Effects of menopause on obstructive sleep apnea

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ÖZET

Obstrüktif uyku apnesinde menopozun etkisi

Obstrüktif uyku apne (OSA) genel popülasyonda yaklaşık olarak erişkin erkeklerin %4'ünü, kadınların %2'sini etkilemektedir. Öte yandan menopoz ile birlikte kadınlarda bu prevalans dramatik bir artış göstermektedir. Klinik pratikte kadınlarda OSA tanısı büyük ölçüde gözden kaçırılmaktadır, çünkü kadınlar erkeklere göre daha farklı klinik özelliklere sahiptir. Günümüzde, menopozun OSA için önemli bir risk faktörü olduğuna ve hormon replasman tedavisinin de OSA'ya karşı koruyucu bir rol üstlendiğine ilişkin çok sayıda epidemiyolojik çalışma yayınlanmıştır. Bu derlemede, menopozun OSA üzerine etkisinin gözden geçirilmesi amaçlanmıştır.

Anahtar Kelimeler: *Obstrüktif uyku apne, menopoz, hormon replasman tedavisi, kadın.*

SUMMARY

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Obstructive sleep apnea (OSA) affects approximately 4% of adult men and 2% of adult women in the general population. However, this prevalence in women shows a dramatic increase with the menopause. The presence of OSA in women may

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be largely underestimated in clinical practice, possibly, because OSA has different clinical features and characteristics in women with respect to men. Recently, many epidemiological data were published pertinent to menopause as a risk factor and hormone replacement therapy as a protective factor for OSA. So, it's aimed to review the effects of menopause on OSA in this review.

Key Words: *Obstructive sleep apnea, menopause, hormone replacement therapy, woman.*

Sleep, a basic physiological need of all humans, appears to be both integrative and restorative. However, studies have reported that 33-51% of women show a dramatic increase in sleep disturbance in the mid-life years, a time when they enter menopause. Menopause is associated with insomnia due to several factors including hot flashes, mood disorders and increased sleep-disordered breathing (1).

Obstructive sleep apnea (OSA) is a disorder characterized by repetitive upper airway collapse during sleep that affects approximately 4% of adult men and 2% of adult women in the general population (2). A high prevalence of sleep disordered breathing (SDB) poses a public health burden, since it might lead to cerebrovascular and cardiovascular complications such as stroke, heart failure, myocardial infarction, arrhythmias and hypertension (3-15). And it also correlated with daytime vigilance decrements. Sleep apnea is now recognized as an independent risk factor for hypertension (16). Also, OSA is closely associated with obesity and aging (17,18). Prevention and early intervention may be the most feasible ways to reduce this burden.

Menopause is an established risk factor for SDB, but evidence to support this is lacking. Bixler et al. had provided epidemiological data pertinent to menopause as a risk factor and hormone replacement therapy (HRT) as a protective factor for SDB (19).

Gender Differences in OSA

In the past, most patients referred to sleep clinics with sleep disordered breathing were men. This is mainly owing to the fact that early epidemiological studies on obstructive sleep apnea (OSA) included only men and reports in the 1970s and 80s suggested that OSA was primarily a disease of men, with a male-to-female ratio of 10/1 or greater (20-23). In 1993, for the first time, Young et al. included women in a study examining the prevalence of OSA in the general population, and more recent studies reported a male-to-female ratio of only 2/1-3/1 (19,24-26). The presence of OSA in women may be largely underestimated in clinical practice, possibly because OSA has different clinical features and characteristics in women with respect to men.

Big difference in the prevalence of SDB between men (4%) and women (2%) could be explained by the protective effects of progesterone on respiratory system. Because progesterone is a respiratory stimulant and plays a protective role against sleep apnea by some mechanisms (27-29):

1. It increases resting ventilation,
2. It increases hypoxic ventilatory response,
3. It decreases upper airway collapsibility,
4. It increases genioglossus muscle tone, and
5. It has a central action on CO_2 receptors that stimulates respiration during wakefulness.

Women experience an increase in ventilatory drive during the luteal phase of the menstrual cycle when progesterone levels are the highest. Oral progesterone has been associated with slight but definite improvement in ventilatory indices during in both male and female sleep apnea patients.

In addition, the difference between men and women might be due to the differences in central respiratory drive, in upper airway neuromuscular control or due to the differences in upper airway anatomy between two genders (30-35). It has been shown that, although women had higher body mass indexes (BMI) and smaller pharynges than men, they had less severe OSA. Collapsibility of the upper airway depends on its size, the surrounding muscle tone, and the characteristics of the tissue. The size of airway seems to make

a difference in men, and this may be an effect of a difference in muscle tone (lower in men) and tissue characteristics (floppier in men).

