ORIGINAL ARTICLE

Sleep disorders in polycystic ovary syndrome: influence of obesity and hyperandrogenism

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SUMMARY

OBJECTIVE: *This study aims to evaluate the sleep of subjects with polycystic ovary syndrome (PCOS), with and without hyperandrogenism, in comparison with a healthy control group and examine the effects of hyperandrogenism and obesity on sleep parameters.*

METHODS: *A total of 44 volunteers were recruited to participate in the study. Clinical, biochemical and polysomnographic parameters were used to diagnose PCOS and hyperandrogenism. The evaluation of sleep quality was made using validated questionnaires and polysomnography test. The frequency of obstructive sleep apnea was also compared between the groups.*

RESULTS: *The study revealed that women with PCOS presented poorer subjective sleep quality, increased incidence of snoring and a higher risk of obstructive sleep apnea, based on the Berlin questionnaire. Also, after adjusting for body mass index, PCOS subjects had rapid eye movement (REM) time lower than those in the control group. PCOS women versus those without hyperandrogenism did not differ on any sleep measurement. Women with obstructive sleep apnea were only diagnosed in the PCOS group.*

CONCLUSIONS: *Our results indicate that PCOS impairs subjective sleep quality, as well as objective sleep quality, due to a reduction in REM sleep stage time in women diagnosed with the syndrome. Obesity affected sleep-related parameters but hyperandrogenism had no effect. Only the PCOS group had obstructive sleep apnea diagnosis.*

ABBREVIATIONS: *AHI = apnea-hypopnea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea; PCOS = polycystic ovary syndrome; PSG = polysomnography; PSQI = the Pittsburgh Sleep Quality Index; REM = rapid eye movement;*

KEYWORDS: *hormonal; hyperandrogenism; polycystic ovary syndrome; sleep; women.*

INTRODUCTION

Obstructive sleep apnea (OSA) is a syndrome characterized by recurrent events of partial or total obstruction of the upper airway during sleep, leading to intermittent hypoxemia, which has obesity as the pillar of its physiopathology.[1,2] Studies suggest that androgens influence sleep architecture, favoring the development of OSA.[3-5] In general, symptoms of OSA include fatigue, tiredness, maintenance insomnia, with polysomnography findings showing an increase in the apnea-hypopnea index (AHI), hypoxia

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and some impact on sleep architecture[6,7] Sleep complaints in women vary according to hormonal fluctuations dictated by their menstrual cycles.

Although women have proportionally less severe OSA and it is considered to predominantly affect the male population, a recent study found the disease in 26.1% of women[8]. The problem is likely to be more common, as women with sleep-disordered breathing are 2 to 3 times less likely to report classic symptoms of the disease (snoring, gasping, snorting and sleep apnea), which may lead to reduced clinical recognition of OSA in women compared to men.[9] Women suffering from PCOS tend to have higher levels of respiratory sleep events. It has been suggested that this may be linked to the increased androgen levels often associated with the syndrome.[2] Sleep itself acts as an important modulator of several aspects of endocrine function, making the relationship between these factors difficult to elucidate.[4,10,11]

Polycystic ovary syndrome (PCOS) is the most common endocrine disease, affecting approximately 8% of women in the reproductive stage.[12,13] It is well known that OSA prevalence is increased in women with PCOS compared with women without the disease.[13-15] There also are a broad range of hormonal and metabolic abnormalities in PCOS, and it has been suggested that the hormonal profile of those with the condition is associated with OSA.[16] Previous studies have shown higher levels of testosterone in PCOS patients to be related to OSA.[12,17] However, neither the outcomes of OSA nor the relationship of the symptoms with sleep architecture have been fully explored in this population. It has been hypothesized that obesity and hormonal factors, caused by the disease, act synergistically to impair quality of sleep. Therefore, our hypothesis is that females with PCOS are at increased risk of OSA and other sleep disorders. Our aim is to clarify this, and examine whether hyperandrogenism has any effect on sleep parameters by evaluating PCOS subjects (with and without hyperandrogenism) using polysomnography and sleep questionnaires and compare these patients with a healthy control group.

METHODS

Population

A total of 55 subjects were selected to participate in the study. The volunteers, ranging in age from 16 to 45 years, were recruited from the Endocrinology Division of the Federal University of São Paulo, Brazil. The diagnosis of PCOS was based on the latest 2003 Rotterdam consensus,[18] requiring the presence of at least two of the following features: (*1*) oligomenorrhea or chronic anovulation, (*2*) clinical and/or biochemical hyperandrogenism, and (*3*) ultrasound appearance of polycystic ovaries. These women were distributed into two groups: SOP with hyperandrogenism and SOP without hyperandrogenism.

