



CLINICAL ARTICLE

Apnea–hypopnea index in nonobese women with polycystic ovary syndrome

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ARTICLE INFO

Article history:

Received 5 December 2008

Received in revised form 9 January 2009

Accepted 2 February 2009

Keywords:

Androstenedione

Apnea–hypopnea index

Obstructive sleep apnea

Polycystic ovary syndrome

Testosterone

ABSTRACT

Objective: To assess the influence of polycystic ovary syndrome (PCOS) on respiratory events during sleep in nonobese Taiwanese women. **Method:** Overnight polysomnography was recorded in 18 nonobese women with PCOS who had not received treatment (body mass index [BMI] 21.7 ± 0.57 , age 29.1 ± 1.43 years) and in 10 age- and BMI-matched women without PCOS (BMI 20.9 ± 0.58 , age 31.6 ± 3.87 years). **Results:** The nonobese women with PCOS had a higher total apnea–hypopnea index (AHI) especially during the non-rapid eye movement stage (AHI_{NREM}) than the women who did not have PCOS. The women with PCOS had higher serum levels of high-sensitivity C-reactive protein (hsCRP) and this was positively correlated with AHI_{REM}. Total testosterone level was positively correlated with AHI_{NREM}, and androstenedione was negatively correlated with AHI_{NREM}. **Conclusion:** PCOS was directly linked to increased obstructive respiratory events during sleep in nonobese women in Taiwan.

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1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age (4%–12%) [1]. PCOS is associated with increased risk of obesity, insulin resistance (IR), glucose intolerance, diabetes, dyslipidemia, hypertension, and cardiovascular disease [2]. Obesity amplifies most of the metabolic aberrations of this syndrome. On the other hand, obesity is considered to be an explanation for the increase in the incidence of PCOS [1,2].

PCOS is also a significant risk factor for obstructive sleep apnea (OSA) after controlling for age and body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) [3,4]. Women with PCOS have a significantly higher apnea–hypopnea index (AHI) as determined by polysomnography, the gold standard test for diagnosing OSA. OSA is characterized by repetitive partial or complete upper airway obstructive episodes during sleep that result in recurrent arousal and episodic oxyhemoglobin desaturation [5]. These episodes elicit oxidative stress, promote systemic inflammation, increase tonic levels of sympathetic activities, increase blood pressure, and induce cardiac

arrhythmias [6]. IR and high-sensitivity C-reactive protein (hsCRP) have been correlated with AHI in patients with OSA [6].

The intermittent hypoxia seen in OSA might lead to IR. On the contrary, OSA can worsen pre-existing IR through arousal or abnormal sympathetic activity [5,7]. Obesity and PCOS are both characterized by IR and both are related to OSA [1,2,5,7,8]. IR is considered to be a stronger risk factor than BMI or testosterone level for OSA in women with PCOS [3,9]. Therefore, OSA and PCOS share similar links to obesity and IR. Previous studies have rarely focused on apneic–hypopneic events in nonobese females with PCOS [2,3,4,9,10]. There are few reports on the respiratory events during sleep in Taiwanese women with PCOS. Therefore, the aim of the present study was to evaluate the influence of PCOS on respiratory events during sleep in nonobese Taiwanese women.

2. Patients and methods

Women with PCOS aged 18–45 years and with a BMI of less than 27 were consecutively recruited after initial screening for PCOS when they presented with oligomenorrhea at the Obstetric and Gynecology Clinic of Taipei Medical University Hospital between May 2006 and January 2007. Exclusion criteria were women who had taken any medication affecting the hypothalamic–pituitary–ovarian axis within the last 6 months, women who had been pregnant within the last year, and

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women with diabetes, hypertension, other diseases associated with obesity, hyperprolactinemia, abnormal thyroid function tests, and congenital adrenal hyperplasia. Twenty-seven women were eligible for inclusion at this stage. Written informed consent regarding blood tests, pelvic ultrasound, and polysomnography was obtained from all participants at this stage.

Women who were subsequently found to have undiagnosed diabetes ($n = 1$), hyperprolactinemia that did not show up on the initial test ($n = 1$), pelvic endometriosis ($n = 2$), women who did not demonstrate polycystic ovaries on pelvic ultrasound ($n = 3$), and women who had only hyperandrogenism but not hyperandrogenemia ($n = 2$) were also excluded.

