Obstructive Sleep Apnea in Women

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Received November 26, 2019

Revised December 18, 2019

Accepted December 18, 2019

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Obstructive sleep apnea is known to be more prevalent in men. In women the prevalence varies throughout her life span as she goes through different stages; puberty, reproductive years, pregnancy and post-menopausal state. The disparity of prevalence within the lifespan of women and in comparison, to men is not only due to different pathophysiologic factors like upper airway anatomy, chemoreflexes, sex hormones but also due to under recognition of sleep disordered breathing in women due to atypical presentation and difference in polysomnographic phenotypes. This review summarizes the literature regarding sleep-disordered breathing in women, its pathophysiology, sex differences in phenotypes and implications of sex differences on management.

J Sleep Med 2019;16(2):75-80

Key Words: Obstructive sleep apnea, Sex differences, Sex characteristics, Sleep apnea syndromes, Sleep-disordered breathing.

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive collapse of the upper airway during sleep, often associated with oxygen desaturation and/or arousal from sleep. Prevalence data show that more men than women are affected by OSA even after correcting for age and body mass index (BMI) (Table 1).¹⁻⁶

Sleep apnea tends to be less severe in pre-menopausal women or women receiving hormone replacement treatment compared to untreated post-menopausal women. Likewise, severe OSA [apnea-hypopnea index (AHI) ≥ 30] is more prevalent in middle-aged men and elderly women.^{7,8} Thus, variations in the physiological mechanisms that impact the manifestation of the symptoms linked to sleep disordered breathing (SDB) is likely sex hormone dependent. Sex hormones may lead to differences in the upper airway function and respiratory stability. In addition, women and men may present with disease differently. The limited data available suggest that although the prevalence and severity of OSA may be lower in women, the consequences may be similar or worse, with women suffering greater risk for hypertension and endothelial dysfunction, as well as anxiety and depression. Therefore,

treatment options should be specifically considered in men and women in order to provide best outcomes in women.

Recognition, presenting symptoms, and healthcare utilization

Factors contributing to sex differences in the prevalence of SDB include variations in the reporting of symptoms in men compared to women. Snoring and excessive daytime sleepiness are considered primary hallmarks of sleep apnea. Our screening tools (e.g. Stop Bang, Epworth Sleepiness Scale) also target these typical symptoms which are reported less frequently by women compared to men experiencing a similar degree of SDB.⁹ Women are more likely to report non-specific symptoms of SDB including headache, fatigue, depression, anxiety, sleep onset insomnia and sleep disruption.^{3,4} A population-based sample found that up-to 40% of women with an AHI >15 /h did not report any of the classic OSA symptoms (e.g. snoring, witnessed apneas, and day time sleepiness).⁷ These typical symptoms may be deemed less socially acceptable by females, and as a result are underreported. Atypical symptom presentation results in fewer referrals of women to a sleep clinic, delay in diagnosis, and this leads to increased health care utilization.^{5,6,10} Additional assessment tools, including fatigue, may be necessary to diagnose sleep apnea in women. Hence, we need more comprehensive and specific screening tools for women in general, and likely in different age-groups of women.

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Table 1. Prevalence estimates of moderate to severe OSA in men and women in the general population

	Age (years)	Population	Moderate-severe OSA (AHI ≥ 15 /hr)	
			Males (%)	Females (%)
Young et al. ¹	30–60	USA	9	4
Heinzer et al. ²	40–85	Switzerland	50	23
Durán et al. ³	30–70	Spain	14	7

Different definitions of AHI, and different diagnostic tools were used to define OSA. Please refer to the individual studies for these specifics. OSA: obstructive sleep apnea, AHI: apnea-hypopnea index

Pathophysiology

Airway anatomy

There are many factors that contribute to alterations in airway caliber leading to recurrent pharyngeal obstruction during sleep. These include size and stiffness of the pharyngeal lumen, and the pressure gradient across the pharyngeal wall. Differences in properties of the upper airway exist between men and women, and could provide explanation for the dissimilar prevalence.¹¹ For example the pharyngeal airway in healthy men is longer compared to women independent of height, and a longer airway tends to collapse more.^{11,12} Similarly in men thickening of the soft tissue on the lateral walls may increase the susceptibility of airway collapse by increasing extraluminal and reducing intraluminal pressure.^{13,14} Sleep apnea is more severe in men compared to women matched for BMI.¹⁵ Consequently, for a given severity of sleep apnea women tend to be more obese than men. One potential explanation for this difference is the fat distribution between the sexes. For the same BMI, men tend to have higher mean body weight, free fat mass, and neck circumference compared with women.¹⁴ Upper airway fat distribution in males tends to be particularly in the posterior tongue, which is important in the pathogenesis of OSA.⁴

Ventilatory control and chemo reflex properties

Alongside anatomical differences, variation in neurochemical control of chest wall and upper airway muscle activity contributes to sex differences in the prevalence of sleep-disordered breathing.