The control group was comprised of 17 women. Inclusion criteria: a regular menstrual cycle of 28-30 days, normal BMI and in the follicular phase of the menstrual cycle. Exclusion criteria: neurologic conditions and/or being under psychiatric treatment; use of medication for chronic diseases that might interfere with the study results; participation in another clinical study or having participated in a clinical study within a period of 3 months; being a carrier of a disease; having a history of stroke; use of hypnotic, psychotropic, psychostimulant, and/or analgesic drugs; use of hormonal contraceptives; and presence of dysmenorrhea or endometriosis that may interfere with sleep patterns.

All procedures performed in the studies involving human participants followed the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee for Research of the Federal University of Sao Paulo (#0588/2010), and informed written consent was obtained from all subjects.

Subjects with other known causes of hyperandrogenism (such as congenital adrenal hyperplasia, androgen-secreting tumors and Cushing's syndrome), using oral contraceptives, corticosteroids, antidiabetic or lipid-lowering drugs in the previous 3 months, having a history of liver disease (such as viral hepatitis B and C, hemochromatosis and autoimmune hepatitis), diabetes mellitus, untreated hypothyroidism, renal, hepatic, cardiac or pulmonary disease, receiving treatment for sleep apnea using medications that alter liver enzymes, with a daily ingestion of more than 20 grams of ethanol, using drugs (sympathomimetics, sympatholytics, and β-blockers), with depression or with chronic diseases were excluded.[16]

Clinical, Anthropometric and Sonographic Measurement

Questionnaires were used to document clinical history, including regularity and length of menstrual cycles, and ovulation status. Signs of androgen excess (hirsutism, alo-

pecia, acne) were noted in the physical examination. Hirsutism with a Ferriman-Gallwey score of 8 or above was considered clinical evidence of androgen excess. Weight (in kilograms) and height (in meters) were measured. The body mass index (BMI) was calculated from the ratio of the weight to height squared.

All subjects underwent an ultrasound examination of the pelvis by the same radiologist. LOGIQ P5 (GE Healthcare®, Wauwatosa, WI) with an 8 MHz transvaginal transducer was used for the ultrasound of the pelvis.

Evaluation of Sleep and Polysomnography

Full-night polysomnography (PSG) was performed, using a digital system (EMBLA® S700®, Embla Systems Inc, Broomfield, CO) at the sleep laboratory for one night. Trained technicians visually scored all of the PSG data according to standardized criteria for investigating sleep.[19] Electroencephalogram arousals and sleep-related respiratory events were scored following the criteria outlined in the American Academy of Sleep Medicine Manual for Scoring Sleep and Associated Events.[20] OSA classification was defined according to the AHI.[21] Participants were diagnosed with OSA if they presented an AHI≥5 and sleep complaints. Participants with an AHI≥15 were diagnosed with OSA, regardless of whether they had any additional complaint.

For subjective evaluation of sleep, we used the Pittsburgh Sleep Quality Index (PSQI), which is an instrument for evaluating the subjective quality of sleep, as well as the number of sleep disturbances occurring during a period of 1 month.[22,23] The Berlin questionnaire, previously validated in a Brazilian Portuguese version, was used to assess the risk for sleep apnea.[24,25] Using this questionnaire's total score, it is possible to differentiate "good sleepers" (score≤5) and "poor sleepers" (score>5). Also, daytime somnolence was evaluated subjectively using the Epworth sleepiness scale (ESS),[26] with a score ≥10 considered excessive daytime sleepiness.