This left 18 PCOS patients eligible for the study. The Rotterdam criteria were used for the initial diagnosis of PCOS [11]. To make the phenotype more consistent, we included patients who had both biochemical hyperandrogenemia and polycystic ovaries [12]. Ten age-matched and BMI-matched women who did not have PCOS were recruited as a control group from the same community during the same period. Women were excluded from the control group if they had irregular menstruation or oligomenorrhea, abnormal serum thyroid-stimulating hormone or prolactin, or biochemical hyperandrogenemia. The experimental protocol was approved by the Ethics and Research Committee of the Institutional Review Board for Human Investigation of the Taipei Medical University.

Blood samples were obtained between 08:00 and 10:00 AM after an overnight fast on the third to fifth days of the menstrual cycle or after a progestogen-induced bleed. Anthropometric data were collected using standard procedures. Body composition was determined by an impedance analysis (InBody 320; Biospace, Seoul, Korea).

Total testosterone (TT) was measured by radioimmunoassay using a DSL-4000 kit (Diagnostic System Laboratories, Webster, TX, USA) with a lower limit of sensitivity at 0.08 ng/mL. The inter-assay coefficient of variation (CV) ranged from 8.4% to 9.1%, whereas the intra-assay CV ranged from 7.8% to 9.6%. Androstenedione (AS) was measured by radioimmunoassay using a DSL-3800 kit (Diagnostic System Laboratories) with a sensitivity of 0.03 ng/mL. The inter-assay CV ranged from 6.0% to 9.8%, whereas the intra-assay CV ranged from 2.8% to 5.6%. Biochemical hyperandrogenemia was defined as a high serum concentration of TT (>0.8 ng/mL) or AS (>2.44 ng/mL). The presence of polycystic ovaries was determined by pelvic ultrasound performed by a single qualified technician [13]. Hirsutism was confirmed by the same doctor when the Ferriman–Gallwey score was greater than 8. Ferriman–Gallwey method scores the degree of hirsutism and reflects the clinical manifestations of hyperandrogenism in patients with PCOS [1,2]. Serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were measured by electro-chemoluminescence assay (ECLIA). Prolactin (ECLIA, Elecsys 2010 analyzer; Roche Diagnostics, Indianapolis, USA), thyroid stimulating hormone (MEIA technology; Abbott Laboratories, Abbott Park, IL, USA), dehydroepiandrosterone sulfate (radioimmunoassay; Diagnostic System Laboratories), and 17-hydroxyprogesterone (radioimmunoassay; Diagnostic System Laboratories) levels were also evaluated.

We also measured fasting plasma glucose (glucose oxidase technique, GA03R; A&T Corporation, Fujisawa, Japan), insulin (ECLIA, Elecsys 2010 with a sensitivity of 0.20 uIU/mL), sex hormone-binding globulin (ECLIA, Elecsys 2010), and hsCRP (Coulter STKS automatic cell analyzer; Beckman Coulter, Fullerton, CA, USA).

All patients were recorded for one full night by standard polysomnography using a computerized sleep-scoring system (Sandman; Tyco Ltd, Ottawa, ON, Canada) in the sleep laboratory of Taipei Medical University Hospital. We recorded 4 channels of the electroencephalogram (C3/A2, C4/A1, O1/A2, and Fpz/A1–A2), right and left channels of the electro-oculogram, 1 channel of the electrocardiogram (modified V2 lead), 1 channel of submental and 2 channels of anterior tibialis muscles, and 1 set of chest/abdomen movements. Heart rate and pulse oximetry were also continuously monitored by a finger probe. Airflow was detected

through a nasal cannula pressure transducer and a mouth thermistor. In addition, body position sensors and neck microphones were applied. Whole-night data were analyzed manually in 30-second epochs by the same trained physician and technician. At least 7 hours of recordings were available for each woman.