The ventilatory response to changes in chemical stimuli (i.e. hypoxia and hypercapnia) is an integrated response of peripheral and central chemoreflexes. The change in ventilation as a function of the change in the partial pressure of end-tidal carbon dioxide (PETCO₂) is a measure of chemoreflex sensitivity (i.e. a steeper slope indicates higher sensitivity).^{16,17} Chemoreflex sensitivity during sleep is often measured by obtaining the slope of the decrease in ventilation that occurs in response to step wise reductions in carbon dioxide (CO₂). The chemoreflex threshold, which is typically referred to as the apneic threshold during sleep is the point at which ventilation ceases as a consequence of reductions in PETCO₂.^{18,19} The

CO₂ reserve is the difference between baseline levels of PETCO₂ and the PETCO₂ at which ventilation is abolished. Low CO₂ reserve promotes breathing instability, because minor increase in ventilation will drop the PETCO₂ below the apneic threshold causing apnea.²⁰ Hence high chemoreflex sensitivity and decreased CO₂ reserve during sleep will promote apnea. There are sex differences in these parameters contributing to the variability in prevalence of SDB. Zhou et al. showed during sleep chemoreflex sensitivity to CO₂ is greater in men compared to women.²¹ Similar findings were observed in other studies, however during wakefulness, and not sleep.^{22–31} Mixed findings have been reported in terms of sex differences in hypoxic ventilatory response.^{24,25,28}

Respiratory plasticity

Respiratory plasticity is defined as a persistent change in the neural control system based on prior experience. Plasticity may involve structural and/or functional alterations (most commonly both) and can arise from multiple cellular/synaptic mechanisms at different sites in the respiratory control system. In sleep apnea there is recurrent intermittent hypoxia which initiates at least two forms of respiratory plasticity; progressive augmentation of the hypoxic ventilatory response and long-term facilitation of respiratory motor output (i.e. sustained increase in respiratory motor output (hypoglossal and/or phrenic) that persists even in normoxic condition) following exposure to intermittent hypoxia.^{32–36} This can contribute to breathing instability during sleep and indeed supports the findings that apnea severity increases from the beginning to end of the night in individuals with sleep apnea.^{37–41} These ventilatory responses to CO₂ after episodic hypoxia are seen to be worse in men compared with women.²⁶

Hormones

It has been reported that women with clinically significant SDB have lower levels of estradiol and/or progesterone when matched for age, menstrual cycle phase or post-menopausal status.⁴² Additionally, the prevalence of sleep apnea in post-menopausal women that do not receive hormone replacement therapy is significantly greater compared to those who receive hormone replacement therapy.⁴³ There are conflicting findings on the potential impact that estrogen/progesterone

has on ventilatory sensitivity to hypercapnia and hypoxia.⁴⁴⁻⁴⁷ Rowley et al. supported that estrogen/progesterone decrease the apneic threshold to CO₂ and the sensitivity to hypercapnia or hypoxia, leading to decrease in breathing instability, hence explaining the fact that sleep apnea is less prevalent in menstruating females.⁴⁴

The PETCO₂ that demarcates the apneic threshold in premenopausal women is further from baseline compared to that of post-menopausal women. Likewise, treatment with medroxyprogesterone acetate and estrogen leads to increased difference between the apneic threshold and baseline PETCO₂ in post-menopausal women (i.e. greater CO₂ reserve).

Female sex hormones also have a protective effect on upper airway patency. This was supported by findings seen in postmenopausal female volunteers that showed activity of the genioglossus muscle significantly increased after 2 weeks of hormone replacement therapy,⁴⁸ potentially explaining the marked increase of prevalence and severity of SDB in women after menopause.^{43,49,50}

Pregnancy is associated with an increase in the ventilatory sensitivity to hypoxia and hypercapnia.⁴⁵⁻⁵¹ The increase in sensitivity is due at least in part to the effects of estrogen and progesterone on the carotid body.⁵¹ Pregnancy is a state of increased risk for OSA despite increased sex hormones since hormonal changes may lead to other risk factors such as a larger neck circumference or naso-oropharyngeal edema.⁵²⁻⁵⁶ Anatomical changes related to pregnancy also contribute to OSA risk. For example, a growing uterus leads to elevation in the diaphragm with decrease in functional residual capacity.

