

Gender-related Differences in the Obstructive Sleep Apnea Syndrome

Geschlechtsspezifische Unterschiede beim Obstruktiven Schlafapnoesyndrom

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Abstract

The obstructive sleep apnea syndrome (OSAS) is associated with increased morbidity and mortality. Epidemiological studies suggest a two-fold higher prevalence of OSAS in men than in women. Differences in pharyngeal collapsibility and central respiratory drive may play a significant role in the gender-specific pathogenesis. Compared with their male counterparts, female patients experience OSAS at an older age (postmenopausal) and with higher body-mass-index. Female OSAS patients furthermore more frequently report atypical symptoms, such as insomnia, depression, and/or restless legs, and thus are less likely to be referred for the evaluation of sleep disordered breathing. Knowledge about these distinct gender-related differences in clinical features of OSAS may contribute to an increased awareness, improved diagnosis and its therapeutic consequences.

Zusammenfassung

Das obstruktive Schlafapnoesyndrom (OSAS) ist eine Erkrankung mit hoher Morbidität und Mortalität. Epidemiologischen Studien zufolge sind Männer doppelt so häufig von OSAS betroffen wie Frauen. Unterschiede bei pharyngealer Kollapsibilität und zentraler Atemregulation scheinen eine wesentliche Rolle in der geschlechterspezifischen Pathogenese zu spielen. Im Vergleich zu Männern mit OSAS tritt das Syndrom bei Frauen meist im späteren Lebensalter (postmenopausal) und bei höherem Body-Mass-Index auf. Frauen mit OSAS berichten häufiger über atypische Symptome, wie zum Beispiel Insomnie, Depression und/oder Restless Legs, und werden daher im Vergleich zu Männern seltener einer Abklärung zur Diagnostik von Schlafatemstörungen zugeführt. Das Wissen um die hier dargestellten geschlechterspezifischen Unterschiede in Klinik und Ausprägung des OSAS könnte zu einem erhöhten Bewusstsein für das Krankheitsbild bei Frauen und zu einer Verbesserung von Diagnostik und den entsprechenden therapeutischen Konsequenzen führen.

Introduction

The obstructive sleep apnea syndrome (OSAS), a disorder characterized by episodic collapse or narrowing of the upper airway during sleep, is an important cause of morbidity and mortality [1]. Closure of the upper airway results in hypoxemia which is accompanied by incremental breathing efforts that culminate in arousal, re-opening of the upper airway and brief hyperventilation followed by return to sleep. Patients suffering from this condition usually exhibit more than 15 apneic (complete flow limitation) or hypopneic (partial flow limitation) events during sleep. Repetitive arousals due to these events result in sleep fragmentation and increased sympathetic activity

[2]. Sympathetic overactivity in combination with recurrent hypoxemia places OSAS patients at an increased risk of cardiovascular morbidity and mortality. Typical symptoms include snoring, excessive daytime sleepiness, and cognitive dysfunction. Gold standard of OSAS treatment involves continuous positive airway pressure (CPAP). CPAP alleviates symptoms of OSAS, improves quality of life, and reduces cardiovascular risk [3].

There are several known risk factors for OSAS such as obesity, increased age, cigarette smoking, and craniofacial abnormalities. Male gender is also recognized as an independent risk factor for the development of the syndrome. Epidemiological studies suggest a two to threefold higher prev-

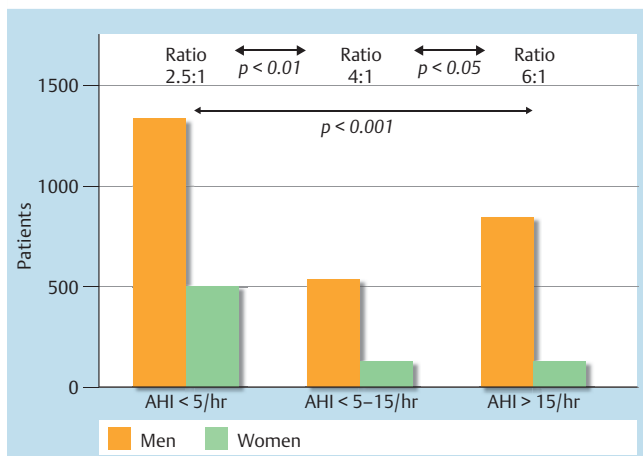


Fig. 1 Gender-related differences in Apnea-Hypopnea-Index in a large clinical population sample of patients who underwent overnight polysomnography (Valipour et al, Sleep 2007) [9].