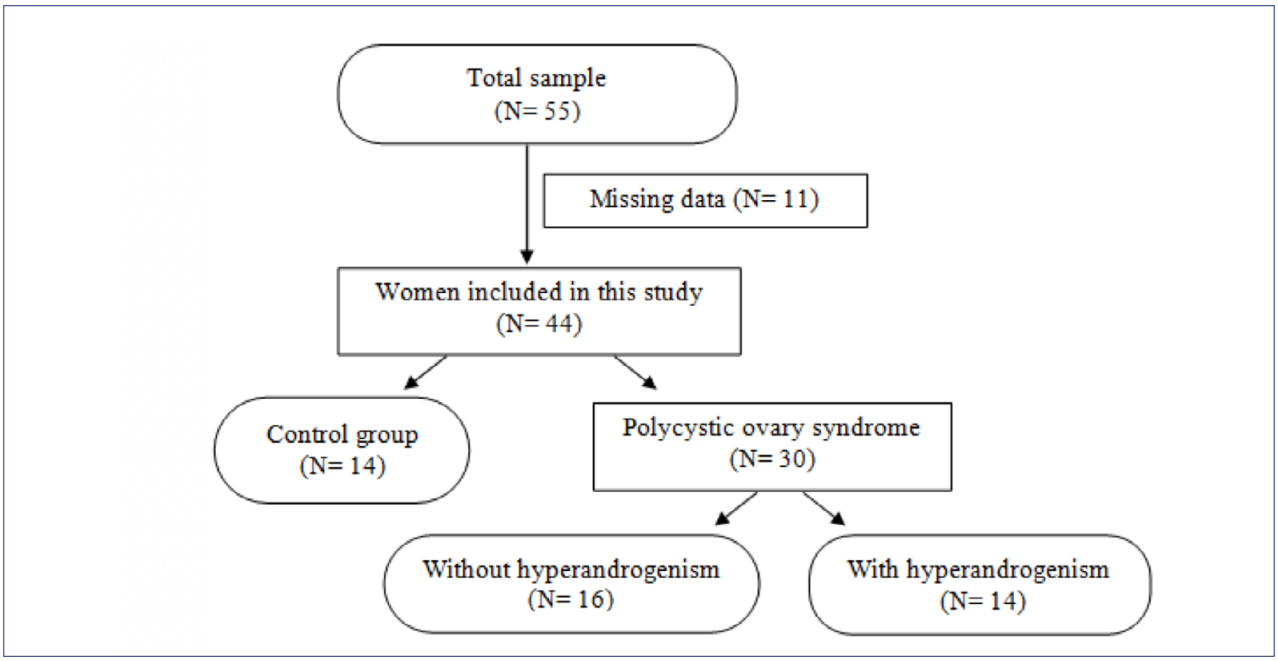
Laboratory Analysis

Total testosterone levels were measured using a UniCel Dxl 800 Immunoassay System (Beckman Coulter®, Brea, CA). The within-assay coefficient of variation for testosterone was 1.99%, and the between-assay coefficient was 4.22%. There are some limitations to measuring testosterone using a chemiluminescence immunoassay, but this was the only laboratory technique available. Serum-free testosterone and bioavailable testosterone were estimated using a previously validated formula.[27] All biochemical assays were performed at the Sleep Institute laboratory.

Statistical analysis

The variables were evaluated regarding normality (Shapiro-Wilk's test) and homogeneity (Levene's test). When the distribution was demonstrated to be nonparametric, the data were standardized through

FIGURE 1. FLOW CHART OF THE DESCRIPTION OF THE STUDY SAMPLE.



Z-score. Statistical analysis of the sample was carried out using the General Linear Model through one-way analysis of variance for continuous variables, and Pearson's chi-squared test was performed to determine the association between categorical variables. To evaluate the relationship between age and BMI with the sleep-related factors, Pearson's correlation test was performed. BMI and age were used as adjustment factors in evaluating the effect of PCOS and hyperandrogenism on sleep, respectively. The results were submitted to adjustment only when the groups had significant statistical differences in age or BMI. The significance level was set to $P<0.05$. Data are presented as mean±standard error of the mean or as frequency (percentage).

RESULTS

From a total of 55 women initially included in the study, 11 individuals were excluded because of missing data (8 related to the PSQI and 3 to BMI). Our final sample of 44 women comprised 14 healthy women and 30 women with PCOS, of whom 14 had a diagnosis of hyperandrogenism (Figure 1).

The descriptive data of the sample analyzed in the study were distributed as healthy women (control group) and women with PCOS. We observed a higher BMI in the PCOS group ($F1,42=36,404$; $P<0.001$) compared to the control group. Regarding the sleep evaluation questionnaires, a higher frequency of women with PCOS was categorized as: high risk (Berlin Questionnaire) ($\chi^2=12,156$; $df=1$; $P<0.001$), poor sleepers (PSQI) ($\chi^2=8,696$; $df=1$; $P<0.01$), snorers ($\chi^2=3,889$; $df=1$; $P<0.05$) and OSA ($\chi^2=5,280$; $df=1$; $P<0.05$). There were no differences in frequency of sleepiness as measured by the Epworth Sleepiness Scale between women with PCOS and the control group. Results presented in Table 1 indicated that age was not statistically different between the groups since the inclusion criteria of the study were strictly followed. Table 2 shows the polysomnography results from the PCOS group adjusted for BMI, which indicate that the percentage of REM sleep was lower in the PCOS group than in the control group ($F1,41=7,245$; $P<0.05$). The effect of BMI as confounding factor was a significant covariate for Pittsburgh sleep scale ($P=0.039$), N1 sleep stage ($P=0.010$), N3 sleep stage ($P=0.003$), REM sleep stage ($P=0.043$), number of Arousals ($P=0.002$), arousals index ($P<0.001$), PLM index ($P=0.021$) and mean oxygen saturation ($P=0.033$).

We also evaluated the possible effect of hyperandrogenism on the objective and subjective aspects of sleep in women with PCOS. A description of the sample indicated that women with hyperandrogenism were younger than the PCOS subjects without hyperandrogenism, 32.2±1.3 for women without hyperandrogenism and 25.6±1.4 3 for women with hyperandrogenism ($F1,28=15,674$; $P<0.001$). There were no observed differences in the following variables: BMI, the frequency of women with high-risk of apnea according to the Berlin Questionnaire, poor sleepers, sleepiness, snoring and those diagnosed with OSA. No differences were seen in the scores for the ESS and the PSQI questionnaires, and there were no differences in the polysomnographic parameters of women with hyperandrogenism in comparison with those without hyperandrogenism when adjusted for age.