Polysomnographic (PSG) findings also differ between men and women with OSA. Women have lower apnea hypopnea index (AHI) results than men, most of the difference in AHI occurs in NREM sleep, the factors protecting women from upper airway collapse in NREM sleep disappers in REM sleep (36).

Cardiovascular complications of OSA might show differences between men and women. Recently in a study Peker et al. found that the risk of developing cardiovascular disease was increased in middle-aged OSA subjects independently of age, BMI, SBP, DBP, and smoking (37).

OSA in Women and Effects of Menopause

The menopause is the cessation of cyclic ovarian function as manifeasted by the occurrence of final menstrual period. This occurs at a mean age of 51 years. Women typically live over one-third of their life after the onset of menopause (38).

Sex hormones have also been thought to influence the development of OSA. The prevalence of OSA changes across the menopause, and it is also possible that the pathogenetic mechanisms resulting in OSA vary between pre and postmenopausal women (Figure 1) (39).

Bixler et al. had performed PSG on a population based sample of 1000 women aged 20-100 years and found a higher prevalence of SDB in menopausal women (3.9%) when compared with pre-menopausal women (0.6%) (19). In that study postmenopausal women without HRT had a prevalence of SDB that was significantly higher than the prevalence in premenopausal with HRT (2.7% versus 0.6%, p= 0.02) and was more similar to the prevalence in men (3.9%).

The Framingham Heart Study showed that postmenopausal women, compared with pre-menopausal women, had four times the incidence of

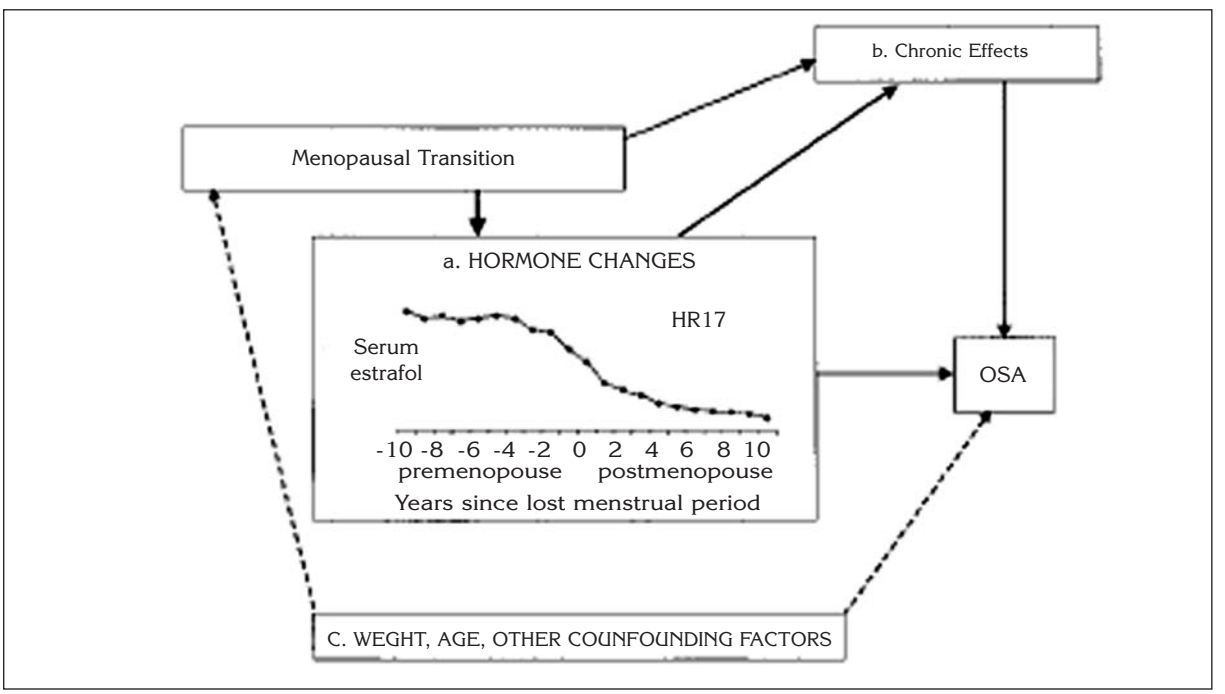

Figure 1 (39). Conceptual model of the role of menopausal changes in OSA. The pattern of hormonal changes, illustrated by the decline of estradiol over several years, (a) and modification by hormone replacement therapy (HRT), (b) demonstrates the limitation of using the simple dichotomy of premenopause and postmenopause to define the menopausal transition. The effects of hormonal change may be acute or chronic, (c) demonstrating the need to consider the length of postmenopause and pattern of HRT. Increased age and weight are strongly associated with both menopausal changes and OSA and, along with other potential confounding factors, must be taken into account in study design and analyses.

