İstanbul Med J 2016; 17: 99-103
DOI: 10.5152/imj.2016.62207

Original Article

Evaluation of Obstructive Sleep Apnea in Menopausal Women

Pınar Mutlu[1], Bahriye Oya İtil[2], Murat Celiloğlu[3], Ahmet Ömer İkiz[4], İbrahim Öztura[5]

Abstract

Objective: To demonstrate a correlation between neuroendocrine hormone changes in menopause and obstructive sleep apnea syndrome (OSAS), excluding risk factors, i.e., depression, and treatment of cases where the disease has been diagnosed.

Methods: This was a case study (2009-2010) of 194 menopausal patients, excluding surgically induced cases, performed at the Obstetrics and Gynocology Clinic of Dokuz Eylül University School of Medicine Hospital.

Results: Patients were queried on their demographic data, menopause and OSAS symptoms, and Epworth Sleepiness Scale (ESS) results. Fourteen patients having 10 points and above in the ESS were hospitalized for one night in Dokuz Eylül University Sleep Center and underwent polysomnography (PSG). In our study, OSAS prevalence for postmenopausal patients was found in 6.21% of the patients. Further, 28.6% of 12 patients having OSAS were found to have mild and 57.2% were found to have moderate–severe OSAS. By PSG, 14 patients were detected to have 398.5 min of average sleep time and 23.9 of Apnea–Hypopnea Index. Three patients were suggested to undergo the palliative care and 9 were suggested to undergo continuous positive airway pressure (CPAP) therapy. The average CPAP was 7.1 mmHg. A correlation was found between body mass index and LH, prolactin, E2, and free testosterone levels and OSAS.

Conclusion: OSAS risk increases during menopause. Menopause is an independent risk factor for OSAS; therefore, detailed research with PSG is suggested to be performed when required.

Keywords: Obstructive sleep apnea syndrome, menopause, epworth sleepiness scale

Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by episodes of complete (apnea) or partial (hypopnea) upper respiratory tract obstruction and recurring during sleep, frequently with a decrease in blood oxygen saturation (1).

The ratio of men to women is generally 10:1 in sleep centers. This difference in gender was first emphasized by Wynne et al. (2); however, evidence suggests that the gap is not as high as previously thought. Schmidt and his friends Norwara et al. found that in a small study group, 1.1% of women and 2.3% of men had an Apnea–Hypopnea Index (AHI) of >10 (3).

There is speculation that progesterone and estrogen released during the pre-menopausal period serve as a protection against OSAS. The fact that a majority of women with OSAS are morbidly obese and are generally in the post-menopausal period adds to this speculation. For example, one study showed that genioglossus muscle activity was higher in pre-menopausal women than in post-menopausal women, with an increase in muscle activity after estrogen and progesterone therapy in post-menopausal women (4, 5).

In the Wisconsin Sleep Cohort Study (6), it was found that menopause was a risk factor for OSAS. When age, alcohol consumption, smoking, hypertension, exercise, cardiovascular disease, and physical condition were not taken into account, it was found that post-menopausal women experienced mild OSAS 2.6-times more, with severe OSAS 3.5-times greater, than those in pre-menopausal women. However, there is no official study to date showing a correlation between neuroendocrine hormone changes and OSAS and menopause symptoms. We aimed to study the correlation and specifications of menopause and neuroendocrine hormone changes with OSAS free from risk factors such as aging, comorbid diseases, and depression and to arrange therapies for patients with the disease.