AHI is defined by the number of obstructive apneic and/or hypopneic events lasting more than 10 seconds of sleep that result in either arousal or 4% oxyhemoglobin desaturation. Apnea is defined as a cessation in airflow, whereas hypopnea is defined as a reduction in airflow of 30%. An AHI of 5 or more on polysomnography is defined as OSA [14]. The total arousal index (ARI) is defined as the number of arousals on the electroencephalogram per hour. Daytime sleepiness was assessed subjectively using a validated Chinese version of the Epworth Sleepiness Scale (ESS) questionnaire provided by Ning-Hung Chen (Chang Gung Memorial Hospital, Taipei, Taiwan) [15].

Statistical analyses were performed with the Stata software, version 8.0 (Stata Corp, College Station, TX, USA). All values are expressed as mean $\pm$ standard error of mean (mean $\pm$ SE). Differences between the 2 groups were compared using a 2-tailed unpaired t test. Multiple linear regressions were performed on AHI and hsCRP on body composition parameters, and polysomnographic, hormonal, and metabolic measurements in all patients. A Tobit regression model was also used to avoid biased parameter estimates. This model is based on the maximum likelihood estimation and is more robust than ordinary least square regressions, especially in analyzing cases of censored observations such as determinants of health status [16].

Two regression models were used to evaluate the effect of androgens on non-rapid eye movement (non-REM) stage AHI. The first model (AHI_{REM-1}) examined influences from AS and TT separately. As serum AS is the precursor of testosterone and could compete with testosterone for the androgen receptors, we tested whether the conversion rate or relative concentration of AS and TT, in addition to individual androgens, were related to respiratory events. We used the ratio of AS to TT instead of levels of AS and TT in our second model (AHI_{REM-2}). $P < 0.05$ was considered statistically significant.

3. Results

Baseline characteristics and hormone and metabolic measurements of the women in the nonobese PCOS and control groups are summarized in Tables 1 and 2. Nonobese women with PCOS had a higher waist circumference, waist-to-hip ratio, free androgen index, Ferriman–Gallwey score, LH/FSH ratio, serum levels of AS and TT, LH, prolactin, and hsCRP compared with the age- and BMI-matched control group who did not have PCOS. The women in the PCOS group also had lower sex hormone-binding globulin levels than the women in the control group. In the diagnosis of biochemical hyperandrogenemia, 88.9% (16 of

Table 1
Baseline characteristics of women in the nonobese PCOS and control groups^a.

	Control group (n = 10)	PCOS group (n = 18)	P value ^b
Age, y	31.6 $\pm$ 3.87	29.1 $\pm$ 1.43	0.549
Body weight, kg	53.6 $\pm$ 1.69	56.3 $\pm$ 1.57	0.259
Body height, cm	160 $\pm$ 1.75	161 $\pm$ 0.95	0.771
BMI	20.9 $\pm$ 0.58	21.7 $\pm$ 0.57	0.293
Waist circumference, cm	77.1 $\pm$ 1.51	85.4 $\pm$ 1.06	<0.001
Hip circumference, cm	93.7 $\pm$ 1.14	95.4 $\pm$ 1.03	0.289
Waist-to-hip ratio	0.82 $\pm$ 0.01	0.90 $\pm$ 0.01	<0.001
Nuchal circumference, cm	30.9 $\pm$ 0.47	31.7 $\pm$ 0.37	0.247
Body fat, %	26.8 $\pm$ 1.26	28.2 $\pm$ 1.11	0.409
Ferriman–Gallwey score	6.50 $\pm$ 1.82	15.2 $\pm$ 0.97	<0.001
Systolic BP, mm Hg	109 $\pm$ 4.14	109 $\pm$ 2.20	0.998
Diastolic BP, mm Hg	71.1 $\pm$ 3.65	68.3 $\pm$ 2.14	0.523

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PCOS, polycystic ovary syndrome; BP, blood pressure.

^a Values are given as mean $\pm$ SE.

^b P value from unpaired t test.

Table 2Hormone and metabolic characteristics of women in the nonobese PCOS and control groups^a.

