Clinical Manifestations and Consequences of Obstructive Sleep Apnea

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■ Obstructive sleep apnea is a common respiratory disorder that is underdiagnosed and associated with a variety of adverse health and safety consequences. Treatment is effective in improving quality of life and reducing morbidity. This underscores the importance of considering the diagnosis in suitable patients, verifying the diagnosis, and initiating prompt, effective therapy. In this review, the risk factors, symptoms and signs, diagnosis, clinical consequences, and treatment of obstructive sleep apnea are discussed.

K E Y W O R D S

continuous positive airway pressure

diagnosis

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sleep apnea syndromes

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Obstructive sleep apnea (OSA) is a common respiratory disorder characterized by repetitive episodes of airflow cessation (apnea) or airflow reduction (hypopnea), which occur as a consequence of reduced upper airway patency during sleep. These events result in sleep fragmentation, hypoxemia, hypoventilation, and activation of the sympathetic nervous system. Obstructive sleep apnea has been associated with a variety of adverse health and safety consequences. It is estimated that 9% of middle-aged men and 4% of middle-aged women have moderate to severe OSA[1] and that its prevalence increases with age and increased body mass index (BMI).[2] In this review, the risk factors, symptoms and signs, diagnosis, clinical consequences, and treatment of OSA are discussed.

RISK FACTORS FOR OSA

Obesity, particularly indicators of central obesity such as enlarged neck circumference, is a major risk factor for OSA.[3] While the exact mechanisms for this are not entirely clear, the increased risk may be due to obesity-related alterations in upper airway structure or function, imbalances between ventilatory drive

and load, and reduction in lung volume causing a reduction in upper airway stability.[4] In a prospective population-based study of 602 middle-aged adults, obesity was found to be a significant risk factor for an apnea-hypoxia index (AHI) of 5 or higher ($P < .001$).[1] Increments of 1 SD in measures of weight and BMI were associated with odds ratios for OSA (AHI $\geq$ 5) of 2.00 (95% confidence interval [CI], 1.68–2.24) and 4.17 (95% CI, 2.89–6.04), respectively.

Obstructive sleep apnea is approximately twice as prevalent in men as it is in women; several gender-related differences might provide an explanation.[5] Women may exhibit increased upper airway dilator muscle activity, lessening the likelihood of upper airway closure during sleep. Upper airway soft tissue structures are larger in men than in women, although the reasons for this are not well understood. In addition, fat deposition (eg, lateral parapharyngeal fat pads) in the upper airway might be more significant in men because they tend to predominantly have fat distribution localized to the upper body (whereas women tend to have it distributed to the lower body). Furthermore, this disparity in prevalence may be partially accounted for by differences in respiratory control between the sexes (perhaps mediated by female hormones).

Female hormones appear to have a protective role with respect to OSA. Risk for having OSA (not accounted for by BMI, age, or other factors) has been found to increase 2- to 3-fold for postmenopausal women in comparison with premenopausal women.[6,7] Conversely, the use of high-dose exogenous testosterone therapy may worsen OSA in men.[8,9] Further research is required to better understand the mechanisms behind this, although it is generally agreed that the contribution of testosterone is independent of any upper airway–related anatomical changes.

The observed intrafamilial prevalence of OSA has led to a significant amount of research into a possible underlying genetic basis for this disorder.[10,11] Individuals are found to have steadily increasing risk for OSA with increasing number of affected relatives.[12] Several studies have shown AHI heritability to be between 30% and 35%, which suggests that one-third of the variability in this metric is explained by shared familial factors.[13,14] Patel et al[15] found that roughly 40% of the genetic variance in the AHI is attributed to obesity, which allows the majority of the genetic basis for OSA to be explained by obesity-independent factors. To date, however, no compelling genetic markers of OSA have been identified.