Methods

This study was conducted between 2009 and 2010 after receiving approval on July 23rd, 2009 from Dokuz Eylül Universty Clinic and the Laboratory Research Ethics Committee. One hundred ninety-four cases patients the Menopausal Clinic of Obstetrics and the Gynecology Department of Dokuz Eylül University School of Medicine Hospital were chosen; the patients were contacted by phone and briefed about the study; consent forms were signed. A survey was performed, and

[1]Department of Chest Diseases, Çanakkale Onsekiz Mart University School of Medicine, Çanakkale, Türkiye
[2]Department of Chest Diseases, Dokuz Eylül University School of Medicine, İzmir, Türkiye
[3]Department of Gynecological Diseases, Dokuz Eylül University School of Medicine, İzmir, Türkiye
[4]Department of Ear, Nose and Throat, Dokuz Eylül University School of Medicine, İzmir, Türkiye
[5]Department of Neurology, Dokuz Eylül University School of Medicine, İzmir, Türkiye

Address for Correspondence
Pınar Mutlu,
E-mail: pinarmutlu78@yahoo.com

Received:
08.02.2016

Accepted:
15.06.2016

hormone tests from all patients were sent for analysis to the Dokuz Eylül University School of Medicine Hospital Central Laboratory. According to the ESS test results, patients with points between 0 and 9 are not considered to be at risk of OSAS, while patients with 10 points and above are. The ESS test consists of eight questions on a scale of 0–24 and is used to measure daytime sleepiness. Ten points and more indicate clinical daytime sleepiness as opposed to a tendency of sleepiness (7-9). The validity and reliability research study for use in Turkey was conducted in 1999 by Ağargün et al. (10) (Table 1).

Fifteen patients at risk of OSAS were chosen and invited to the Dokuz Eylül Universty School of Medicine Hospital Chest Diseases Polyclinic for evaluation. One patient was rejected. Fourteen patients had their height, weight, and neck circumference measurements taken in different days in a reserved room. The Baster MLC-150 III (Baster; İzmir, Turkey) device was used to take height and weight measurements, and the Star brand tape was used to measure the neck circumference.

One of the 14 patients consented to the detailed research to determine OSAS risk, but rejected the ear, nose, and throat consultation. Upper respiratory tract consultations of 13 patients were done by a doctor on different days in Dokuz Eylül Universty School of Medicine Hospital Ear, Nose and Throat Polyclinic.

The fourteen patients who were at risk of OSAS were hospitalized for one night in the Dokuz Eylül University School of Medicine Hospital Sleep Disorder Center, and their polysomnographic assessments were done via a 32 channel Medcare Embla A 10 PSG (Texas, USA) device. During polysomnographic recording, EEG, EOG, and EMG tests on the sub-mental and tibialis anterior muscles were also performed. C4-A1, C3-A2, O2-A1, and O1-A2 derivations were used for EEG, EOG-L (left), and EOG-R (right) derivations for EOG.

A heat-sensitive cannula was used for nasal air flow during reportorial monitoring, resulting in the detection of apnea and hypopnea in the patients.

Oxygenation was followed up by a finger-mounted pulse oximeter, reading the values in the color spectrum of oxyhemoglobin and measuring the arterial oxygen saturation. Snore follow-up was fulfilled by a microphone planted on the skin at the larynx. EKG recording of heart rate and rhythm were monitored throughout the night. PSD data were assessed and reported by the same attending technician.

Statistical analysis

Statistical Package for Social Sciences for Windows 17.0 (SPSS 17, IBM, Corp.; New York, USA) was used to perform statistical analysis and assessment of data. The chi-square test was used to determine qualitative variables, and the independent T-test was used to determine quantitative variables. Results were evaluated between 95% confidence interval and relevance in $p<0.05$ level of significance.

Results

The average age of the patients was 55.45±67.1 years. Table 2 shows education levels and occupation and marital statuses of the patients.

One of the 15 patients having more than 10 points on the ESS scale rejected ear, nose, and throat consultation. Another patient rejected ear, nose, and throat consultation and PSG. Table 3 shows the specifications of the 14 patients.

