Research Article (Araştırma Makalesi)

Polycystic Ovary Syndrome and Sleep Disorders: Association Between Metabolic and Androgenic Alterations with Sleep Components

Polikistik Over Sendromu ve Uyku Bozuklukları: Uyku Bileşenleri ile Metabolik ve Androjenik Bozukluklar Arasındaki İlişki

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Özet

Amaç: Polikistik over sendromlu (PKOS) hastalarda uyku kalitesinin araştırılması ve metabolik parametrelerin uyku bozuklukları üzerine etkilerini incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya PKOS tanısı alan 50 hasta ve 51 normal sağlıklı gönüllü dahil edildi. Uyku kalitesini değerlendirmek için Pittsburgh Uyku Kalitesi İndeksi (PSQİ) kullanıldı. İndeks, 18 madde ve yedi bileşenden oluşmaktadır ve endekse göre alınan beş veya daha fazla toplam puan, kötü uyku kalitesini göstermektedir. Uyku kalitesi skorları belirlendikten sonra serum insülin, trigliserit, kolesterol, açlık glikoz ve androjen seviyeleri geriye dönük olarak kaydedildi ve tüm parametreler gruplar arasında karşılaştırıldı.

Bulgular: PKOS'lu hastalarda uyku kalitesi, sağlıklı kontrol grubuna göre daha düşüktü fakat istatistiksel olarak anlamlı değildi ($p>0.05$). Serum Dihidroepiandrosteron sülfat (DHESO4) ve total testosteron düzeyi ile uyku süresi ve toplam PSQİ skorları arasında anlamlı negatif korelasyon vardı. Ek olarak serum total testosteron düzeyi ile de uyku gecikmesi, uyku bozuklukları ve öznel uyku kalitesi arasında anlamlı negatif korelasyon saptandı. Ayrıca uyku kalitesi düşük olan hastaların serum DHESO4 ve testosteron düzeyleri normal uyku kalitesine sahip olanlara göre anlamlı olarak daha düşüktü ($p<0.05$).

Sonuç: Polikistik over sendromundaki androjenik değişiklikler uyku komponentlerini olumsuz yönde etkileyebilir. Bu hastaların rutin takiplerinde metabolik ve androjenik bozuklukların yanı sıra uyku bozuklukları da olabileceği akılda tutulmalıdır.

Anahtar kelimeler: Dislipidemi, Pittsburgh Uyku Kalitesi İndeksi, Polikistik over sendromu, Uyku kalitesi

Abstract

Objective: To investigate the sleep quality in patients with polycystic ovary syndrome (PCOS) and to examine the effects of metabolic parameters on sleep disturbances.

Material and Methods: The study included 50 patients diagnosed as PCOS and 51 normal healthy volunteers. The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate the sleep quality. Index consists of 18 items and seven components and according to the index, the total scores of five or more indicate a poor sleep quality. After the sleep quality scores were determined, serum insulin, triglyceride, cholesterol, fasting glucose and androgen levels were recorded retrospectively and all parameters compared between groups.

Results: The sleep quality was lower in the patients with polycystic ovary syndrome than in the healthy control group but this was not statistically significant ($p>0.05$). Serum dehydroepiandrosterone sulfate (DHESO4) and total testosterone level had a significant negative correlation with sleep duration and total PSQI scores. In addition, serum total testosterone level also had a significant negative correlation with sleep latency, sleep disturbance and subjective sleep quality. Besides, the patients with the poor sleep quality had significantly lower serum dehydroepiandrosterone sulfate and testosterone levels than those with a normal sleep quality ($p<0.05$).

Conclusion: Androgenic alterations in polycystic ovary syndrome may have a negative effect on their sleep components. It should be kept in mind during routine follow-ups of these patients that they can have sleep disturbances as well as metabolic and androgenic disorder.