Both alcohol use and smoking have been found to put individuals at increased risk for OSA. Ethanol consumption before sleep significantly increases the number of hourly nocturnal apneic events,[16] even in individuals who are asymptomatic for OSA under standard conditions.[17] Kashyap et al[18] compared the smoking history of groups of patients who were diagnosed with OSA (AHI $\geq$ 10) with those who were not diagnosed with OSA (AHI $\leq$ 5), and they found current smokers to be 2.5 times more likely to have OSA than nonsmokers and former smokers combined (95% CI, 1.3–4.7, $P = .0049$). Other known risk factors include nasal occlusion,[19] endocrine disorders such as hypothyroidism[20] and acromegaly[21] (both of which may increase soft tissue size in the upper airway and/or affect respiratory control), use of benzodiazepines[22] or other muscle relaxants,[23] and upper airway structural abnormalities (such as large tonsils).

SYMPTOMS AND SIGNS

The presence of OSA is often initially suspected on the basis of the daytime experience of the patient and the nighttime experience of the bed partner. Characteristic symptoms include loud snoring, witnessed apneas, gasping at night, and nocturnal awakenings. The sleep fragmentation that characterizes OSA is linked to electroencephalographic arousals and poor sleep quality.[24] Depending on their frequency and severity, these arousals may result in excessive daytime sleepiness. The Epworth Sleepiness Scale is a validated tool for quantifying this otherwise subjective measure.[25]

DIAGNOSIS

An *apnea* is defined as the cessation of airflow for at least 10 seconds. A *hypopnea* occurs when either (1) there is at least a 30% decrease in airflow from baseline, for a minimum of 10 seconds duration, with at least 4% desaturation from baseline, or (2) there is at least a 50% decrease in airflow for a minimum of 10 seconds duration, with at least 3% desaturation or an arousal.[26] The severity of sleep apnea is usually defined by the *AHI*, which is the number of apneas plus hypopneas per hour of documented sleep. *Mild OSA* has been defined as an AHI of 5 to 15 events per hour, *moderate OSA* as an AHI of 15 to 30 events per hour, and *severe OSA* as an AHI of 30 or more events per hour.[27] The AHI correlates poorly with symptom severity,[28] and it has been questioned whether AHI is the best predictor for clinically relevant outcomes. Some believe that other indices, for example, based on degree of hypoxemia, may be more useful.[29,30]

The most effective validated diagnostic technique for OSA is overnight in-laboratory polysomnography (PSG).[31] This involves continuously recording several physiologic variables including airflow, electroencephalography, electromyography, chest/abdominal movement, and oxygen saturation, and it is usually accompanied by video and audio recordings.

Given the personnel and laboratory resources required for PSG, efforts have been made to develop and validate ambulatory diagnostic devices. In patients with high probability of OSA, verification of the diagnosis by an ambulatory study is likely sufficient to initiate appropriate therapy.[32] Many of these devices measure similar physiologic variables to full overnight PSG, but with a reduced number of signals, which allows them to be less expensive and more ambulatory.[33] For example, Ayas et al[34] found that overnight use of a wrist-worn device that measures physiologic markers of peripheral vasoconstriction and sympathetic activation in conjunction with oxygen desaturation index (number of ≥4% desaturations per hour) was a reasonably sensitive and specific means of diagnosing OSA.

CONSEQUENCES OF OSA

Quality of Life

It is well documented that quality of life is adversely affected for those with sleep-disordered breathing; the impact of undiagnosed OSA is on par with other chronic disorders of moderate severity.[35,36] Studies show that this illness may be responsible for significant psychosocial disruptions, such as divorce and impaired work performance.[37,38] Those with severe OSA experience the greatest deficits, with an odds ratio of approximately 1.5 times as those with less severe disease for having significantly impacted quality of life.[35] Quality of life of bed partners is negatively impacted as well. Bed partners report decreased sleep efficiency and continuity of sleep and experience moderate to severe sleep disturbance from patient snoring, apneic episodes, and restlessness.[39]

Safety

Obstructive sleep apnea is associated with a number of safety concerns. Excessive daytime sleepiness results in reduced vigilance and compromises safe driving practices; compared with controls, patients with untreated OSA have been shown to be 2 to 7 times more likely to have a motor vehicle crash,[40] and they are at increased risk for multiple crashes.[41] Furthermore, Mulgrew et al[42] found that motor vehicle crashes are more severe in patients with OSA than in controls and patients without OSA.