	Control group (n = 10)	PCOS group (n = 18)	P value ^b
FSH, IU/L	8.80 ± 0.92	6.37 ± 0.44	0.032
LH, IU/L	6.24 ± 0.89	12.6 ± 2.53	0.027
LH/FSH	0.72 ± 0.11	1.99 ± 0.33	0.002
TT, ng/mL	0.41 ± 0.03	0.77 ± 0.10	0.005
AS, ng/mL	1.90 ± 0.12	3.52 ± 0.18	<0.001
DHEAS, µg/dL	183 ± 15.9	210 ± 17.2	0.266
17-OHP, ng/mL	1.64 ± 0.40	1.95 ± 0.27	0.522
SHBG, nmol/L	66.5 ± 5.40	47.7 ± 4.97	0.017
Free androgen index, ^c	2.08 ± 0.22	6.84 ± 2.09	0.036
Prolactin, ng/mL	11.6 ± 0.77	18.2 ± 1.44	<0.001
TSH, µU/mL	1.37 ± 0.33	1.58 ± 0.27	0.632
Fasting insulin, µU/mL	7.09 ± 0.81	7.33 ± 1.54	0.891
Fasting glucose, mg/dL	89.3 ± 1.34	87.1 ± 1.38	0.254
HOMA-IR ^d	1.57 ± 0.18	1.60 ± 0.35	0.940
hsCRP, mg/L	0.04 ± 0.01	0.18 ± 0.05	0.019

Abbreviations: PCOS, polycystic ovary syndrome; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TT, total testosterone; AS, androstenedione; DHEAS, dehydroepiandrosterone sulfate; 17-OHP, 17-hydroxyprogesterone; SHBG, sex hormone-binding globulin; TSH, thyroid-stimulating hormone; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein.

^a Values are expressed as mean ± SE.

^b P value from the unpaired t test.

^c The free androgen index = TT (ng/mL) × 3.47 × 100 / SHBG (nmol/L).

^d HOMA-IR = fasting glucose (mg/dL) × fasting insulin (µU/mL) / 405.

18) of PCOS patients had a serum androstenedione level greater than 2.44 ng/mL, 33.3% (6 of 18) of PCOS patients had a serum testosterone level greater than 0.80 ng/mL, and 22.2% (4 of 18) PCOS patients had both (data not shown). The serum levels of prolactin and thyroid stimulating hormone were all within normal limits.

The results of the overnight polysomnography recordings are shown in Table 3. A higher mean AHI (0.79 ± 0.21 vs 0.29 ± 0.09, *P* = 0.041) was recorded in the nonobese women with PCOS compared with the control group. The difference was more pronounced during the non-REM stage (AHI_{NREM}, 0.57 ± 0.19 vs 0.03 ± 0.03, *P* = 0.014). There was no difference between the PCOS and the control groups in any of the other polysomnographic variables. None of the 28 women had an AHI greater than 5, which is the standard for OSA. The range of AHI was 0–2.9 in the PCOS group and 0–0.8 in the control group. The percentage of women who had an AHI of 0 was 11% (2 of 18) in the PCOS group and 40% (4 of 10) in

Table 3Results of polysomnography for women in the nonobese PCOS and control groups^a.

	Control group (n = 10)	PCOS group (n = 18)	P value ^b
Sleep efficiency, %	92.5 ± 1.35	93.4 ± 1.19	0.640
Sleep latency, s	496 ± 99.5	671 ± 121	0.272
REM percentage	23.5 ± 1.27	23.3 ± 1.01	0.885
REM latency, min	84 ± 7.00	101 ± 9.53	0.166
AHI (total)	0.29 ± 0.09	0.79 ± 0.21	0.041
AHI _{REM}	0.26 ± 0.08	0.22 ± 0.06	0.744
AHI _{NREM}	0.03 ± 0.03	0.57 ± 0.19	0.014
ARI (total)	8.31 ± 1.30	11.2 ± 0.96	0.092
ARI _{REM}	6.04 ± 0.91	4.93 ± 0.73	0.348
ARI _{NREM}	8.9 ± 0.89	13.0 ± 1.22	0.011
ARI (spontaneous)	7.04 ± 1.31	9.46 ± 0.92	0.146
ARI (PLM-related)	1.38 ± 0.82	1.19 ± 0.53	0.851
PLM index, per h	1.92 ± 0.86	4.22 ± 1.77	0.254
ESS	9.00 ± 1.29	9.63 ± 0.95	0.703

Abbreviations: PCOS, polycystic ovary syndrome; REM, rapid eye movement stage; AHI, apnea–hypopnea index; NREM, non-rapid eye movement stage; ARI, arousal index; PLM, periodic limb movement; ESS, Epworth Sleepiness Scale.

