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Menopause and Sleep Apnea

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Highlights

- Specific individual evaluations, including of menopausal status, are needed to better characterize sleep-related breathing disorders and to optimize early treatment.
- The mechanisms through which menopause may influence the development of obstructive sleep apnea are not fully understood.
- The present work analyzes the relationship between breathing patterns during sleep and gender, in particular exploring the potential role of menopausal status.

ABSTRACT

Obstructive sleep apnea (OSA) is a chronic and common adult disorder characterized by recurrent episodes of upper-airway obstruction and reopening during sleep. OSA is associated with intermittent hypoxia, sympathetic overactivity, oxidative stress and high cardiovascular mortality and morbidity. It is known to be more common in men than women, partly due to differences in anatomy and functional respiratory components. There are also gender differences in reported symptoms, leading to potential under-diagnosis in females. This gender difference tends to decrease after menopause, demonstrating a role of menopausal status itself in OSA phenotypes. Aging, fat mass distribution, sex hormones and upper-airway collapsibility are postulated to play a

major role in these findings. This review focuses on the most recent studies exploring gender differences in the prevalence, pathogenesis and clinical features of OSA. It discusses the role of menopause in this, and explore the underlying pathophysiological mechanisms.

Keywords: menopause; gender; sleep apnea; sleep-related breathing disorders

INTRODUCTION

Obstructive sleep apnea (OSA) is the most common form of sleep disordered breathing (SDB). OSA is characterized by recurrent collapses of the upper airway during sleep and it is associated with intermittent hypoxia, sleep fragmentation, surges of sympathetic tone, and oxidative stress, finally resulting in increased cardiovascular risk and excessive daytime sleepiness. The prevalence of OSA has been reported to be 22% among men and 17% among women[1]. Women, though, are less likely to report typical OSA symptoms such as loud snoring, excessive sleepiness, and choking during sleep. Conversely, women often complain of insomnia, fatigue, headache, mood disorders and lack of energy [2, 3], which may delay the diagnosis of OSA. Female gender is also associated with particular polysomnographic features. OSA is generally less severe in women, who also have a higher prevalence of REM-related apnea events, a lower prevalence of positional OSA and a predominance of hypopneas [4].

Although it is known that, in the general population, OSA is more common in men than women[1], this difference tends to become less pronounced with aging. A significant increase in the prevalence of OSA is seen in women after menopause, as shown in Figure 1 [5]. Menopause is characterized by several changes in endogenous hormones due to a depletion of ovarian follicles, starting at about 47 years of age. Progesterone and estrogen levels gradually decline across the menopausal transition, in association with some typical emerging symptoms, including vasomotor symptoms (hot flashes and sweating), sleep disturbances and mood alterations[6]. Several sleep disorders, such as restless legs syndrome, insomnia and periodic limb movements, increase in prevalence during the menopausal transition [7]. Among these, OSA is of particular importance due to the OSA-related increase in cardiovascular risk (higher incidence of systemic arterial hypertension, heart failure, myocardial infarction, diabetes and stroke) [8]. For the health of older women, it is important to understand whether menopause represents a risk factor for OSA and its complications, and if so why.

METHODS

The present work is a narrative review of the literature on the specific topic of menopause and sleep apnea. A PubMed search was performed with the following terms: sleep apnea, women, and menopausal status. Further articles were obtained and evaluated from citations in relevant articles.

PREVALENCE AND SEVERITY OF SLEEP APNEA IN MENOPAUSE

The effects of gender and menopausal status on OSA determinants and comorbidities have been recently analyzed by Heinzer et al. in a population of 2121 unselected subjects [5]. As shown in Figure 1, the prevalence of OSA was higher in men than in women, and in post-menopausal versus

pre-menopausal women [5]. Considering moderate to severe sleep apnea only, defined as an apnea-hypopnea index (AHI) >15/h, the prevalence of OSA was 50% in men, 23% in women, 9% in pre-menopausal women and 30% in post-menopausal women [5].

The specific association between menopausal status and sleep apnea, both obstructive and central, was investigated by Young et al. in a population-based sample of 589 women enrolled in the Wisconsin Sleep Cohort Study [9]. After adjusting for age, BMI (body mass index) and smoking, peri- and post-menopausal women were 2.6 times more likely to have an AHI of 5 or more per hour of sleep and 3.5 times more likely to have an AHI of 15 or more per hour of sleep, compared with pre-menopausal women [9] (Figure 2). In the same sub-cohort, Mirer et al. analyzed more specifically the differences between peri- and post-menopausal women, performing polysomnography every 6 months to track trends in AHI [10]. Transition from pre-menopause to post-menopause was associated with increased severity of sleep apnea, after adjusting for age and changes in body habitus. Among women who had begun peri-menopause, each additional year in menopause was associated with a 4% greater AHI (95% confidence interval (CI) 2-6%). These results provide evidence for an exposure–response relationship between progression through menopause and sleep apnea: mean AHI values in peri-menopause were between the AHI values in pre-menopause and those in post-menopause[10].