The effect of age as a confounding factor was a significant covariate for the following factors: N3 sleep stage ($P=0.039$) and REM sleep stage ($P=0.026$). Sleep-related factors were correlated with age and BMI through Pearson's correlation test considering all participants. The REM sleep stage was the only significant parameter in the correlation between age and sleep-related factors ($r=0.329$, $P=0.029$). On the other hand, the correlation between BMI and sleep-related

TABLE 1. DESCRIPTIVE PARAMETERS OF ALL THE PATIENTS RECRUITED FOR THIS STUDY.

Variables	Control (N=14)	PCOS (N=30)	P-value
Age (years)	27.9±1.7	29.7±1.2	0.412
Body Mass Index (weight/height2)	22.4±1.6	34.3±1.1***	<0.001
High risk for OSA (Berlin questionnaire)	1 (7.1%)	19 (63.3%)***	<0.001
High daytime sleepiness (ESS, score≥10)	5 (35.7%)	15 (50%)	0.375
Poor sleep quality (PSQI, score>5)	7 (50%)	27 (90%)**	0.003
Reported snoring	10 (71.4%)	28 (93.3%)*	0.049
Meet criteria for OSA (from PSG)	0 (0%)	9 (30%)*	0.022

Legend: ESS, Epworth sleepiness scale; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome; PSQI, Pittsburgh sleep quality index. The data were presented as mean±SEM or number (%).Note: *P<0.05, **P<0.01 and ***P<0.001 compared to the control group.

TABLE 2. SUBJECTIVE AND OBJECTIVE PARAMETERS OF SLEEP FOR EVALUATION OF POLYCYSTIC OVARY SYNDROME (PCOS) AND CONTROL GROUP, P-VALUE WAS ADJUSTED PER BODY MASS INDEX.

Variables	Control (N=14)	PCOS (N=30)	P-value
ESS score	8.4±1.2	8.5±0.8	0.575
PSQI score	4.6±0.8	8.5±0.5	0.105
Sleep latency (min)	15.9±5.2	26.3±3.5	0.432
REM latency (min)	120.7±16.0	126.6±10.9	0.742
Total sleep time (min)	366.8±16.4	339.4±11.2	0.396
Sleep efficiency (%)	88.0±2.9	80.0±2.0	0.358
N1 sleep stage (% TST)	3.3±1.6	11.5±1.1	0.144
N2 sleep stage (% TST)	47.7±2.3	45.9±1.6	0.585
N3 sleep stage (% TST)	27.9±2.6	25.2±1.8	0.152
REM sleep stage (% TST)	20.5±1.6	17.3±1.1*	0.010
WASO (min)	30.7±10.7	59.1±7.3	0.596
Arousal index (events/h)	12.6±3.2	18.9±2.2	0.198
PLM (events/h)	0.3±0.7	1.5±0.5	0.630
AHI (events/h)	1.6±3.8	9.2±2.6	0.765
Basal oxygen saturation	97.3±0.3	96.9±0.2	0.714
Mean oxygen saturation	96.6±0.3	95.9±0.2	0.873
Minimum oxygen saturation	92.0±1.3	89.5±0.9	0.890

Legend: AHI, apnea-hypopnea index; ESS, Epworth sleepiness scale; PCOS, polycystic ovary syndrome; PLM, periodic limb movements; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement; WASO, wake after sleep onset. The data were presented as mean±SEM. Note: *P<0.05 compared to the control group.

TABLE 3. SUBJECTIVE AND OBJECTIVE PARAMETERS OF SLEEP FOR EVALUATION OF HYPERANDROGENISM, P-VALUE WAS ADJUSTED PER AGE.

	Women with polycystic ovary syndrome		
Variables	Without hyperandrogenism (N=16)	With hyperandrogenism (N=14)	P-value
ESS score	8.8±1.2	8.2±1.3	0.380
PSQI score	8.2±1.0	8.8±1.1	0.739
Sleep latency (min)	22.9±5.4	30.2±5.8	0.677
REM latency (min)	116.6±16.1	138.1±17.2	0.480
Total sleep time (min)	337.6±15.3	341.4±16.4	0.883
Sleep efficiency (%)	80.4±3.1	79.6±3.3	0.469
N1 sleep stage(% TST)	10.7±1.8	12.5±1.9	0.276
N2 sleep stage (% TST)	45.0±2.1	46.8±2.3	0.599
N3 sleep stage (% TST)	26.1±2.3	24.3±2.5	0.095
REM sleep stage (% TST)	18.3±1.3	16.3±1.4	0.605
WASO (min)	61.6±11.9	56.3±12.7	0.437
Arousal index (events/h)	18.6±3.2	19.3±3.4	0.515
PLM (events/h)	1.4±0.8	1.6±0.8	0.320
AHI (events/h)	6.1±4.3	12.8±4.6	0.507
Basal oxygen saturation	96.9±0.3	96.9±0.3	0.573
Mean oxygen saturation	96.1±0.4	95.8±0.4	0.407
Minimum oxygen saturation	91.1±1.4	87.7±1.5	0.184