Extensive research has yet to be done on occupational risks of OSA; however, one would expect that heightened sleepiness would similarly lead to increased risk for injury in this context. Lindberg et al[43] prospectively studied 2,874 men aged 30 to 64 years who answered a series of snoring- and sleepiness-related questions. Ten years later, 2,009 participants responded to a work-related follow-up questionnaire. Multivariate analysis of results showed that, adjusting for several potential confounding factors, men who reported symptoms of excessive daytime sleepiness and snoring at baseline were at risk for occupational accidents, with an odds ratio of 2.2 (95% CI, 1.3–3.8). While this study did not use a validated method of screening for OSA, it suggests that symptomatic individuals in particular are at increased risk. Other studies[44,45] have drawn similar conclusions.

Cardiovascular Disease

Although no definitive, large, randomized controlled trials have conclusively shown that OSA increases risks of cardiovascular events, there are compelling data implicating OSA in the pathogenesis of cardiovascular and cerebrovascular diseases. Patients suffering from OSA typically exhibit a variety of physiologic and biochemical changes known to be risk factors for cardiovascular disease. These include systemic inflammation, sustained activation of the sympathetic nervous system, oxidative stress, glucose intolerance/insulin resistance, hypertension, hypercoagulability, and endothelial dysfunction.[46]

Systemic hypertension has been found to be associated with OSA independent of age, sex, and obesity and is likely a key source of heightened cardiovascular risk.[47] Indeed, the characteristically increased levels of sympathetic activation and aldosterone in patients with OSA contribute to the development of hypertension. Peppard et al[48] prospectively assessed the association between sleep-disordered breathing and hypertension in 4-year follow-up with 709 participants of the Wisconsin Sleep Cohort Study. They found a dose-response relationship between the severity of OSA at baseline and the prevalence of hypertension at follow-up, with a maximum odds ratio of 2.89 (95% CI, 1.46–5.64) for patients with moderate to severe disease (AHI ≥ 15 events per hour). Furthermore, experimentally induced OSA in dogs leads to elevated daytime and nocturnal blood pressure.[49]

Obstructive sleep apnea is also common in patients with coronary disease. Andreas et al[50] found an AHI of 10 or more in 25 of 50 patients (50% prevalence)

who were diagnosed with coronary artery disease by angiography. The results of the Sleep Heart Health Study similarly reflect a significant cross-sectional association of OSA with prevalent cardiovascular disease.[51] In-home PSG was completed for 6,424 participants, and after adjusting for multiple potential confounders, those in the upper quartile of AHI (≥11.0 events per hour) had 42% (95% CI, 13–78) greater odds of prevalence for cardiovascular disease (including congestive heart failure, stroke, and coronary heart disease) than participants in the lowest quartile of AHI (>1.3 events per hour). The analysis included adjustment for hypertension, indicating that increased blood pressure is not the only mechanism for increased cardiovascular risk in individuals with OSA. The prospective analysis of the Sleep Heart Health Study has recently been completed and results should be reported in the near future.

Epidemiologic studies have shown that patients suffering from OSA are more susceptible to experiencing incident cardiovascular events. For instance, Marin et al[52] showed that over a mean follow-up duration of 10 years, men with untreated severe OSA were at increased risk for fatal and nonfatal cardiovascular events (including myocardial infarction, stroke, coronary artery bypass surgery, and coronary angiography) compared with healthy individuals, with respective odds ratios of 2.87 (95% CI, 1.17–7.51) and 3.17 (95% CI, 1.12–7.51). In this observational study, patients treated for their OSA had a markedly reduced rate of events.