Table 1. The Epworth sleepiness scale

The Epworth sleepiness scale
How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they may affect you. Use the following scale to choose the most appropriate number for each situation:
0=would never doze
1=slight chance of dozing
2=moderate chance of dozing
3=high chance of dozing
Situation Chance of dozing
Sitting and reading
Watching TV
Sitting, inactive in a public place (e.g., a theater or meeting)
As a passenger in a car for an hour without a break
Lying down to rest in the afternoon when circumstances permit
Sitting and talking to someone
Sitting quietly after lunch without alcohol
In a car, while waiting for a few minutes in the traffic
Thank you for your cooperation

Table 2. Demographic data of patients

		n	%
Educational Background	Literate	3	1.5
	Primary Education	92	47.4
	High School	56	28.9
	University	43	22.2
	TOTAL	194	100
Occupation	Lawyer	1	0.5
	Pharmacist	1	0.5
	Pensioner	61	31.4
	Housewife	112	57.7
	Nurse	1	0.5
	Officer	2	1
	Teacher	11	5.7
	Physician	1	0.5
	Freelancer	2	1
	TOTAL	194	100
Marital Status	Single	5	2.6
	Married	161	83
	Widow	28	14.4
	TOTAL	194	100

The average total sleep time of the 14 patients who underwent PSG was 398.57±49.75 min. The average sleep efficiency value was 84.57%; the average AHI was 23.90±22.23, and the lowest oxygen saturation average value was 81.64±7.72.

Table 3. Symptom specifications of patients having 10 points and more in the ESS

		n	%
Ear, Nose, and Throat Consultation	Rejected	2	13.3
	Accepted	13	86.7
	TOTAL	15	100
Tongue Size	Normal	10	76.9
	Big	1	7.7
	Above occlusal line, big	1	7.7
	A little big	1	7.7
	TOTAL	13	100
Nasal Obstruction	No	8	61.5
	Yes	3	23.1
	Only at night	2	15.4
	TOTAL	13	100
Obstructive Sleep Apnea Syndrome	Normal	2	14.3
	Mild	4	28.6
	Moderate–Severe	8	57.2
	TOTAL	14	100
Therapy	Palliative	5	35.7
	CPAP	9	64.3
	TOTAL	14	100
		Average±Standard Deviation	
Neck circumference		37.42±3.09	
Total Sleep Time		398.57±49.75	
Sleep Efficiency		84.57±9.33	
Apnea–Hypopnea Index		23.90±22.23	
Lowest Oxygen Saturation		81.64 ±7.72	
CPAP		7.16±1.27	

CPAP: continuous positive airway pressure; EES: epwort sleepiness scale

Nine patients having CPAP consultation were found to have an average CPAP of 7.16±1.27 mmHg.

When calculating the prevalence of OSAS, the patient who had more than 10 points on the ESS and rejected PSG and ear, nose, and throat consultation was omitted. Of 193 patients, 12 (6.21%) were found to have OSAS. The patients were re-grouped again, separating those with detected OSAS from those were undetected.

The average BMI was found to be statistically higher in the group with OSAS ($p<0.026$). Patients in the OSAS group were obese as opposed to patients without OSAS, who had normal to above normal weight levels. Patients with BMIs of 0–29.9 kg/m^2 were defined as normal and above normal, while those with BMIs of 30 kg/m^2 and above were defined as obese. It can also be said that having a BMI above 30 kg/m^2 increased the disease risk (relative risk: by 11.16 times).

Table 4. Comparison of hormone measurements between the two groups

	With OSAS (n=12)	Without OSAS (n=181)	p
	Average±Standard Deviation	Average±Standard Deviation	
TSH	1.66±0.82	1.86±2.07	0.480
Prolactin	6.98±2.20	11.70±7.39	0.036*
FSH	62.8±39.96	77.39±34.64	0.241
LH	22.39±9.66	28.75±11.53	0.048*
E_2	22.33±8.20	38.89±52.86	0.001*
Free testosterone	1.90±0.82	1.24±0.63	0.019*
Testosterone	42.41±15.79	40.06±12.36	0.623
T3	3.19±0.89	2.93±0.50	0.111
DHEA	81.80±27.59	83.91±54.41	0.816
SHBG	33.55±12.38	33.76±17.17	0.955
T4	1.14±0.14	1.13±0.21	0.947

TSH: thyroid-stimulating hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: estradiol; SHBG: sex hormone-binding globulin; DHEA: dehydroepiandrosterone; OSAS: obstructive sleep apnea syndrome

While the average levels of hormones such as thyroid-stimulating hormone, follicle-stimulating hormone, testosterone, T_3, dehydroepiandrosterone, sex hormone-binding globulin, and T_4 were not statistically different ($p>0.05$) between the groups, prolactin, luteinizing hormone (LH), estradiol (E_2), and free testosterone average level were statistically different (Table 4).