Legend: AHI, apnea-hypopnea index; ESS, Epworth sleepiness scale; PCOS, polycystic ovary syndrome; PLM, periodic limb movements; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eyes movements; WASO, wake after sleep onset. The data were presented as mean±SEM.

factors showed statistical significance for: sleep efficiency (r=-0.338, *P*=0.025), N1 sleep stage (r=0.611, *P*<0.001), N3 sleep stage (r=-0.410, *P*=0.006), wakefulness after sleep onset (r=0.388, *P*=0.009), arousals index (r=0.533, *P*<0.001), periodic limb movements (r=0.403, *P*=0.007), apnea–hypopnea index (r=0.406, *P*=0.006), basal oxygen saturation (r=-0.333, *P*=0.027), mean oxygen saturation (r=-0.409, *P*=0.006) and minimum oxygen saturation (r=-0.370, *P*=0.013).

DISCUSSION

The findings of this study revealed that the PCOS group presented poorer sleep quality and reduced REM sleep time when compared to the control group. Also, there was a higher risk of apnea according to the Berlin Questionnaire, poorer sleep quality measured by the PSQI and a higher frequency of snorers in PCOS subjects compared to controls. In women with PCOS, no effect of hyperandrogenism was observed on sleep pattern, neither subjectively or objectively

Obesity is common among women with PCOS, but it is not part of the diagnostic criteria. This association has been previously demonstrated.[28] Moreover, the increased anthropometric measures arising from obesity also impact the following factors: increased obstruction of the upper airway events, hypoxia, sleep fragmentation, fatigue and perception of non-refreshing sleep.[7] Thus, the PSG data were adjusted for BMI in the analysis of the PCOS effect. The effect of PCOS on sleep architecture is controversial in the literature,[29,30] however several studies point to an increased risk of obstructive sleep apnea, decreased REM sleep and sleep efficiency.[12,31-33] These studies demonstrated that PCOS promotes a decrease in REM sleep, which is not seen in an obese control group without PCOS. The cause of decreased REM sleep in women with PCOS is still unknown. Our main hypothesis is that obesity and PCOS are strongly associated, resulting in a variety of consequences for the body, specifically neurophysiological impacts. It is possible that adjusting for BMI is not enough to account for all the repercussions promoted by the synergistic action of both factors. The sleep quality, snoring and diagnosis of OSA are factors clinically important due to the increased weight observed in women with PCOS.

In obese women with PCOS the incidence of OSA is increased at 41–58%[13] with the finding that their BMI does not correlate with their OSA severity.[2,34] In adolescent girls (15 years) with PCOS (n=31) compared with healthy obese girls without PCOS (n=19) neither group had significant OSA although total sleep time, percentage of REM sleep and sleep efficiency was lower in girls with PCOS.[33] Symptoms of PCOS usually begin in adolescence and perhaps OSA develops in a sub-group of females over time along with worsening insulin resistance. Thus, age might have been a protective factor for OSA in the group of women with PCOS and hyperandrogenism in the current study. A relationship between OSA severity with waist-to-hip ratio and elevated serum testosterone may over time contribute to the higher prevalence of OSA in women with PCOS.

The chronic reduction of REM sleep can lead to memory loss, failure to consolidate cognitive processes and metabolic disorders. Thus, untreated PCOS can have long term effects and cause other health problems, in addition to infertility. The findings show that the consequences of the disease were associated with damage to subjective sleep quality. Regarding objective aspects of sleep, the lower percentage of REM sleep in women with PCOS sleep could explain the perception of poor quality sleep in this group. Suppression of REM sleep can jeopardize women's health by damaging long term memory, increasing pain sensitivity and weight gain.[35-37] The reduction of REM sleep observed in women with PCOS (Table 2) does not seem to be related to PCOS, but due to increased BMI, snoring, high-risk group classification in the Berlin Questionnaire and frequency of women diagnosed with OSA. The current knowledge of the pathophysiology of PCOS has no evidence of the influence of the disease on sleep architecture.[38,39]

The negative correlation between sleep efficiency, N3 sleep stage and BMI demonstrated that increased body weight affects the distribution of sleep stages and hinders the deepening of sleep. Simultaneously, increased BMI showed a positive correlation with N1 stage sleep, wakefulness after sleep onset, arousals and apnea-hypopnea index. These results demonstrate a poor quality, fragmented superficial sleep. As a result, oxygen saturation levels were decreased significantly.