absence of OSAS in men than women [4–6]. The ratio of men to women in the sleep laboratory sample, however, is higher than in the community and is typically 6:1 or greater (► **Fig. 1**) [7]. Women who are diagnosed with the syndrome usually suffer from less severe sleep apnea, have a higher prevalence of apneic events during REM sleep, and are at average older than their male counterparts [8,9] (► **Tab. 1**). Furthermore, compared with men, women have significantly higher health care consumption and report significantly lower perceived health status [10]. These factors suggest distinct gender-related differences in the mechanism, severity and clinical presentation of OSAS. The present article will review some of the evidence related to these gender-specific aspects in sleep apnea with particular emphasis on upper airway characteristics, the effects of sex-hormones, and the importance of gender-related differences in the clinical presentation of OSAS.

The upper airway

A variety of reports investigated the influence of gender on upper airway characteristics and gender-related differences in upper airway collapse susceptibility. Guilleminault and co-workers, used cephalometric measurements in men and women with OSAS in order to demonstrate that women had shorter soft palates but equal posterior airway space when compared with men with similar sleep disordered breathing severity [11]. Another report studied upper airway dimensions in a large group of markedly obese male and female subjects using acoustic reflection technique [12]. Surprisingly, both the oropharyngeal junction and pharyngeal cross-sectional area were significantly larger in male than female patients. Rowley and co-workers similarly measured upper airway cross-sectional area in addition to retro-palatal compliance in wakefulness and non-rapid eye movement sleep in equal number of men and women without sleep apnea [13]. Consistent with the previous observation, cross-sectional area tended to be larger in men compared with women in both wakefulness and sleep. After correction for body surface area, however, there were no significant differences in these measurements. Similar findings were observed for retro-palatal compliance, which was higher in men during both wakefulness and

NREM sleep, but similar in men relative to women after correction for neck circumference. Whittle and co-workers used MRI studies to investigate gender-related differences in fat deposition in the regions prone to collapse during sleep [14]. The authors found that the pattern of fat deposition in the neck close to the upper airway differed between men and women, however, it appeared that the larger soft tissue mass in the male neck was mainly due to soft tissue other than fat. The major anatomical structures in the anterior segments inside the mandible at the palatal level, which showed greater fat deposition in men, are the soft palate and the upper part of the tongue. When analysing the cross sectional areas of tissue and fat in these structures in the medial sagittal plane, the authors found no sex difference in fat deposition [14].

On the basis of the above mentioned reports of a larger pharynx in men, one would predict that men have a lower predisposition of upper airway collapse than women, but the opposite is true. In fact, there is a relationship between pharyngeal size and severity of sleep apnea in men but not in women, indicating that OSAS in women is less associated with pharyngeal anatomic size rather than other factors, such as alterations in upper airway tone and/or tissue elasticity [12].

Upper airway tone is mainly driven by upper airway dilator muscle activity, which is higher in patients with OSAS than in normal subjects during wakefulness [15]. During sleep the loss of muscle activation results in increased pharyngeal resistance and upper airway collapse [16]. Few studies with inconsistent results have examined the influence of gender on upper airway tone, some during wakefulness only, others during sleep, and few during wake to sleep transition. White and colleagues demonstrated higher pharyngeal resistance during wakefulness in healthy men in one study but similar waking pharyngeal airway resistance between men and women in another report [17,18]. During the wake-to-sleep transition, Thurnheer et al. observed no significant gender-related difference in upper airway resistance [19]. Trinder and co-workers extended these findings as they have similarly observed no gender-related differences in upper airway resistance during sleep transition, however, significantly higher upper airway resistance in men during NREM sleep, thus suggesting that the male pharyngeal airway is considerably more collapsible than the female pharynx during established sleep. [20]. Finally, Pillar and co-workers have shown that the greater increase in pharyngeal resistance in men was not due to gender-related differences in central respiratory drive [21]. As most of the literature that examined gender-related differences in upper airway pathophysiology was conducted in subjects without sleep apnea, it remains difficult to draw definite conclusions on the effect of gender on upper airway tone in patients with OSAS.