The average levels of prolactin, LH, and E_2 were found to be higher in the group without OSAS, and the average free testosterone level was found to be higher in the group with OSAS (Table 4).

Discussion

OSAS is a frequently seen disease in society and causes serious morbidity and mortality. When diagnosing OSAS in pre-menopausal women, male gender is a free risk factor as 85% of sleep studies are conducted on male participants, whereas risk factors for women increase in the post-menopausal period (11-13).

Excluding age, BMI, and lifestyle, respiratory disorders are 2.6-times higher in light sleepers, with more severe forms being 3.5-times more prevalent in post-menopausal women than in pre-menopausal women (6). In view of recent data, menopause itself is a free risk factor for sleep-disordered breathing. Bixler et al. (12) contacted 12,219 women by phone, and 1000 were selected for studying PSG. It was found that mild and severe OSAS prevalences in post-menopausal women who did not use HRT were 9.7% and 2.7%, respectively, while for pre-menopausal women, it was 3.2% and 0.6%, respectively (12). We calculated the percentage of OSAS to be as high 6.21% in our study, with 28.6% of 12 patients having mild OSAS and 57.2% having moderate–severe OSAS.

The primary mechanism behind the increase in the frequency of OSAS during the menopausal period was the difference in the increase of body fat distribution accompanying menopause (13, 14). There was no significant statistical difference found among meno-

pause patients with or without OSAS in terms of average BMIs, despite all patients being of similar age. It can be said that the group with OSAS was obese and that the group without OSAS had normal to above normal weight. However, in their study on post-menopausal and pre-menopausal women, Yukawa et al. (15) found similarities in terms of AHI - that pre-menopausal women had higher BMI. Guilleminault et al. (16) showed that pre-menopausal women with the same degree of obesity had more severe OSAS than post-menopausal women (16). Therefore, it is not possible to explain the increase in OSAS risk during menopause merely due to obesity.

Another mechanism behind the increasing risk of OSAS during menopause is hormonal changes. It is argued that young women are protected from apnea development by the effect of estrogen on the upper respiratory tract (17).

When women with severe OSAS are compared to those with or without moderate OSAS within the same age range and menopausal condition, it was found that women with severe OSAS had lower E_2 levels (18). However, there are studies showing that low E_2 concentrations are not as important as high BMI and still face morphology (14, 19). In accordance with the hypothesis that E_2 protects women from OSAS, we found E_2 levels to be significantly lower in the group with OSAS than in the group without OSAS. However, we think that the reason for the low E_2 levels, despite having a high BMI in the group with OSAS, is that we had a small number of patients in our study, resulting in low reliability when testing the E_2 level.

One of the reasons for the increased frequency of OSAS in post-menopausal women is caused by an increase in testosterone levels (12). Apart from age, there are clinical studies indicating that hypogonadal men who have testosterone replacement therapy experience developing or deteriorating OSAS symptoms (20-22). Testosterone decreases apnea development (23), and studies have shown that men with low testosterone levels have OSAS (24, 25). Moreover, young women who have increased androgen levels because of polycystic ovarian syndrome are found to have higher AHIs than the healthy control group (26). In light of these data, it is still not possible to clearly understand the role of testosterone in respiration.

Different from E2, testosterone is believed to cause sleep disorder by effecting central mechanisms but not the upper respiratory tract (27). Zhou et al. (23) found that women who had transdermal testosterone replacement therapy developed central apnea during NREM sleep. When patients with OSAS and related symptoms were compared, we concluded that while there was no difference in terms of testosterone levels, free testosterone levels were significantly higher in groups with OSAS. This is contrary to the above-mentioned studies that show the increasing effect of testosterone on ventilation; instead, it supports studies that show that it increases OSAS frequency.