The statistical analysis of the sleep questionnaire shows that the PCOS group are at increased risk for presence of obstructive sleep apnea syndrome. Also, the self-perception of snoring during sleep can be a complementary signal in the clinical assessment of sleep. The frequency of women considered poor sleepers was significantly higher in the PCOS group. The increase in the prevalence of obstructive sleep apnea in PCOS subjects was associated with changes in sex hormones (increased androgens and/or decreased estrogens) and increased visceral adiposity.[13]

Considering only the women with PCOS, this study indicates that there were no differences regarding the risk for OSA in the analysis of the effect of hyperandrogenism. The results show that the

group with hyperandrogenism was younger than those in the group without hyperandrogenism. The adjustments for obesity and age were essential to exclude the influence of potential confounding factors. Also, the subjective and objective parameters of sleep did not differ between groups. This finding reveals that higher testosterone levels do not impair women's sleep quality. The initial hypothesis that testosterone could be responsible for snoring, sleep fragmentation, and respiratory disorder is not supported by our findings.[40] Other studies support the fact that women's sleep quality is not associated with increased testosterone, but that female hormones actually have a protective effect.[41] Progesterone increases respiratory drive and the action of the dilator muscles of the upper airway;[42,43] corroborating the suggestion that hormone therapy in postmenopausal women can act as a protective factor against to the obstructive sleep apnea syndrome.

Exogenous administration of testosterone has been shown to induce sleep apnea events in women.[44] The adverse effects of testosterone therapy on sleep cause a shortened sleep, worsened sleep apnea, and increased hypoxemia.[4] Testosterone increases baseline ventilation during wakefulness, altering the apneic threshold and increasing ventilator sensitivity to CO2 during sleep in healthy women.[3,5,45] However, a randomized, double-blind, placebo-controlled study demonstrated that impaired sleep quality as a consequence of sleep-disordered breathing was fleeting in the first weeks of daily administration of testosterone and that testosterone does not have a long-term effect.[46,47] A large epidemiological study, The Seattle Midlife Women's Health Study, found no significant association between disruption in sleep and testosterone, merely observing a negative trend.[48] Therefore all women with PCOS should undergo a sleep evaluation as there does seem to be a link between PCOS and sleep problems.[49]

In addition to hyperandrogenism and ovulatory dysfunction, PCOS may cause other common characteristics, such as abnormal gonadotrophin secretion, insulin resistance, and dyslipidemia. Insulin resistance and hyperinsulinemia are relevant pathophysiological consequences of the disease, affecting up to 75% of women with the syndrome.[50] Regarding the treatment of PCOS, the first choice is to adopt healthy lifestyle habits, such as dietary reeducation and physical exercise. As a result, weight loss potentially favors the fall of circulating androgens, improving lipid profile, reducing peripheral insulin resistance and regularization of ovulatory function. The prescription of low-dose oral hormonal contraceptives promotes control of menstrual irregularity and reduced risk of endometrial cancer.[51]

Some limitations of the study need to be considered. Biochemical analysis of testosterone was performed only in the sample PCOS women but not in the control group (healthy) because of the absence of clinical criteria for the disease. The analysis of both groups could provide a comparative assessment of the hormone levels in PCOS and hyperandrogenism. Despite these limitations, this study reveals that REM sleep time was reduced in women with PCOS.

CONCLUSIONS

Our results indicate that PCOS impairs subjective and objective sleep quality, due to reduced REM sleep time. Hyperandrogenism, characterized by higher free testosterone levels, did not have any effect on sleep-related parameters. Therefore, the findings confirm the hypothesis that women's sleep is mainly affected by obesity.

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RESUMO

OBJETIVO: *Este estudo objetivou avaliar o sono de mulheres com síndrome do ovário policístico, com e sem hiperandrogenismo, em comparação com um grupo controle saudável, e estudar os efeitos do hiperandrogenismo e da obesidade nos parâmetros do sono.*

MÉTODOS: *Um total de 44 voluntárias foram recrutadas para participar do estudo. Os parâmetros clínicos, bioquímicos e polissonográficos e foram usados para diagnosticar SOP e hiperandrogenismo. A avaliação da qualidade de sono foi feita usando questionários validados e o exame polissonográfico. A frequência de síndrome da apneia obstrutiva também foi comparada entre os grupos.*

RESULTADOS: *O estudo revelou que mulheres com SOP apresentaram menor qualidade de sono subjetiva, incidência aumentada de ronco e maior risco para síndrome da apneia obstrutiva, baseada no questionário de Berlin. Ademais, após o ajuste para índice de*

massa corpórea, mulheres com SOP tiveram menor tempo de sono REM do que aquelas do grupo controle. Dentre as mulheres com SOP, aquelas com hiperandrogenismo não tiveram diferenças em nenhuma variável do sono. Mulheres com síndrome da apneia obstrutiva foram diagnosticadas no grupo SOP.