The same conclusion was reached in a study of 535 Brazilian women, in which those in post-menopause presented more severe sleep apnea than those in pre-menopause[11]. Moreover, sleep fragmentation was more evident and the percentage of rapid eye movement (REM) sleep was lower after the menopause.

POTENTIAL CAUSES

Increased age, changes in the quantity and distribution of body fat, differences in endogenous sex hormones, such as estrogen and progesterone, and pharyngeal dilating muscle activity are postulated to play a role in the observations noted above.

Age

Given that menopause is an aging process and because age is a powerful predictor of sleep apnea, it is crucial to distinguish whether menopause itself is associated with greater risk of sleep apnea or whether it simply reflects an aging process similar to that in men. Cairns et al. analyzed the impact of age on the increased risk of sleep apnea [3]: middle age (≥ 45 years) was a better predictor of moderate to severe OSA in women (odds ratio (OR) 4.7) than in man (OR 3.0) [3], suggesting a non-significant role of age, alone, as a confounding factor in this context. Similar results are supported by the association between early age at menopause and OSA risk, with a hazard ratio of 1.5 if the age at menopause is under 40 years [12]. These observations support the only partial role of aging in the increased prevalence of OSA after menopause.

Fat mass

Obesity is often associated with OSA in middle aged/young males, as they are more likely to present visceral than peripheral adiposity, typical in women of the same age group. Visceral adiposity provokes OSA via excessive fat deposition in the parapharyngeal space and the increased work of breathing. It is already known that post-menopausal women tend to have higher fat mass and a higher fat deposition in the upper body and trunk area than prior to menopause [13][14]. In

a cross-sectional study, waist circumference has been shown to be associated with moderate to severe OSA in post-menopausal women after adjusting for potential confounding factors [15]. Although post-menopausal women had a higher BMI, neck circumference and waist-to-hip ratio than pre-menopausal women, Heinzer et al. did not find a direct causal relationship between obesity and sleep apnea [5]. Therefore, the literature supports at least a partial role of menopause-related fat mass distribution in the etiology of OSA.

Hormonal status

The greater prevalence of SDB after menopause might be due, in part, to loss of the protective effects of female reproductive hormones. In fact, comparing sex hormone levels in women with and without clinically significant SDB, post-menopausal women with an AHI>10 and typical SDB symptoms had lower levels of progesterone, estradiol, and 17-OH progesterone than those without SDB, after matching for age and time-point after the last menstrual cycle[16]. Early onset of menopause as a result of surgical intervention was associated with a 26% higher risk of developing OSA compared with women who had experienced natural menopause, which suggests the important role of early and abrupt cessation of hormone production[12]. This study and others have indicated a possible role of hormone replacement therapy (HRT) in the treatment and prevention of OSA, but the results are controversial. While some earlier experimental studies supported the use of HRT in SDB risk reduction, more recent trials did not confirm these effects[5, 17, 18]. In a placebo-controlled randomized trial, although short-term treatment with medroxyprogesterone acetate ameliorated nightly oxygen saturation and carbon dioxide levels, OSA itself did not improve[17]. These effects are in line with the stimulant action of progestin on respiratory control [18]. In the study by Heinzer et al., although post-menopausal women on HRT had a statistically significant lower mean AHI than women not using HRT, the absolute difference in AHI was only 2, which would not be clinically relevant [5]. Given the inconsistent findings on the effect of HRT on SDB, more needs to be understood about the mechanisms underlying the effects of sex hormones on SDB and related cardiovascular risk. Experimental models have recently shown that the attenuation of intermittent hypoxia by estradiol protects against SDB-triggered cardiopulmonary dysfunction [19].

Pharyngeal dilating muscles

Sex hormones may affect the function of the pharyngeal dilator muscles, influencing airway collapsibility and respiratory control [18]. In fact, the patterns of both airway obstruction and muscle activity have been shown to be different between pre-menopause and post-menopause[18, 20]. Endoscopy shows a tendency to more severe airway obstruction in post-menopausal women than in pre-menopausal women, especially at retropalatal and retro-lingual sites [20]. In awake women, the activity of the genioglossus muscle, one of the most important pharyngeal dilating muscles, was lower after menopause than before[18]. Moreover, in a subgroup of 8 women, genioglossus activity increased significantly after 2 weeks of HRT, confirming the potential role of reproductive hormones in the increased risk of OSA in post-menopausal women[18].