Table 1. Studies concerning HRT and sleep apnea where PSG is used.

First author	Year	n	Main finding	Comment	Design
Block AJ	1981	21	Synt. progestogen reduced the maximum duration of apnea, not the numbers of episodes	Progesterone alone (MPG)	Interventional Randomized, double blind
Picket CK	1989	9	Reduced numbers of apneas and hypopneas in healthy postmenopausal women	MPA and konj. estrogen 7 days	Interventional Randomized, placebo-controlled
Cistulli PA	1994	15	No reduction in the clinical severity of SAS No difference ERT or combined HRT An insignificant reduction in AHI	Diff. ERT with or without MPA 50 days	Interventional Nonblinded No control group
Keefe DL	1999	5	AHI decreased by 25% with ERT and 50% with combined HRT	Estradiol, MPA 3-4 weeks.	Interventional Nonblinded No control group
Bixler EO	2001	1741	Menopause is a significant risk factor of sleep apnea and HRT appears to be associated with reduced risk	Different kind of HRT	Observational
Manber R	2002	6	Estrogen reduced AHI, no additional effect with progesterone	Transdermal estradiol þmicronized progesterone 1 month	Interventional Placebo-controlled
Shahar E	2003	2852	The prevalence of SDB among HRT users was approximately half the prevalence among nonusers	Different kind of HRT	Observational

ERT: Estrogen replacement therapy, MPA: Medroxyprogesteronacetate, OSA: Obstructive sleep apnea, SDB: Sleep-disordered breathing, HRT: Hormone replacement therapy , AHI: Apnea-hypopnea index, PSG: Polysomnography.

coronary heart disease (40). This hypothesis and the question of whether HRT reduces cardiovascular disease (CVD) risk have been intensely pursued for 20 years, with mixed results (41). Controversy over the benefit versus risk of long-term HRT use has been fueled further by studies showing, in addition to a protective effect of HRT, a lack of evidence for natural menopause as a significant risk factor for CVD, increased risks of breast cancer with long-term HRT use, and negative findings from a large randomized trial of HRT and CVD (42). Among women 50 years of age or older who participated in the Sleep Heart Health Study, the prevalence of OSA for AHI > 15 among hormone users was approximately half the prevalence among nonusers (43).

The association of pre-menopause, peri-menopause, and post-menopause with sleep-disordered breathing was investigated with a population-based sample of 589 women enrolled in the Wisconsin Sleep Cohort Study (44). Menopausal status was determined from menstrual history, gynecologic surgery, hormone replacement therapy, follicle-stimulating hormone, and vasomotor symptoms. Sleep-disordered breathing was indicated by the frequency of apnea and hypopnea events per hour of sleep, measured by PSG. Multivariable logistic regression was used to estimate odds ratios for having 5 or more and 15 or more apnea and hypopnea events per hour. Odds ratios (95% confidence interval), adjusted for age, body habitus, smoking, and other potential confounding factors, for 5 or more apnea and hypopnea events per hour were 1.2 with peri-menopause and 2.6 with post-menopause; odds ratios for 15 or more apnea and hypopnea events

per hour were 1.1 with peri-menopause and 3.5 with post-menopause. The menopausal transition is significantly associated with an increased likelihood of having sleep-disordered breathing, independent of known confounding factors. Evaluation for SDB should be a priority for menopausal women with complaints of snoring, daytime sleepiness, or unsatisfactory sleep.

Body Composition and OSA

Body composition is associated in complex ways with midlife aging, with menopause, and with sleep apnea, making control for confounding due to increased weight and fat deposition difficult (45). In midlife, the most significant changes appear to be in the deposition of body fat and loss of lean weight. However, body composition also influences menopause, with lean women reaching menopause at a younger age. Furthermore, HRT use is associated with increases in weight and body fat (46,47). The correlations of both HRT use and OSA with psychosocial and biological factors represent other important sources of potential confounding in the studies of HRT and OSA. HRT use tends to be greater in healthier women, and this would contribute to an overestimation of the protective effect of HRT (48).

Studies concerning OSA and HRT where polysomnography is used are sparse, and the results are difficult to compare between studies (Table 1) (49). The majority have been using medroxyprogesteronacetate as gestagen. The diverging results in different studies so far published concerning OSA and HRT indicate that there are individual effects in HRT-treated women with OSA. This might be explained by variability in bioavailability and in hormone metabolism.

Attention should be drawn to the need for OSA evaluation in perimenopausal and postmenopausal women who are especially in risk of cardiovascular complications, in order to prevent high potential morbidity and mortality.

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