was observed when AHI were in the ranges considered normal or only mildly elevated.

OSA and Metabolic Syndrome

OSA now has a recognized association with metabolic syndrome and a cluster of obesity-related cardio-metabolic factors that are known to increase cardiovascular risk. For this review, the focus will be on the current evidence linking OSA with the development and worsening of type 2 diabetes mellitus (DM). OSA exhibits pathophysiologic mechanisms that may potentially contribute to the development of insulin resistance, including autonomic activation, alterations in neuroendocrine function, and direct effects of hypoxemia on glucose regulation. As well as the release of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor. Epidemiologic data from the Sleep Heart Health Study suggested that patients with mild or moderate to severe OSA have increased risks for fasting glucose intolerance after adjustment for confounding factors. A British study of 1,682 diabetic men found that OSA was prevalent in 23% of subjects and was significantly associated with type 2 DM, independent of age, BMI, and neck size. It is estimated that approximately 40% of people with OSA have type 2 DM.

At the 2008 American Diabetes Association meeting, the International Diabetes Federation (IDF) warned that “type 2 diabetes and OSA are closely related, and that both disorders have significant implications on public health and on individuals”. Studies investigating the effect of continuous positive airway pressure (CPAP) on insulin resistance and glycemic control have been conflicting. With the current evidence, the independent effect of OSA on insulin resistance is still to be confirmed.

Neuropsychological

Daytime hypersomnia is the most common complaint of patients with OSAS. This is mostly related to sleep fragmentation as a result of the frequent arousals that usually terminate the respiratory events. Neuropsychological testing shows decreases in memory, attention, and visual-motor coordination (Fig. 5). Sleep latency (the time needed for a patient to fall asleep) is reduced on objective testing, which
verifies the clinical complaint of sleepiness. As a result of daytime hypersomnolence, patients with OSA are involved in auto crashes approximately 2 to 7 times more frequently than other licensed drivers. The increase in the risk of motor vehicle accidents (MVAs) in patients with moderate to severe OSA (AHI > 34) is up to 15-fold[15]. Moreover, successful treatment of OSA with CPAP therapy for 3 years was associated with a significant reduction in the number of MVAs per year to a normal number[16]. Effective treatment of OSAS may reverse these neuropsychological consequences.

MORTALITY
There are few reported data regarding survival of OSAS. In one report, the mortality of 246 untreated OSA patients with AHI >20 was higher than of those with AHI <20 (8 years, 37% and 4%, respectively)[17]. In a review of 198 patients with OSA, Partinen et al. reported 11% five-year mortality in 127 patients who were treated only by reduction in weight[18]. Sudden death from OSA has also been reported. Between midnight and 6 AM, the frequency of sudden death from cardiac causes was significantly higher in patients with OSA (46% versus 21% in those without OSA). This difference was even more striking when those with OSA were compared to the general population (46% vs. 16%)[19]. In a more recent report, moderate to severe OSA (AHI >15/h) was found to be independently associated with a great increased risk of all-cause mortality in this community-based sample over 14 years of follow-up[20].

DIAGNOSIS
Sleep apnea is classically suspected in male patients who are obese, hypertensive, with habitual snoring and hypersomnolence.

POLYSOMNOGRAPHY
Nocturnal, laboratory-based, polysomnography (PSG) is the recommended method for diagnosing patients with suspected sleep apnea, determining the severity of the disease, and evaluating various other sleep disorders that can exist with or without OSA. Sleep physiology is recorded and the stages of sleep are determined by EEG, electrooculography (EOG), and EMG. Episodes of apnea and hypopnea are defined by a clear reduction in airflow or respiratory effort (thoracic and abdominal), often accompanied by a decrease in oxygen saturation and terminated by an arousal (an interval of 3 s or longer) in which the EEG pattern indicates that the patient is awake (although the patient is usually not aware of it). In addition, sound recordings to measure snoring and limb movements via electrocardiographic lead are monitored. Patients are often monitored with continuously by video.

Figure 5. Demonstrating OSA associated sleep fragmentation resulting in excessive daytime sleepiness and cognitive impairment.
SEVERITY OF OSAS
As per the recommendation of the American Academy of Sleep Medicine (AASM):

- Mild: AHI = 5–15
- Moderate: AHI >15–30
- Severe: AHI >30

TREATMENT
Conservative Treatment and Weight Loss
Conservative treatment strategies include the use of a lateral sleeping position, avoidance of alcohol and sedatives, and weight loss.

The frequency of apnea and hypopnea is greater with a supine sleeping position and after use of a benzodiazepine or alcohol. A 10% reduction in weight was associated with a 26% decrease in the AHI in a population-based study[24]. Hence, weight loss should be recommended for all obese patients with sleep apnea. However, weight loss is time consuming, and only a minority of patients successfully maintains weight loss. In addition, recurrence has been reported despite the absence of weight gain. As a primary treatment, weight loss should be targeted towards patients with mild-to-moderate disease, especially if they are not interested in other options.

Bariatric (weight loss) surgery is strongly considered in patients who are morbidly obese (BMI > 40) and patients with BMI between 35 and 40, who suffer from obesity-related problems (OSA, heart disease and type 2 DM). However, bariatric surgery is beyond the scope of this review and will not be discussed in further detail.