Keywords: Dyslipidemia, The Pittsburgh Sleep Quality Index, Polycystic ovary syndrome, Sleep quality

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is known to be a syndrome which can appear in 6%-8% of the women in their reproductive age and accompanied by metabolic dysfunctions (1). PCOS is characterized by hyperandrogenism, oligomenorrhea or amenorrhea and typical ovarian morphology (2). Currently, there is an agreement that the Rotterdam criteria can be utilized to diagnose PCOS in adult women. Fulfillment of two of the following three characteristics yields the diagnosis: oligomenorrhea or anovulation, hyperandrogenism, or polycystic ovary morphology on ultrasound with exclusion of other disorders (3).

Although studies showing that sleep disorders are common in PCOS are generally conducted on a small number of case groups, the frequency of obstructive sleep apnea (OSA) was found to be significantly higher in the PCOS group. It has been shown that the presence of OSA is accompanied by deterioration in metabolic parameters. It is stated that not only the frequency of OSA but also other forms of sleep disorders are higher in PCOS (4). In a study investigating the pathogenesis of sleep disorders seen in PCOS, it was shown that the REM (rapid eye movements) phase duration of sleep was shortened, sleep efficiency decreased and the time to fall asleep was prolonged in the obese PCOS group (5). For this reason, some guidelines have started recommending screening for sleep disorders in obese women with PCOS (6).

Sleep disturbances are defined as decreased sleep duration, prolonged duration of falling asleep and waking up earlier. Prior studies have shown a relation between PCOS and sleep disturbances (7-14). Patients with PCOS have been reported to have sleep apnea syndrome and hypersomnia more frequently (9). It has been known for years that obesity in patients with PCOS had a relation with OSA (15). The incidence of OSA is about 17% in the adult population, but it can increase to 58% in the overweight population (16). The Pittsburgh Sleep Quality Index (PSQI) is a practical index used to evaluate the sleep quality. It allows a multifaceted evaluation of sleep (17). In fact, it has been reported in the past years that patients with PCOS experience sleep disturbances. However, there have been few studies on the relation between sleep disturbances and typical metabolic alterations in patients with PCOS. Therefore, in this study, the sleep quality was evaluated in patients with PCOS and healthy individuals by using the PSQI and metabolic parameters were compared between patients with PCOS having a low sleep quality and those with PCOS having normal sleep.

MATERIALS AND METHODS

The study included 50 patients presenting to a gynecological and obstetrics outpatient clinic between December 1, 2018 and March 1, 2019, aged 18-45 years and diagnosed as PCOS based on the criteria issued by the Rotterdam European Society for Human Reproduction and the American Society of Reproductive Medicine in 2003 (18) and 51 healthy female volunteers. Cerebral diseases such as epilepsy, any malignancy and pregnancy were accepted as exclusion criteria. Ethical approval was obtained from the Adnan Menderes University Faculty of Medicine Ethics Committee before initiation of the study (Date: 23.11.2018; Protocol No: 2018/1466). In addition, written informed consent was obtained from the participants. The study was planned according to the principles of the Helsinki Declaration.

Demographic features, routine biochemical analyses, 25-OH-vitamin D levels [reference value (RV)=15.7-60.3 ng/ml], androgen levels [Testosterone (Reference value=0.38-1.97 nmol/L) and Dehydroepiandrosterone Sulfate ($DHESO_4$) (Reference value=134.2-407.4 µg/dl)] were recorded retrospectively. The parameters of metabolic risk (including dyslipidemia, hyperinsulinism) was also estimated. (19). Insulin resistance was determined by using Homeostasis Model Assessment (HOMA) (HOMA-insulin resistance=fasting insulin (Reference value=2-25 µu/ml) x fasting plasma glucose (Reference value=70-105 mg/dl)/405). The cut-off value for patients was accepted as 2.36.