Both total AHI and total ARI were further categorized into the rapid eye movement stage (AHI_{REM}, ARI_{REM}, respectively) and the non-REM stage (AHI_{NREM}, ARI_{NREM}, respectively). ARI that was spontaneous or related to periodic limb movements (PLM) was also counted.

^a Values are given as mean ± SE.

^b P value from the unpaired t test.

Table 4Linear Tobit regression results for the AHI during the NREM stage and hsCRP on body composition parameters, and polysomnographic, hormonal, and metabolic measurements in women in both the nonobese PCOS and control groups (*n* = 28).

Model	Variable	Coefficient	SE	P (variable)	P value (model)
AHI _{NREM} -1	AS	-1.036	0.335	0.006	0.0039
	TT	2.039	0.888	0.032	
	HOMA-IR	-0.625	0.257	0.024	
	SHBG	-0.024	0.017	0.187	
	Age	0.043	0.032	0.192	
	Body mass index	0.051	0.130	0.699	
	Presence of PCOS ^a	2.216	0.689	0.004	
AHI _{NREM} -2	AS/TT	-0.387	0.151	0.018	0.0045
	HOMA-IR	-0.493	0.237	0.049	
	SHBG	-0.038	0.022	0.098	
	Age	0.070	0.036	0.063	
	Body mass index	-0.047	0.139	0.738	
	Presence of PCOS ^a	1.710	0.634	0.013	
hsCRP	AHI _{REM}	0.276	0.109	0.020	0.0039
	AS	0.084	0.055	0.141	
	TT	-0.302	0.137	0.039	
	HOMA-IR	0.015	0.039	0.711	
	SHBG	-0.001	0.003	0.845	
	Age	0.002	0.005	0.708	
	Body mass index	0.030	0.020	0.147	
	Presence of PCOS ^a	0.124	0.094	0.202	

Abbreviations: AHI, apnea–hypopnea index; NREM, non-rapid eye movement; hsCRP, high-sensitivity C-reactive protein; PCOS, polycystic ovary syndrome; AS, androstenedione; TT, total testosterone; HOMA-IR, homeostasis model assessment of insulin resistance; SHBG, sex-hormone binding globulin; AS/TT, AS to TT ratio.

^a “Presence of PCOS” is a dummy variable that has a value of 1 when PCOS is present and 0 otherwise.

the control group. Mean arousal index in the non-REM stage (ARI_{NREM}) was higher in the PCOS group than in the control group.

The AHI_{NREM} was positively correlated with testosterone and negatively correlated with AS and homeostasis model assessment of insulin resistance (HOMA-IR) (Table 4) in the first model (AHI_{NREM}-1). Further regression for AHI_{NREM} on AS/TT showed a negative correlation between AHI_{NREM} and AS/TT (model AHI_{NREM}-2). In the model for hsCRP, hsCRP was positively correlated with AHI_{REM}, but negatively correlated with TT (Table 4). The HOMA-IR in all of the 28 patients was positively correlated with BMI (variable *P* = 0.034, model *P* = 0.031) and percentage fat (variable *P* = 0.008, model *P* = 0.007). None of the other polysomnographic measures, including AHI, was correlated with any of the anthropometric, hormonal, or biochemical measurements. No correlation was found between AS or TT and any of the anthropometric parameters.

4. Discussion

The main observation from the present study was that nonobese women with PCOS had more hypopneic–apneic events than the age- and BMI-matched control group. The nonobese PCOS patients had a higher level of hsCRP and this was positively correlated with AHI_{REM}. However, the AHI in the PCOS patients was not high enough to meet the OSA criteria. This could have been the result of the small number of patients, ethnic differences, the relatively low BMI, the specific patient group we chose (with polycystic ovaries and biochemical evidence of androgen excess), or the inclusion of AS in the diagnosis of biochemical hyperandrogenemia.