Other prospective observational studies have also confirmed that OSA is independently associated with incident cardiovascular and cerebrovascular disease.[53,54]

TREATMENT

Lifestyle

Lifestyle modification represents a proactive, effective, and potentially less-invasive means of treatment and is recommended in patients with OSA. The detrimental effects of smoking and alcohol consumption have been described earlier, and cessation in this regard would naturally lead to multiple health benefits beyond improving OSA (Table 1).

With the prominence of obesity as a risk factor for OSA, extensive research has been done to assess the degree to which weight loss improves this disorder. Various studies assessing the efficacy of nonsurgical weight-reduction programs such as very low calorie diet,[55] cognitive-behavioral therapy,[56] and dieting medications[57] have demonstrated positive results. However, forms of bariatric surgery remain the more commonly studied method of weight reduction in this context, likely due to the generally more immediate and dramatic results that this variety of procedure offers. Rasheid et al[58] compared pre- and postoperative qualitative and polysomnographic data in 11 patients undergoing gastric bypass surgery (3- to 21-month follow-up, mean BMI decreased from 62 ± 3 to 40 ± 2 kg/m^2, $P < .001$) and found significant reductions in mean Epworth Sleepiness Scale (from 14 ± 2 to 3 ± 1, $P < .001$) and AHI (from 56 ± 13 to 23 ± 7 events per hour, $P = .041$). Recently, Haines et al[59] carried out a similar study with 6- to 12-month postoperative follow-up in a larger cohort and found that mean AHI decreased from 51 ± 4 to 15 ± 2 events per hour in 101 patients undergoing bariatric surgery, with a reduction in mean BMI from 56 ± 1 to 38 ± 1 kg/m^2.

Continuous Positive Airway Pressure

Nasal continuous positive airway pressure (CPAP) therapy remains the preferred and most effective treatment of OSA.[60] It is, particularly for severe OSA, highly effective in reducing risk of motor vehicle crash[61] and improving quality of life and sleepiness.[39,62] The economic burden of untreated OSA is substantial,[63] and CPAP therapy is a cost-effective means of managing this illness.[64]

Continuous positive airway pressure therapy is delivered by a device consisting of a mask or a mask alternative worn on the face and connected with plastic tubing to a flow generator, and its use originates from research conducted by Sullivan et al[65] in the 1970s and 1980s. This apparatus creates a column of positive pressure in the upper airway that resists episodes of collapse and is titrated to the appropriate therapeutic level by a technician.

The potential for CPAP therapy to curtail the predisposition toward hypertension and cardiovascular events in OSA patients is encouraging. Continuous positive airway pressure has been found to lower blood pressure, particularly in patients with severe disease. However, the overall effect on daytime blood pressure is modest (~2 mmHg reduction in mean blood pressure).[66,67]

The primary shortcoming of CPAP therapy is poor adherence. Adherence with CPAP ranges from 50% to 75%, and subjective reports underestimate actual use.[68] One of the strongest predictors of long-term CPAP adherence is short-term adherence.[69] That is, long-term adherence with CPAP is established very early in the clinical course, suggesting that measures to improve comfort and early experience will improve long-term adherence. Common clinical complaints encountered in patients prescribed CPAP include nasal congestion, mouth leak, uncomfortable/poorly

Table 1 • OBSTRUCTIVE SLEEP APNEA TREATMENT OPTIONS

Treatment options	Pros	Cons	Determinant factors and recommendations
Lifestyle and behavioral changes	Improvement of overall health and well-being ie, cessation of smoking and alcohol consumption Weight loss may improve disease	Difficult to maintain weight loss and other changes	Recommended for all degrees of OSA: weight loss, cessation of smoking, alcohol, irritants, and hypnotic medications
CPAP	Improvement of symptoms and sequelae Highly effective	High cost Potential adverse effects: dry mouth, nasal irritation Restricted movement in bed Poor compliance Noise disruptive to bed partner Requires indefinite nightly use	For AHI > 15 Highly recommended for moderate to severe symptomatic disease
Oral appliance	Most effective in mild-moderate disease Less expensive than CPAP Decreases snoring prevalence and intensity Better compliance than CPAP	Less effective in severe disease Less effective than CPAP Excessive salivation, sore teeth, jaw discomfort Potential for orthodontic side effects Not suitable if preexisting tempomandibular joint dysfunction	Effective alternative if CPAP use is not feasible
Surgery	Immediacy of treatment if effective	Less effective for larger upper airways Significantly invasive Postoperative adverse effects and complications Retropalatal stenosis resulting in repeat OSA Poorly documented long-term effectiveness	Alternative for patients who refuse or are unable to tolerate CPAP/oral appliance Most effective in patients with smaller upper airway (soft palate/tongue size)