Blood specimens results of PCOS patients were obtained retrospectively from our clinical records. Blood specimens for biochemistry analyses were taken into tubes without anticoagulants and centrifuged at 1000g for ten minutes. Serum cholesterol (RV≤200 mg/dl), HDL, triglyceride (RV≤149 mg/dl) and fasting glucose were measured by using the spectrophotometric method on the same day as the specimens were obtained and insulin, total testosterone, 25 OH D vitamin and $DHESO_4$ were measured by using the chemiluminescent microparticle immunoassay (CMIA) at the autoanalyzer (C8000 Architect, Abbott, Abbott Park, IL, USA). LDL levels were calculated with the Friedewald equation. Besides, presence of diabetes mellitus and cardiac conditions like hypertension was recorded.

The PSQI was used to diagnose sleep disturbances. The index was developed by Buysse et al. to evaluate the sleep quality quantitatively. It is composed of 24 questions, of which 19 are directed towards self-evaluation and five are answered by spouses or roommates of individuals. The total score for the index does not involve the responses given by spouses and roommates. It is utilized to determine sleep duration, sleep latency and frequency and severity of sleep problems. The index has 18 items and seven components. Some components are composed of one item while others are composed of several items. Each item is scored from zero to three. The components of the index are divided into seven subgroups as subjective sleep quality, sleep latency/duration/efficiency/disturbance, use of sleep medication and daytime dysfunction. A total score is obtained by adding scores for each component. A total score of five or greater above indicates poor sleep quality (17).

Consequently, all parameters were compared between the groups and the correlation between the scores of the cases and other parameters were examined.

Statistical Analysis

Obtained data were analyzed with IBM SPSS Statistics 22.0. Kolmogorov-Smirnov test was utilized to evaluate whether the data were normally distributed. Categorical data were expressed as numbers (n) and percentage (%) while quantitative data were given as mean±SD and median (25^{th}–75^{th}) percentiles. Student's t test was employed to compare parameters with a normal distribution between two groups and Mann-Whitney U test was used to compare parameters without a normal distribution between two groups. Categorical data were analyzed Continuity corrected Chi-square test. The effects of the presence of PCOS and androgen measurements on having poor quality of sleep was investigated by multiple logistic regression analysis after adjustment for all possible confounding factors. Odds ratios, 95% confidence intervals for each independent variable were also calculated. $p<0.05$ was considered as statistically significant.

RESULTS

The study included a total of 101 individuals, of whom 50 (49.5%) were patients with PCOS (PCOS group) and 51 (50.5%) were healthy controls (control group). Demographic features of the PCOS and control groups are presented in **Table 1**.

There was a significant difference in BMI between the PCOS and control groups ($p<0.01$). PCOS group had higher PSQI score than the control group and the rate of the poor sleep quality was higher in the PCOS group than in the control group (80% vs 70%, respectively) but these results were not statistically significant. ($p=0.163$ and $p=0.387$, respectively).

When adjusted for age and body mass index, there was no statistically significant effect of PCOS on the change in PSQI scores (B=0.989, 95% CI:-0.319-2.298, $p=0.137$).

In **Table 2**, there are comparisons made in terms of demographic characteristics and metabolic measurements between cases with poor sleep quality and cases without poor sleep quality within the PCOS group.

Among the cases with poor sleep quality and those without poor sleep quality in the PCOS group, respectively; There was no statistically significant difference in terms of age, BMI, Fasting Blood glucose) FBG, cholesterol, HDL (High Density Lipoprotein), LDL (Low Density Llipoprotein), vitamin D, insulin, triglyceride and HOMA-IR ($p>0.05$). On the other hand, serum total

Table 1. The comparison of demographic and clinical features between the PCOS and control groups (n=101)

	PCOS (n=50)	Control (n=51)	p-value
Age (year)	20.0 (18.8-23.2)	21.0 (19.0-22.0)	[1]0.770
BMI (kg/m^2)	24.3 (20.5-27.0)	20.7 (19.4-21.8)	[1]<0.001
PSQI Score	7.26±2.99	6.41±3.07	[2]0.163
PSQI			[3]0.387
Normal	10 (20.0%)	15 (29.4%)	
Poor	40 (80.0%)	36 (70.6%)	