CONCLUSÕES: *Nossos resultados indicam que a SOP afeta a qualidade subjetiva de sono, bem como a qualidade objetiva e do sono, em razão da redução do tempo de sono REM em mulheres diagnosticadas com a síndrome. A obesidade afetou parâmetros relacionados ao sono, mas o hiperandrogenismo não teve efeito. A síndrome da apneia obstrutiva somente foi diagnosticada em mulheres com SOP.*

PALAVRAS-CHAVES: *hormonal; hiperandrogenismo; síndrome do ovário policístico; sono; mulheres.*

REFERENCES

1. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 2000;85:1151-8.
2. 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.
3. Behan M, Wenninger JM. Sex steroidal hormones and respiratory control. *Respir Physiol Neurobiol* 2008;164:213-21.
4. Andersen ML, Alvarenga TF, Mazaro-Costa R, Hachul HC, Tufik S. The association of testosterone, sleep, and sexual function in men and women. *Brain Res* 2011;1416:80-104.
5. 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.
6. International classification of sleep disorders. *Diagnostic and coding manual (ICSD-3)*. Westchester, IL: American Academy of Sleep Medicine Task Force (AASM); 2014.
7. Polesel DN, Hirotsu C, Nozoe KT, et al. Waist circumference and postmenopause stages as the main associated factors for sleep apnea in women: a cross-sectional population-based study. *Menopause* 2015;22:835-44.
8. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. *Sleep Med* 2010;11:441-6.
9. Ye L, Pien GW, Weaver TE. Gender differences in the clinical manifestation of obstructive sleep apnea. *Sleep Med* 2009;10:1075-84.
10. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;354:1435-9.
11. Leproult R, Van Cauter E. Role of sleep and sleep loss in hormonal release and metabolism. *Endocr Dev* 2010;17:11-21.
12. Mokhlesi B, Scoccia B, Mazzone T, Sam S. Risk of obstructive sleep apnea in obese and nonobese women with polycystic ovary syndrome and healthy reproductively normal women. *Fertil Steril* 2012;97:786-91.
13. Tasali E, Van Cauter E, Ehrmann DA. Polycystic Ovary Syndrome and Obstructive Sleep Apnea. *Sleep Med Clin* 2008;3:37-46.
14. Nandalike K, Strauss T, Agarwal C, et al. Screening for sleep-disordered breathing and excessive daytime sleepiness in adolescent girls with polycystic ovarian syndrome. *J Pediatr* 2011;159:591-6.
15. Nitsche K, Ehrmann DA. Obstructive sleep apnea and metabolic dysfunction in polycystic ovary syndrome. *Best Pract Res Clin Endocrinol Metab* 2010;24:717-30.
16. Tock L, Carneiro G, Togeiro SM, et al. Obstructive sleep apnea predisposes to nonalcoholic Fatty liver disease in patients with polycystic ovary syndrome. *Endocr Pract* 2014;20:244-51.
17. Yang HP, Kang JH, Su HY, Tzeng CR, Liu WM, Huang SY. Apnea-hypopnea index in nonobese women with polycystic ovary syndrome. *Int J Gynaecol Obstet* 2009;105:226-9.
18. Group REA-SPCW. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004;81:19-25.
19. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Los Angeles, CA: Brain Information Service/Brain Research Institute, UCLA; 1968.
20. Iber C, Ancoli I, Cheeson A, Quan S. *The AASM manual for scoring of sleep associated events: rules, terminology and techical specifications*. Wetchester, IL: American Academy of Sleep Medicine; 2007.
21. *Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research*. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667-89.
22. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193-213.
23. Bertolazi AN, Fagondes SC, Hoff LS, et al. Validation of the Brazilian Portuguese version of the Pittsburgh Sleep Quality Index. *Sleep Med* 2011;12:70-5.
24. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999;131:485-91.
25. Massierer D, Martinez D, Fuchs SC, et al. Obstructive sleep apnea, detected by the Berlin Questionnaire: an associated risk factor for coronary artery disease. *Cad Saude Publica* 2012;28:1530-8.
26. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-5.
27. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 1999;84:3666-72.
28. Esmaeilzadeh S, Andarieh MG, Ghadimi R, Delavar MA. Body mass index and gonadotropin hormones (LH & FSH) associate with clinical symptoms among women with polycystic ovary syndrome. *Glob J Health Sci* 2015;7:101-6.
29. de Sousa G, Schlüter B, Buschatz D, et al. The impact of insulin resistance and hyperandrogenemia on polysomnographic variables in obese adolescents with polycystic ovarian syndrome. *Sleep Breath* 2012;16:169-75.
30. Moran LJ, March WA, Whitrow MJ, Giles LC, Davies MJ, Moore VM. Sleep disturbances in a community-based sample of women with polycystic ovary syndrome. *Hum Reprod* 2015;30:466-72.
31. Tasali E, Van Cauter E, Ehrmann DA. Relationships between sleep disordered breathing and glucose metabolism in polycystic ovary syndrome. *J Clin Endocrinol Metab* 2006;91:36-42.
32. de Sousa G, Schlüter B, Menke T, Trowitzsch E, Andler W, Reinehr T. A comparison of polysomnographic variables between adolescents with polycystic ovarian syndrome with and without the metabolic syndrome. *Metab Syndr Relat Disord* 2011;9:191-6.
33. de Sousa G, Schlüter B, Menke T, Trowitzsch E, Andler W, Reinehr T. Relationships between polysomnographic variables, parameters of glucose metabolism, and serum androgens in obese adolescents with polycystic ovarian syndrome. *J Sleep Res* 2011;20:472-8.
34. Gopal M, Duntley S, Uhles M, Attarian H. The role of obesity in the increased prevalence of obstructive sleep apnea syndrome in patients with polycystic ovarian syndrome. *Sleep Med* 2002;3:401-4.
35. Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. *Sleep* 2006;29:145-51.
36. Liu X, Forbes EE, Ryan ND, Rofey D, Hannon TS, Dahl RE. Rapid eye movement sleep in relation to overweight in children and adolescents. *Arch Gen Psychiatry* 2008;65:924-32.
37. Meerlo P, Mistlberger RE, Jacobs BL, Heller HC, McGinty D. New neurons in the adult brain: the role of sleep and consequences of sleep loss. *Sleep Med Rev* 2009;13:187-94.
38. Suri J, Suri JC, Chatterjee B, Mittal P, Adhikari T. Obesity may be the common pathway for sleep-disordered breathing in women with polycystic ovary syndrome. *Sleep Med* 2016;24:32-9.
39. Franik G, Krysta K, Madej P, et al. Sleep disturbances in women with polycystic ovary syndrome. *Gynecol Endocrinol* 2016;32:1014-7.
40. Cistulli PA, Grunstein RR, Sullivan CE. Effect of testosterone administration on upper airway collapsibility during sleep. *Am J Respir Crit Care Med* 1994;149:530-2.
41. Hachul H, Andersen ML, Bittencourt L, Santos-Silva R, Tufik S. A popu-