Abbreviations: AHI, apnea-hypoxia index; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

fitting mask, discomfort with pressure, or inadequate pressure with persistent sleep apnea. All of these potential problems, once recognized, can be easily addressed by the healthcare practitioner, suggesting that more intensive patient follow-up may improve CPAP adherence substantially.

Oral Appliance

Given the poor adherence with CPAP and other prohibitive factors related to its use (such as general discomfort, nasal obstruction, and claustrophobic tendencies), oral appliances (OAs)[70] have become increasingly popular as an effective alternative therapy. These devices modify mandibular posture, thereby altering the upper airway, and are particularly effective for patients with mild to moderate OSA. In a randomized crossover study comparing OA with CPAP therapy in 25 mild-moderate OSA patients, Ferguson et al[71] found that CPAP yielded lower AHI and a greater percentage of treatment successes than OA (3.5 ± 1.6 vs 9.7 ± 7.3, $P < .05$; 62% vs 48%, respectively). However, CPAP afforded significantly more common adverse effects and poorer patient satisfaction ($P < .005$), leading the authors to conclude that, although CPAP should be the primary form of treatment of severe symptomatic OSA, OA should be considered as an effective treatment of mild to moderate OSA.

While common side effects of OA therapy include mucosal dryness, tooth discomfort, and hypersalivation, none are significant enough to discontinue treatment; however, it is advised that patients still be followed up during therapy to minimize potential orthodontic changes.[72]

Surgical Intervention

Uvulopalatopharyngoplasty (UPPP) aims to reduce pharyngeal obstruction by surgically removing excessive distal palatal tissue while keeping proximal palatal musculature intact.[73] In a prospective study using 3-dimensional computed tomography to visualize the upper airways of 60 UPPP candidates, Ryan et al[74] found that this surgery is most effective for patients with smaller upper airways, particularly in relation to soft palate and tongue size. Overall effectiveness of UPPP has been estimated at 50%.

Uvulopalatopharyngoplasty is primarily indicated in cases in which other less-invasive interventions have failed or were refused by the patient; issues of long-term ineffectiveness,[75] postoperative side effects and complications,[76] and patient dissatisfaction[77] have called its overall usefulness into question.

The pillar implant technique was introduced as a minimally invasive, office-based procedure that uses polyethylene terephthalate implants to stiffen the soft palate to improve snoring.[78] Short-term studies have shown that pillar implant technique might be a potentially effective adjunctive procedure[79,80]; however, large randomized controlled trials are needed to establish efficacy prior to its widespread use.

Laser-assisted uvuloplasty is another brief surgical procedure that can be performed by using local anesthesia and without postoperative hospitalization. It involves using a carbon dioxide laser to remove the uvula and part of the free edge of the soft palate and is otherwise distinguishable from UPPP in that the tonsils and the pharyngeal pillars are not altered, and substantially less palatal tissue is eliminated. The current practice parameters of the American Academy of Sleep Medicine cite a paucity of evidence in support of laser-assisted uvuloplasty effectiveness in treating OSA, and as such do not recommend its use (particularly as a replacement for UPPP).[81]

SUMMARY

Obstructive sleep apnea is a highly prevalent, yet largely underdiagnosed respiratory sleep disorder. This illness is related to a number of significant health and safety risks, as well as markedly decreased quality of life. As therapy is highly effective in improving symptoms and preventing morbidity, it is of considerable importance that the clinical relevance of OSA is well-understood and managed accordingly.

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