The role of hormones

Gender-related differences in the prevalence of OSAS decrease as age increases. The latter phenomenon is largely due to a significant increase in the prevalence of sleep disordered breathing after menopause [22]. In one of the earlier studies, Block and co-workers investigated nocturnal breathing in pre- and postmenopausal women. The authors showed a significantly higher prevalence of apneas, hypopneas, and episodes of oxygen desaturation in postmenopausal women [23]. Dancey and co-workers extended these findings as they have demonstrated that both prevalence and severity of sleep apnea increased in women after

menopause, even after controlling for BMI and neck circumference [24]. The definition of menopause in both studies, however, was not based on objective measures of menopausal status.

In the Wisconsin Sleep Cohort, Young et al. used cross-sectional and longitudinal data on menstrual history, hormonal replacement therapy use, gynecologic surgery, and serum follicle-stimulating hormone levels to classify women on stage of menopause and years of postmenopause [22]. Menopausal transition in that report was associated with an increased likelihood of sleep disordered breathing irrespective of the AHI cut-off after controlling for age, body, habitus, and several lifestyle factors. Compared with premenopausal women, postmenopausal women in that report were 3.5 times more likely to have OSAH.

The overall lower prevalence of sleep apnea in women before menopause suggests a protective effect of female sex hormones on upper airway patency and/or ventilatory drive. In fact, Popovic and co-workers observed that the activity of the genioglossus muscle during wakefulness was lower in postmenopausal women than in premenopausal women, yet significantly increased in eight postmenopausal women after 2-week treatment with conventional doses of replacement hormones [25]. Vice versa, testosterone levels have been shown to be associated with upper airway collapsibility in patients with sleep apnea and there have been reports of sleep apnea in women by exogenous administration of testosterone [26,27]. These findings suggest sex hormone dependence of upper-airway dilator muscle activity. Progesterone and possibly estrogen may also play a role in the regulation of the ventilatory drive, raising the hypoxic ventilatory response and stimulating ventilation in conditions of hypoventilation [28, 29]. Declining levels of these hormones might therefore predispose some women to sleep-disordered breathing by lowering the ventilatory drive to the upper airway, which could lead to an imbalance between forces that compromise upper airway patency and counteracting forces, however, much more study is required to understand the complex relationship between sleep apnea and hormonal function.

On the basis of the above mentioned effects of sex-hormones, one might speculate that replacement therapy with female hormones may alleviate sleep disordered breathing. Studies that systematically investigated the effects of hormone replacement therapy in women have provided inconsistent results. While some reports have shown that administration of estradiol, estrogen, or progestin to postmenopausal women resulted in a reduction of time awake, an increase in the proportion of rapid eye movement sleep, and a reduction in apnea-hypopnea-index [30,31], others found no reduction in sleep-disordered breathing events after hormone replacement therapy in a group of postmenopausal women [32,33]. Most of these studies, however, suffered from small sample size and other methodological limitations.

Larger studies such as the one by Bixler et al. confirmed that postmenopausal women with hormone replacement therapy had a prevalence of sleep apnea that was similar to the prevalence in premenopausal women [34]. Vice versa, the absence of hormone therapy in postmenopausal women appeared to be associated with a higher prevalence of sleep apnea than that in premenopausal women. Further, the prevalence of sleep apnea in postmenopausal women without hormone replacement therapy was higher than in postmenopausal women with. Noteworthy, the prevalence of sleep apnea in postmenopausal women in that report remained significantly less than that in men, when controlling for age and body-mass-index.