In addition, it has been suggested that obese women with OSAS who are free from menopause have higher androgen levels than women who are not obese (28, 29). This also is compatible in patients with OSAS who are obese and have higher free testosterone levels.

While there are many studies in the literature showing that prolactin and LH secretion is inconsistent in patients with OSAS (20, 30-33), we think that the reason for this difference between the two groups in terms of prolactin and LH levels (prolactin, p=0.036 and LH, p=0.048) is insignificant, considering the number of patients who were studied. If the number of patients increases, there is a probability this will also disappear.

Conclusion

We think that an increased OSAS risk during menopause is a health problem related to multi-factorial reasons associated with cardiovascular disease, neurocognitive insufficiency, and daytime sleepiness. Although the disease is frequent and causes serious social problems, unfortunately, there are not enough studies about this condition in Turkey or worldwide. We hope that our study will stimulate future studies on this issue.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committe of Dokuz Eylül University School of Medicine.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.M., B.O.İ.; Design - P.M., B.O.İ.; Supervision - P.M., B.O.İ.; Funding - M.C., İ.Ö.; Materials - A.Ö.İ., İ.Ö.; Data Collection and/or Processing - A.Ö.İ., M.C.; Analysis and/or Interpretation - P.M., B.O.İ.; Literature Review - P.M., İ.Ö.; Writing - P.M.; Critical Review - M.C., İ.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Buysse DJ, eds. International Classification of Sleep Disorders, version 2: Diagnostic Coding Manual., in American Academy of Sleep Medicine, Rochester MN. 2005.
2. Wynne JW, Block AJ, Hemenway J, Hunt LA, Flick MR. Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive lung disease (COLD). Am J Med 1979; 66: 573-9. [CrossRef]
3. Schmidt-Nowara WW, Coultas DB, Wiggins C, Skipper BE, Samet JM. Snoring in a Hispanic-American population. Risk factors and association with hypertension and other morbidity. Arch Intern Med 1990; 150: 597-601. [CrossRef]
4. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328: 1230-5. [CrossRef]
5. Popovic RM and White DP. Upper airway muscle activity in normal women: influence of hormonal status. J Appl Physiol 1998; 84: 1055-62.
6. Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med 2003; 167: 1181-5. [CrossRef]
7. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14: 540-5.
8. Banno K, Kryger MH. Sleep apnea: clinical investigations in humans. Sleep Med 2007; 8: 400-26. [CrossRef]
9. Lindberg E, Berne C, Elmasry A, Hedner J, Janson C. CPAP treatment of a population-based sample--what are the benefits and the treatment compliance? Sleep Med 2006; 7: 553-60.
10. Agargün MY. The validity and reliability of the Epworth Sleepiness Scale. Turkish Journal of Psychiatry 1999; 10: 261-7.
11. Shahar E, Redline S, Young T, Boland LL, Baldwin CM, Nieto FJ, et al. Hormone replacement therapy and sleep-disordered breathing. Am J Respir Crit Care Med 2003; 167: 1186-92. [CrossRef]

12. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 2001; 163: 608-13. [CrossRef]
13. Wilhoit SC and Suratt PM. Obstructive sleep apnea in premenopausal women. A comparison with men and with postmenopausal women. Chest 1987; 91: 654-8. [CrossRef]
14. Carskadon MA, Bearpark HM, Sharkey KM, Millman RP, Rosenberg C, Cavallo A, et al. Effects of menopause and nasal occlusion on breathing during sleep. Am J Respir Crit Care Med 1997; 155: 205-10. [CrossRef]
15. Yukawa K, Inoue Y, Yagyu H, Hasegawa T, Komada Y, Namba K,et all. Gender differences in the clinical characteristics among Japanese patients with obstructive sleep apnea syndrome. Chest 2009; 135: 337-43. [CrossRef]
16. Guilleminault C, Palombini L, Poyares D, Chowdhuri S. Chronic insomnia, postmenopausal women, and sleep disordered breathing: part 1. Frequency of sleep disordered breathing in a cohort. J Psychosom Res 2002; 53: 611-5. [CrossRef]
17. Block AJ, Wynne JW, Boysen PG, Lindsey S, Martin C, Cantor B. Menopause, medroxyprogesterone and breathing during sleep. Am J Med, 1981; 70: 506-10. [CrossRef]
18. Shaver JL. Sleep and women. Sleep Med Rev 1998; 2: 209-12. [CrossRef]
19. Guilleminault C, Partinen M, Praud JP, Quera-Salva MA, Powell N, Riley R. Morphometric facial changes and obstructive sleep apnea in adolescents. J Pediatr 1989; 114: 997-9. [CrossRef]
20. Saaresranta T, Polo O. Hormones and breathing. Chest 2002; 122: 2165-82. [CrossRef]
21. Liu PY, Swerdloff RS and Veldhuis JD. Clinical review 171: The rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. J Clin Endocrinol Metab 2004; 89: 4789-96. [CrossRef]
22. Grunstein RR, Handelsman DJ, Lawrence SJ, Blackwell C, Caterson ID, Sullivan CE. Neuroendocrine dysfunction in sleep apnea: reversal by continuous positive airways pressure therapy. J Clin Endocrinol Metab 1989; 68: 352-8. [CrossRef]
23. Zhou XS, Rowley JA, Demirovic F, Diamond MP, Badr MS. Effect of testosterone on the apneic threshold in women during NREM sleep. J Appl Physiol 2003; 94: 101-7. [CrossRef]
24. Hanafy HM. Testosterone therapy and obstructive sleep apnea: is there a real connection? J Sex Med 2007; 4: 1241-6.
25. Kirbas G, Abakay A, Topcu F, Kaplan A, Unlu M, Peker Y. Obstructive sleep apnoea, cigarette smoking and serum testosterone levels in a male sleep clinic cohort. J Int Med Res 2007; 35: 38-45. [CrossRef]
26. Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A, White DP. Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 2001; 86: 1175-80. [CrossRef]
27. Matsumoto AM, Sandblom RE, Schoene RB, Lee KA, Giblin EC, Pierson DJ, et al. Testosterone replacement in hypogonadal men: effects on obstructive sleep apnoea, respiratory drives, and sleep. Clin Endocrinol (Oxf) 1985; 22: 713-21. [CrossRef]
28. Goodman-Gruen D, Barrett-Connor E. Total but not bioavailable testosterone is a predictor of central adiposity in posmenopausal women. International journal of obesity 1995; 19: 293-8.
29. Mantzoros CS, Georgiadis EI, Evangelopoulou K, Katsilambros N. Dehydroepiandrosterone sulfate and testosterone are independently associated with body fat distribution in premenopausal women. Epidemiology 1996; 7: 513-6. [CrossRef]
30. Lanfranco F, Gianotti L, Pivetti S, Navone F, Rossetto R, Tassone F, et al. Obese patients with obstructive sleep apnoea syndrome show a peculiar alteration of the corticotroph but not of the thyrotroph and lactotroph function. Clin Endocrinol (Oxf) 2004; 60: 41-8. [CrossRef]
31. Spiegel K, Follenius M, Krieger J, Sforza E, Brandenberger G. Prolactin secretion during sleep in obstructive sleep apnea patients. J Sleep Res 1995; 4: 56-62. [CrossRef]
32. Meston N, Davies RJ, Mullins R, Jenkinson C, Wass JA, Stradling JR. Endocrine effects of nasal continuous positive airway pressure in male patients with obstructive sleep apnoea. J Intern Med 2005; 254: 447-54. [CrossRef]
33. Clark RW, Schmidt HS, Malarkey WB. Disordered growth hormone and prolactin secretion in primary disorders of sleep. Neurology 1979; 29: 855-61. [CrossRef]