CONCLUSIONS

The evidence supports the on-going “phenotyping theory” in OSA, suggesting that a “general” comparison between individuals on the basis of physical characteristics such as sex or age does

not necessarily provide an accurate picture of SBD etiology and features. Conversely, specific individual evaluations, including OSA risk factors and quantification of cardiovascular load, are needed to better characterize SBD and to optimize early treatment. We have focused on menopausal status in women, which also needs to be taken into account. Although the literature shows notable differences in SBD prevalence and symptoms between pre- and post-menopausal women, the mechanisms through which menopause may influence the development of OSA are not fully understood.

Practice points

- Menopausal status in women needs to be taken into account during clinical evaluation for OSA risk.
- Menopausal status needs to be taken into account in the diagnosis and treatment of OSA.

Research agenda

Further studies are needed to better understand the mechanisms underlying the role of menopause in the etiology of the OSA, including:

- effects of reproductive hormones on respiratory control
- effects of reproductive hormones on upper-airway anatomy
- effects of reproductive hormones on upper-airway muscle function.

Contributors

All three authors contributed equally to the literature analysis and the drafting of the review.

Conflict of interest

The authors declare that they have no conflict of interest.

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Provenance and peer review

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Figure 1: Prevalence of sleep-disordered breathing by in men and women, and by menopausal status in women. Reprinted from: R. Heinzer, H. Marti-Soler, P. Marques-Vidal, N. Tobback, D. Andries, G. Waeber, M. Preisig, P. Vollenweider, J. Haba-Rubio, *Impact of sex and menopausal status on the prevalence, clinical presentation, and comorbidities of sleep-disordered breathing*, *Sleep Med* 51 (2018) 29-36 [5]

Figure 1

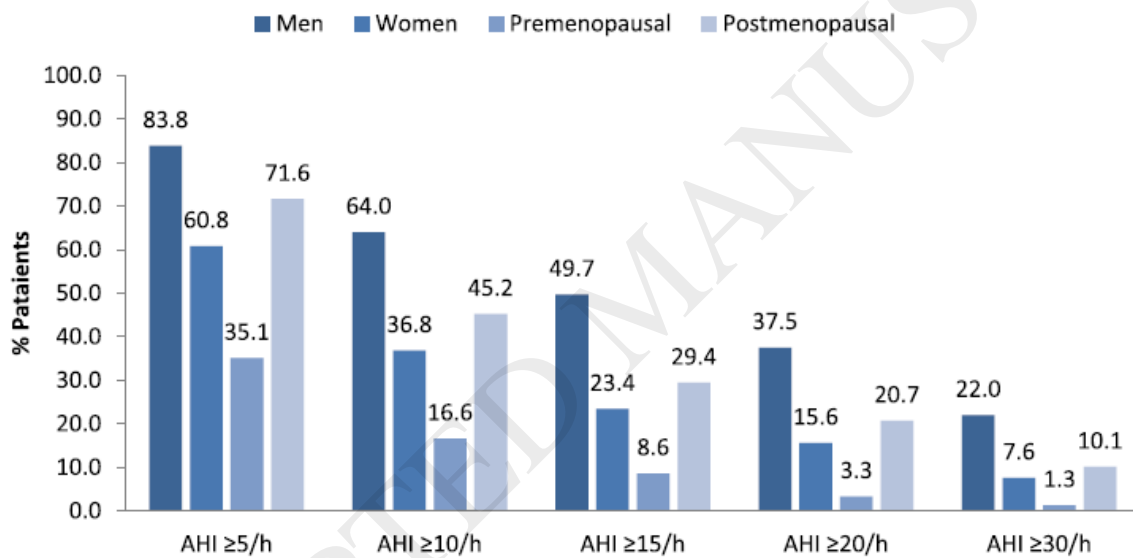


Figure 2: Prevalence of sleep-disordered breathing indicated by apnea–hypopnea index (AHI) of 5 or greater for premenopausal women and perimenopausal plus postmenopausal women by age. Values represent a 5-year moving average. *Reprinted with permission of the American Thoracic Society. Copyright © 2018 American Thoracic Society. Cite: T. Young, L. Finn, D. Austin, A. Peterson, Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study, Am J Respir Crit Care Med 167(9) (2003) 1181-5. [9] The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society*

Figure 2