Polysomnographic features

One of the largest reports of polysomnographic features of OSAS was performed by O'Connor and co-workers [8]. In a retrospective study of 830 patients with OSAS, diagnosed by overnight polysomnography, the authors observed that the severity of sleep apnea was similar in women and men during REM sleep, but less severe in women during NREM sleep. Thus, women with OSA had a greater proportion of their respiratory events during REM sleep than do men, and a higher prevalence of REM related sleep apnea events (62% REM-OSAS in women vs. 24% in men). In contrast, postural OSAS appeared to occur predominantly in men. These differences did not appear to be age- or weight dependent according to that report. Similarly, there was no evidence of an influence of medications, such as anti-depressants, on the prevalence of REM-OSAS. While these observations are consistent with the above stated sex-related differences in upper airway mechanics, the clinical relevance of these observations has yet to be determined. The long-term effects of (isolated or predominant) disruption of REM sleep, may contribute to explain why women are symptomatic at lower apnea-hypopnea-index compared with their male counterparts.

Symptoms of OSAS in men and women

Despite increasing knowledge about the mechanisms that may contribute to explain why male gender is associated with a higher risk of developing sleep apnea, OSAS in women remains frequently underdiagnosed [35]. A variety of reasons may be responsible for the apparent gender discrepancy between clinic and community populations. It may be possible that fewer women seek help for sleep apnea symptoms than men. However, general care seeking patterns do not support the hypothesis [36]. In fact, Smith and co-workers demonstrated that women had significantly more frequent physician visits and hospitalizations prior to the diagnosis of OSAS than men [37]. The discrepancy between greater health care utilization and clinical underrecognition of OSAS in women may suggest that medical care providers fail to suspect or to diagnose sleep apnea in female patients. Using data from the Wisconsin University Sleep Laboratory, Young et al observed that nearly all men and women with an apnea-hypopnea-index greater than 20/hr were diagnosed with OSAS, but a lower proportion of women than men with an AHI in the range of 5–20/hr were given a diagnosis of sleep apnea [38]. This phenomenon may be due to gender-related differences in symptom expression at lower apnea-hypopnea-index particularly with respect to characteristic symptoms that have become the hallmark of the syndrome such as excessive daytime sleepiness, habitual snoring, and witnessed apneas.

Only few population-based studies systematically investigated gender-related differences in sleep disordered breathing symptoms. In the Wisconsin Sleep Cohort Study, there were no significant gender-related differences in snoring, self-reported breathing pauses, or restless legs in subjects with an AHI of 15/hr or greater [39]. It should be acknowledged, however, that this study may have been underpowered to detect a gender-specific difference in these symptoms, since only 17 female subjects with an AHI greater than 15/hr were included. In contrast, Redline and co-workers noted that the “classic” symptoms of sleep apnea, such as snoring and witnessed apnea were reported two- to three-fold more likely in males [4]. The best available evidence

Table 1 Characteristics of OSAS in female patients.

Older age (frequently post-menopausal)
Higher body-mass-index
Lower AHI
REM-related OSAS
Atypical OSAS symptoms (Insomnia, Depression, Fatigue, Restless Legs)
Lower CPAP pressure requirements

from the community sample, however, comes from the Sleep Heart Health Study. Baldwin and colleagues demonstrated that women were significantly more likely to report insomnia, difficulties falling asleep, and awakening with leg cramps than men [40].

Studies conducted in the sleep laboratory have demonstrated a similar picture. In a retrospective chart-review analysis, Sheperdycky and co-workers reported that women with OSAS less often reported on witnessed apnea compared with men [41]. Interestingly, women in that report described their main presenting symptoms as insomnia and were more likely to have a history of depression. Supporting these observations, we have similarly reported that women with suspected sleep disordered breathing were more likely to suffer from “atypical” symptoms, such as insomnia, depression, restless legs and nightmares [9]. In fact, an analysis of gender-related differences in morbidity and total health care utilization 5 years prior to diagnosis of OSAHS by Greenberg-Dotan and co-workers, demonstrated that women were significantly more likely to receive treatment with antipsychotics, anxiolytics, and/or antidepressants, suggesting that these patients may experience insomnia, anxiety, and depression [10].