[1] Mann-Whitney U test, [2]Student's t test, [3]Continuity corrected χ^2 test, BMI: Body Mass Index, PSQI: Pittsburgh Sleep Quality Index PCOS: Polycystic ovary syndrome

Table 2. The distribution of demographic and metabolic parameters according to PSQI scores in PCOS group			
	Normal PSQI (n=10)	**Poor PSQI (n=40)**	**p-value**
Age (year)	19.5 (18.0-21.2)	20.0 (19.0-24.7)	[1]0.356
BMI (kg/m^2)	23.1 (20.4-28.2)	24.3 (20.2-26.9)	[1]0.896
FBG	87.0 (80.0-89.5)	86.0 (82.0-91.0)	[1]0.668
Cholesterol	168.0 (134.7-215.2)	162.0 (142.0-201.0)	[1]0.840
HDL	63.1±18.5	60.8±16.6	[2]0.707
LDL	88.0 (60.5-113.7)	86.0 (72.0-102)	[1]0.989
Vitamin D	13.7 (9.3-15.8)	13.1 (9.6-15.4)	[1]0.657
Insulin	8.3 (6.5-13.5)	11.5 (7.5-15.1)	[1]0.358
Testosterone	1.8 (1.6-2.2)	1.4 (0.9-1.6)	[1]0.002
$DHESO_4$	433.4 (356.0-555.0)	271.2 (223.9-426.0)	[1]0.020
Triglyceride	64.5 (57.0-112.0)	76.0 (54.0-109.0)	[1]0.600
HOMA-IR	2.0 (1.5-3.0)	2.4 (1.5-3.5)	[1]0.571

[1] Mann-Whitney U test, [2]Student's t test, [3]Continuity corrected χ^2 test, PSQI: Pittsburgh Sleep Quality Index, BMI: Body Mass Index, FBG: Fasting blood glucose, HOMA-IR: Homeostatic model assessment of insulin resistance, DHESO4: Dehydroepiandrosterone sulfate

Table 3. The results of correlation analysis within PCOS group				
	Total testosterone		**DHESO4**	
	Correlation Coefficient	**p-value [1]**	**Correlation Coefficient**	**p-value [1]**
Subjective Sleep Quality	-0.329	0.029	-0.071	0.646
Sleep Latency	-0.328	0.030	-0.216	0.160
Sleep duration	-0.499	<0.001	-0.321	0.034
Sleep disturbance	-0.438	0.003	-0.243	0.112
Daytime dysfunction	-0.029	0.854	-0.061	0.693
Total PSQI	-0.538	<0.001	-0.378	0.011

[1] Spearman's correlation analysis, $DHESO_4$: Dehydroepiandrosterone sulfate, PSQI: Pittsburgh Sleep Quality Index PCOS: Polycystic ovary syndrome

testosterone and $DHESO_4$ levels were significantly lower in the patients with a poor sleep quality than in those with a normal sleep quality (p=0.002 and p=0.020).

Although metabolic parameters (cholesterol, HDL, LDL, triglyceride, glucose) had no significant correlation with subjective sleep quality, sleep latency, sleep disturbance, use of sleeping medication and daytime dysfunction, serum $DHESO_4$ and total testosterone level had a significant negative correlation with sleep duration and total PSQI scores. In addition, serum total testosterone level also had a significant negative correlation with sleep latency (r=-0.328, p=0.030), sleep disturbance (r=-0.438, p=0.003), and subjective sleep quality (r=-0.329, p=0.029) (**Table 3**).

When adjusted for other confounding factors such as age and body mass index, the statistically significant effects of both testosterone (OR=0.604, 95% CI:0.234-1.562, p=0.298) and $DHESO_4$ (OR=0.994, 95% CI:0.988-1.000, =0.055) on the levels on sleep quality disappeared (**Table 4**).