Continuous Positive Airway Pressure (CPAP)
Nasal CPAP, which prevents apnea by maintaining adequate upper airway patency, is currently the treatment of choice for OSA since many well conducted studies have proved its efficacy in reducing long-term consequences including neurocognitive, CVD complications and mortality[12,13,16,25,26]. This works by splinting the walls of upper airways using pressurized air. Kribbs and colleagues objectively evaluated the pattern of patient CPAP use by installing covert time and pressure monitors in the CPAP devices. Patients tried to use their CPAP most nights (70%) and patients succeeded in using their CPAP 4 hrs or more a night for approximately 55% of the time. Only 20% of the time they were able to use their CPAP all night. Compliance over time was stable; with use at 3 months, the same as the use after 1 month[27]. It has been shown, however, that such CPAP compliance rates may be significantly increased with early intervention, ranging from weekly telephone calls or providing written information on OSA and CPAP to intensive in-hospital and home care support[28].

The level of CPAP pressure required to maintain adequate upper airway patency during sleep is usually determined in the sleep laboratory. There are various nasal mask and nasal prong sizes and types available. Some patients may require chin straps when using nasal interfaces to prevent mouth leaks that precipitate arousal or preclude attainment of the target pressure. In addition, oronasal masks are also available for interfacing between the positive pressure device and the patient.

Over the years, there have been improvements in the machines that deliver CPAP. Some have a built-in ramp feature in which pressure is slowly increases when the patient first goes to bed. This provides a window of time at lower, albeit sub-therapeutic, pressures, which can make it easier to fall asleep. Some machines have automatic systems to determine the CPAP pressure needed to overcome various degrees of upper airway resistance during sleep, while others can deliver bi-level pressure in which the expiratory pressure is lower than the inspiratory pressure. The difference in pressure in the latter machines can also be used to assist ventilation. However, the added benefit of these features is not clear.

Indications for Treatment (see Fig. 6)
Based on the American College of Chest Physicians’ consensus statement[11], CPAP is indicated for

1. All OSA patients with AHI ≥ 30 regardless of symptoms and based on the increased risk of hypertension as evident from the Wisconsin Sleep Cohort Study data.
2. Patients with AHI of 5-30 accompanied by symptoms or documented CVD.

CPAP is not indicated for asymptomatic patients without CVD who demonstrate mild OSA[11].

Surgical Procedures
Surgery is sometimes performed even in the absence of a strictly defined anatomic abnormality. Uvulopalatopharyngoplasty (UPPP) has been used, but the outcomes have not been uniformly successful and are difficult to predict. In some cases, maxillofacial surgery has been combined with UPPP. The American Academy of Sleep Medicine does not recommend the use of laser-assisted UPPP as a substitute for surgical UPPP[29]. Therefore, it’s suggested that UPPP be considered only for patients where CPAP is not an option. This recommendation is based, in part, and upon evidence that prior UPPP reduces the maximal level of pressure tolerated by patients treated with CPAP. Additionally, it may also compromised subsequent CPAP therapy by promoting pressure leakage through the mouth.

Less invasive techniques utilizing radiofrequency tissue ablation (RFA) of the tongue base have been developed to treat sleep-breathing disorders. Early evidence suggests that reduction of palatal soft tissue using RFA is associated with little clinical improvement. RFA has the potential to improve daytime symptoms (ESS), respiratory disturbance index (RDI), but do not seem to improve lowest oxygen saturation in one meta-analysis[30].
Obstructive Sleep Apnea Syndrome: An Overview
Krayem, A.B., and Boudal, A.M.

Who should be treated?

POLYSOMNOGRAPHY

AHI <5
Daytime symptoms
None or mild
Conservative treatment

AHI, 5-30
Daytime symptoms
None or mild
Conservative treatment

AHI >30
Daytime symptoms
Moderate to severe
Check for other causes (insufficient sleep, circadian-rhythm abnormality, narcolepsy, periodic limb movement disorder)

Trial of CPAP

Figure 6. A diagram showing various treatment strategy of OSA based on AHI and daytime symptoms.

Oral Appliances

There are an increasing number of devices designed to improve upper airway patency during sleep in OSA patients. Some of these devices protrude the mandible forward and others hold the tongue in a more anterior position, away from the posterior pharyngeal wall. Although data from randomized, prospective studies on the effectiveness of oral appliances for OSA are very limited, an appliance worn during sleep may be an acceptable, but suboptimal alternative treatment to CPAP for some patients. Currently such therapy may be used in patients with mild-moderate sleep apnea [31].

Who should receive non-CPAP treatments?

1. Asymptomatic individuals with mild-moderate sleep apnea
   • Conservative measures Individuals who refuse or fail CPAP treatment
   • Oral appliances or surgery
2. Young individuals with reversible causes such as anatomical deformities
   • Surgery

SUMMARY

OSA is perhaps the most common under-recognized public health problem that requires high index of suspicion and increasing awareness. Risk factors include increasing age, male gender, snoring, obesity, systemic hypertension, upper airway structural abnormalities and excessive daytime sleepiness. ESS is a validated tool to subjectively evaluate patients with EDS that may result from fragmented sleep related to OSA and is a useful tool to screen patients with other risk factors of OSA. In the lab, PSG is currently the standard of care to diagnose and treat OSA with CPAP titration and has to be considered in high risk patients with significant comorbidities, even without daytime hypersomnolence. CPAP is the recommended treatment of choice in most patients with OSA; however, other alternate treatments can be considered on case to case bases.

REFERENCES