Consistent with previous studies we also observed substantial gender-related differences in excessive daytime sleepiness in OSAS, with sleepiness being more pronounced in female patients. Curiously, in our clinical sample men had a significantly higher arousal index than women irrespective of AHI category. These observations may either suggest gender-related differences in the perception of sleepiness or a discrepancy between polysomnographic parameters of sleep fragmentation and subjective sleepiness reports. In fact, Kingshott and co-workers found no significant relationship between arousal frequency and subjective (Epworth Sleepiness Scale) or objective measures of sleepiness [43]. It has to be noted, however, that there is a strong relationship between excessive daytime sleepiness and complaints such as fatigue, depression or insomnia, symptoms which are also more commonly reported by women.

The findings from both clinical and population-based studies suggest that women suffer from a number of atypical symptoms of sleep apnea. This observation raised concerns as to whether frequently used diagnostic tools, such as the Epworth Sleepiness Score, may not be adequate enough to assess the full spectrum of OSAS symptoms in women. The distinction between the more traditional symptoms usually attributable to OSAS and the above-mentioned “atypical” symptoms is important, as clinicians rely more on self-reported apnea and the quantitative aspects of snoring, which have been associated with OSAS in predominantly male populations. The presentation of women with these atypical symptoms could make physicians turn to other diagnostic possibilities such as depression or insomnia, rather than to the actual diagnosis of sleep apnea. The latter may also explain greater utilization of health-care resources in women with OSAS compared with men [10].

Conclusion

The prevalence of OSAS in the general population is higher in men than women, yet the reasons for this gender disparity remains unclear. While there is some evidence suggesting increased susceptibility of the male pharynx to collapse during sleep, most of the studies that investigated the effect of gender on upper airway resistance were conducted in small samples of subjects without sleep apnea. Similarly, there is few data with respect to the effects of sex hormones on upper airway patency, which may explain some of the changes in OSAS prevalence and sleep apnea severity in females that occur after menopause. Given the evidence of clinical under-recognition of OSAS in women, a better understanding of the effect of gender-specific mechanisms and increasing awareness of the clinical presentation of OSAHS in women should be demanded both in the primary care as well as by sleep specialists. Finally, there appear to be gender-related differences in CPAP pressure requirements.

Therapy

There have been no systematic studies of gender-related differences with respect to the efficacy of non-CPAP therapies for OSAS. Similarly, there is paucity of data for the role of gender on CPAP acceptance, adherence, and/or efficacy. There appears to be no sex-difference in the type of interfaces used for CPAP therapy or in overall satisfaction with mask treatment [43]. A cross-sectional Japanese case-control study, however, observed that female patients require significantly lower levels of CPAP than male patients matched for BMI [44]. A more recent US study confirmed these findings and the effect of gender persisted after correction for the severity of OSA [45]. This observation is in line with evidence of a lower pharyngeal critical closing pressure in women. There are conflicting results as to whether there are gender-related differences in CPAP treatment adherence. Sin and co-workers [46] observed higher CPAP usage in female OSAS patients, a recent study in contrast observed slightly higher CPAP adherence data in male counterparts [47]. Unpublished data from our own institution is in line with the findings from Sin et al., with evidence of more regular usage of the CPAP device in female OSAS patients, which is consistent with higher usage of healthcare resources in female patients previously discussed [37]. While the magnitude of improvement in clinical outcomes does not vary by gender [48], Mermigkis and co-workers [49] recently demonstrated that CPAP therapy for OSAS may reverse elevated markers of systemic inflammation faster in male than female patients. This may suggest gender-related differences in CPAP effects on cardiovascular risk factors, however, further studies on the role of gender-related outcomes in response to OSAS treatment are required.

Conflict of interest

The author has no conflict of interest.

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