lation-based survey on the influence of the menstrual cycle and the use of hormonal contraceptives on sleep patterns in São Paulo, Brazil. *Int J Gynaecol Obstet* 2013;120:137-40.

42. Martins AB, Tufik S, Moura SM. Physiopathology of obstructive sleep apnea-hypopnea syndrome. *J Bras Pneumol* 2007;33:93-100.

43. Marcouiller F, Boukari R, Laouafa S, Lavoie R, Joseph V. The nuclear progesterone receptor reduces post-sigh apneas during sleep and increases the ventilatory response to hypercapnia in adult female mice. *PLoS One* 2014;9:e100421.

44. Johnson MW, Anch AM, Remmers JE. Induction of the obstructive sleep apnea syndrome in a woman by exogenous androgen administration. *Am Rev Respir Dis* 1984;129:1023-5.

45. Ahuja D, Mateika JH, Diamond MP, Badr MS. Ventilatory sensitivity to carbon dioxide before and after episodic hypoxia in women treated with testosterone. *J Appl Physiol* 2007;102:1832-8.

46. Killick R, Wang D, Hoyos CM, Yee BJ, Grunstein RR, Liu PY. The effects of testosterone on ventilatory responses in men with obstructive sleep apnea: a randomised, placebo-controlled trial. *J Sleep Res* 2013;22:331-6.

47. Melehan KL, Hoyos CM, Yee BJ, et al. Increased sexual desire with exogenous testosterone administration in men with obstructive sleep apnea: a randomized placebo-controlled study. *Andrology* 2016;4:55-61.

48. Woods NF, Smith-Dijulio K, Percival DB, Tao EY, Taylor HJ, Mitchell ES. Symptoms during the menopausal transition and early postmenopause and their relation to endocrine levels over time: observations from the Seattle Midlife Women's Health Study. *J Womens Health (Larchmt)* 2007;16:667-77.

49. Chatterjee B, Suri J, Suri JC, Mittal P, Adhikari T. Impact of sleep-disordered breathing on metabolic dysfunctions in patients with polycystic ovary syndrome. *Sleep Med* 2014;15:1547-53.

50. Junqueira PAA, Fonseca AM, Aldrighi JJ. Síndrome dos Ovários Policísticos. *Rev Assoc Med Bras* 2003; 49:13-4.

51. Lopes IM, Baracat MC, Simões MdeJ, Simões RS, Baracat EC, Soares Junior JM. Endometrium in women with polycystic ovary syndrome during the window of implantation. *Rev Assoc Med Bras* 2011;57:702-9.