The results of the present study are consistent with the results of Fogel et al. [4] who found that women with PCOS had a higher AHI than BMI-matched controls. More specifically, without the direct effect of obesity, PCOS patients still had more hypopneic–apneic events during

sleep than the controls. Obesity may be a confounding factor in studies examining the link between OSA and PCOS [4,17]. Obesity is known to be a potential risk factor for OSA that is related to PCOS [2,8]. Increased adiposity has also been associated with hyperandrogenemia, IR, and glucose intolerance. Obesity changes the pattern of hyperandrogenemia in women with PCOS. The level of TT, rather than AS, is higher in obese than in nonobese patients with PCOS [18]. In Chinese women with PCOS, the prevalence of being overweight (BMI >24) was 30.4% [19]. Nevertheless, a cross-sectional study in Taiwanese women with PCOS revealed lower prevalence rates of overweight and obesity of 8.57% and 5.26%, respectively [20]. Compared with the results from Western countries where at least half of the patients with PCOS are overweight or obese [1,2], most Taiwanese women with PCOS are not obese. In our direct comparison between nonobese PCOS patients and age- and BMI-matched women without PCOS, it should be easier to determine to what extent PCOS itself is related to respiratory changes during sleep.

None of the patients with PCOS had an AHI that was high enough to fit the standard for diagnosing OSA. This result is compatible with a study by Ip et al. [21] in which the prevalence of OSA in Chinese women aged 30–39 years with a BMI of less than 23 was 0%. The mean BMI in women with PCOS in the present study was much lower than in previous studies in which women with PCOS were found to be more likely to have OSA than the women in the control group. This could be the reason why no OSA was detected in the present study. Nonetheless, Fogel et al. [4] found that women with PCOS were more likely than the BMI-matched controls (36.9 ± 1.3 vs 36.9 ± 1.4) to have symptomatic OSA (44.4% vs 5.5%). Similarly, Vgontzas et al. [3] showed that 8.3% of the nonobese women with PCOS (BMI <32.3) had OSA, compared with 0.0% of the controls. In a study by Tasali et al. [9], 56% of women with PCOS (BMI 35.3 ± 1.4 SE) and 19% of the controls (BMI 35.3 ± 1.6) had OSA. Insulin levels and measures of glucose tolerance in women with PCOS are strongly correlated with the risk and severity of OSA [4,9,10]. The finding in the present study that the women with PCOS did not exhibit OSA may have been related to the fact that their HOMA-IR was not higher than that of the controls. However, there may be ethnic differences in the prevalence of OSA due to genetic predispositions [8]. According to our preliminary results in Taiwan, it is unlikely that premenopausal patients with PCOS have OSA if they are not obese. PCOS itself might be a factor inducing or aggravating sleep apneic–hypopneic events. However, PCOS cannot induce OSA easily without the occurrence of obesity.

The AHI_{NREM} was positively correlated with serum TT in the present study. This is to a certain extent compatible with the results of Fogel et al. [4] in which the AHI was correlated mainly with serum TT but not with age or BMI in women with PCOS. Testosterone seems to have a negative or no effect on respiration [22]. It delays fetal lung development, and is the main active androgen secreted by human lung cell lines [23]. Zhou et al. [24] revealed that transdermal administration of testosterone facilitates development of central apnea during non-REM sleep in women.

Besides obesity, ethnicity also affects the presentation of androgen profiles in women with PCOS. Measuring androstenedione was considered important for documenting hyperandrogenism in Icelandic women [18,25]. Unexpectedly, our AHI_{NREM} was negatively correlated with serum AS. A further regression revealed a negative relationship between AS/TT and AHI_{NREM}. Androstenedione is a less potent androgen than testosterone. There have been few studies on AS and respiration. Androstenedione and testosterone are the only two androgens that compete for androgen receptors [22]. More AS indicates more competition for androgen receptors and hence the negative effect of testosterone on respiration might be weakened. Similarly, a relatively higher AS/TT ratio reflects a weaker conversion of AS into testosterone.

We selected patients with a BMI of less than 27 to exclude the effect of obesity. The small sample size is the main limitation to generalization of our findings. PCOS in nonobese women in Taiwan is linked to

increased obstructive respiratory events during sleep. Total testosterone levels in serum might play a role in this relationship. The high hsCRP levels in nonobese women with PCOS were positively correlated with rapid eye movement stage AHI.

Acknowledgments

This work was supported by a grant from Taipei Medical University, Taipei, Taiwan (95TMU-TMUH-09).

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