Finally, increased prevalence of sleep apnea is reported in women with polycystic ovarian syndrome, which is characterized by elevated testosterone levels, compared to reproductively healthy women. Correlation is seen between the AHI and serum testosterone and unbound testosterone in women with polycystic ovarian syndrome.^{13,57-59}

OSA Phenotypes

The main metric for capturing SDB has been coined to be the AHI. However, there are likely various phenotypes of SDB with differential impact on clinical outcomes. The AHI is greater in men in non-rapid eye movement (NREM) sleep and particularly in supine position.⁶⁰ In women, AHI is equivalent if not greater in rapid eye movement (REM) sleep, when age and BMI are controlled.⁶¹⁻⁶³ Since NREM sleep forms the bulk of the total sleep time, this can contribute to overall increased prevalence of sleep apnea in men compared to women.^{62,64,65} Also many women remain underdiagnosed and under treated if their total AHI is mild or <15/hr even though there is greater REM AHI. Given recent data showing adverse cardiovascular

outcomes due to REM-OSA (independent of NREM-OSA), ignoring this metric when diagnosing disease or for insurance reimbursement, may result in under-treatment of at-risk women who have greater proclivity for SDB during REM sleep.

Other manifestations of SDB in women that may get ignored as they do not qualify for frank apneas or hypopneas during polysomnography is upper airway resistance syndrome.⁶⁶⁻⁶⁹ The underlying characteristic of upper airway resistance syndrome is progressive upper airway narrowing and flow limitation. Sex differences in terms of load responsiveness or central breathing stability may serve to mitigate breathing instability and prevent the development of obstructive or central apnea respectively in women.^{12,21} Hence this upper airway resistance causing high work of breathing and recurrent arousals has been shown to translate into symptoms of non-restorative sleep, daytime fatigue and depression but its effect on other clinical outcomes remain to be studied.⁷⁰

Sleep position has only a small effect on OSA in women, as reflected by the low prevalence of posture-dependent OSA (supine predominant OSA) in women.⁶² Polysomnographic data show that women have shorter apnea events and less severe oxygen desaturations than men.¹⁵ Another interesting finding is that women are symptomatic at lower AHI cut-off values compared with men with the same AHI.⁷¹ Females with an AHI of 2–5/h had a similar level of symptoms to men with an AHI of ≥ 15 /h. It is possible this may be due to more symptomatic effects of REM sleep disruption.⁷²

Clinical Implications

Clinical trials on consequences of OSA mostly focus on the male population, and only recently have studies looked at female OSA patients.⁷³ Greenberg-Dotan et al. found that women with OSA were more likely to have a comorbid condition like cardiovascular disease and diabetes.⁷⁴ Another study showed that women with OSA were more likely to develop dementia and cognitive decline. Correlation was also seen between cognitive decline and increased oxygen desaturation during apneic and hypopneic events in women.⁷⁵ Increased brain white matter changes have been seen in women with OSA compared to male with OSA and is postulated to be responsible for the poor quality of life reported by women.⁷⁶

Overall there is scant data on OSA outcome in female patients, but the available data suggests that long-term consequences of untreated OSA are equal if not worse in women.⁶³

Treatment

Sex differences in treatment response for OSA have not been well studied. The limited data indicate that usage is simi-

lar between males and females.^{77,78} The positive airway pressure (PAP) requirements however seem to be higher for males than females, after adjusting for baseline OSA severity and BMI.^{79,80} No significant difference has been observed in terms of types of interface used or satisfaction with mask treatment in males and females.⁸¹ Studies are ongoing to determine the efficacy of PAP devices that have algorithms targeting female-specific characteristics. A randomized, double-blind, crossover clinical trial found this modality to be as effective as standard continuous PAP.⁸² Non-PAP treatments have rarely been studied in the female-specific population. Weight loss has been seen to be more beneficial for males than females based on the fat distribution in the upper airway of males.⁸³ Mandibular advancement devices have been shown to be more successful in females with mild OSA than males likely due to less fat distribution in upper airway in females.⁸⁴ However, more research is needed in these areas to promote personalized therapy.

Conclusion

As our understanding improves in the area of sex differences in pathophysiology, symptoms presentation and disease manifestation, we need to develop better screening and diagnostic tools for OSA in women, as well as better understand sex-related phenotypes of SDB.

Acknowledgments

None.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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Author Contributions

Christine HJ Won contributed to conceptualization and editing. Samia Ayub contributed to data curation and writing.

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