DISCUSSION

In the present study, the patients with PCOS were found to have poor sleep quality than the healthy individuals but this was not statistically significant**.** There have been studies showing that the sleep quality decreases in patients with PCOS (12,15,3). In a previous study, the prevalence of sleep apnea syndrome was high at 66% in PCOS (20). Conflicting with the above mentioned evidence, Moran et al. reported no difference in the sleep quality between patients with PCOS and healthy controls (8). The poor sleep quality may result from many fa-

Table 4. The Results of Multiple Logistic Regression Analysis in order to Determine the best Predictors Which Effect on PSQI Status after Adjustment for Confounding Factors

	OR	95% CI	p-value
Age	1.073	0.845-1.363	0.563
BMI	0.881	0.723-1.073	0.207
Testosterone	0.604	0.234-1.562	0.298
$DHESO_4$	0.994	0.988-1.000	0.055

OR: Odds ratio, CI: Confidence interval, BMI: Body Mass Index, $DHESO_4$: Dehydroepiandrosterone sulfate, PSQI: Pittsburgh Sleep Quality Index

ctors in patients with PCOS, characterized by metabolic dysfunctions. The high rate of sleep disturbances in patients with PCOS suggests that it is of great importance to examine their sleep quality.

It has been shown in the literature that high insulin levels and high HOMA-IR are associated with obstructive sleep apnea characterized by low, slow-wave sleep activities, sleep deprivation and hypoxia in patients with PCOS (21). Congruent with the literature**,** insulin levels were reported as high in patients with poor sleep quality in this study, but this result was not statistically significant**.**

Simon et al. emphasized that the poor sleep is related to high triglyceride levels in patients with PCOS (10). It is known that insulin resistance reduces inhibition of the adipocyte lipolysis, which increased serum free fatty acids and triglycerides in patients with PCOS. Therefore, it can be suggested that the sleep quality should be questioned in patients with PCOS if they have high triglyceride levels (22). In our study, triglyceride level was found within normal range in both groups. This might be due to the relatively young mean age of the patients in the study.

Concerning the effect of androgen levels on the sleep quality, the present study showed lower serum total $DHESO_4$ in the PCOS group with a poor sleep quality compared to the PCOS group with a normal sleep quality. In addition, total testosterone levels were significantly low in the PCOS group with the low sleep quality. It has been reported in the literature that increased serum insulin plays a regulatory role and decreases serum $DHESO_4$ in females (23). In the present study, the PCOS group having a low sleep quality had higher insulin levels than the PCOS group having a normal sleep quality but this result was not statistically significant. Besides, elevated insulin increases free testosterone levels by reducing sex hormone-binding globulin (23), which is not supported by the present study. Furthermore, several studies have demonstrated that increased testosterone, typically appearing in PCOS, is related to obstructive sleep apnea syndrome (14-16). However, there are two studies showing no relation between increased testosterone and obstructive sleep apnea (12,15). In fact, de Sousa reported that changes in the pharyngeal anatomy can cause obstructive sleep apnea (24). In light of this evidence in the literature, increased serum testosterone might have led to obstructive sleep apnea in the patients with PCOS. Therefore, this might decrease the sleep quality in patients with PCOS. We think that because the patients in our study were relatively young, metabolic and androgenic disorders of PCOS might not have fully emerged yet.

In this study, the negative relationship between subjective sleep quality, sleep delay, sleep duration, sleep disturbances, total PSQI scores and testosterone was found. Likewise, significant negative relationship was found between $DHESO_4$ and both sleep duration and total PSQI scores. In fact, low levels of melatonin which cause a shortage of sleep time, have been previously reported in the literature (25). For this reason, supportive melatonin may be given to increase sleep duration in PCOS patients. This issue should be supported by prospective studies with more participants in the future.

This study had some limitations. First, the PCOS group had a higher BMI than the control group. It was quite difficult to find obese individuals without PCOS in the young population. In addition, the sample size could have been larger and patients in the study were not evaluated for the serum melatonin levels.

CONCLUSION

Androgenic alterations can have a negative effect on the sleep components in PCOS. It should be remembered in routine follow-ups that patients with PCOS may

experience sleep disturbances as well as metabolic and androgenic disorder.

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