SLEEP QUALITY IS RELATED TO HYPERINSULINEMIA IN POSTMENOPAUSAL WOMEN

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SUMMARY

Objective: *In this study, our aim was to investigate the relationship among sleep disturbances and biochemical, hormonal and inflammatory parameters.*
Material and methods: *In this prospective study, 58 postmenopausal women without any concomitant disease other than metabolic syndrome were included. We applied Pittsburgh Sleep Quality Index (PSQI) and asked self-reported sleep duration of participants. We compared the results with hormonal and metabolic parameters.*
Results: *Participants with a poor PSQI were older (p=0.022), had a higher hip circumference (p=0.03) and had a longer duration of menopause (p=0.012) when compared to participants with a good PSQI. Participants with a poor PSQI had lower HDL (p=0.008) and higher insulin (p=0.027) when compared to participants with a good PSQI. There was no association between sleep duration and the parameters searched.*
Conclusion: *Sleep complaints are related to hyperinsulinemia and lipid abnormalities.*

Key words: CRP, inflammation, insulin, postmenopausal, sex-hormones, sleep
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POSTMENOPOZAL KADINLARDA UYKU KALİTESİ HİPERİNSULİNEMİ İLE İLİŞKİLİDİR

ÖZET

Amaç: *Bu çalışmada amacımız uyku bozuklukları ile biyokimyasal, hormonal ve inflamatuar parametreler arasındaki ilişkiyi anlamaktı.*
Gereç ve yöntemler: *Bu prospektif çalışmaya metabolik sendrom dışında bir hastalığı olmayan 58 postmenopozal hasta çalışmaya dahil edildi. Çalışmaya katılanlara Pittsburg Uyku Kalite İndeksi (PUKİ) uygulandı ve katılımcıların bildirdikleri uyku süresi öğrenildi. Sonuçlar hormonal ve metabolik parametrelerle karşılaştırıldı.*
Bulgular: *PUKİ'si kötü olan hastalar PUKİ'si iyi olan hastalarla karşılaştırıldığında daha yaşlı (p=0.022), daha büyük kalça çevresine sahip (p=0.03) ve daha uzun süredir menopozda (p=0.012) oldukları görüldü. PUKİ'si kötü olan hastalar PUKİ'si iyi olan hastalarla karşılaştırıldığında daha düşük HDL (p=0.008) ve daha yüksek insulin seviyelerine sahip oldukları görüldü.*
Sonuç: *Uyku şikayetleri hiperinsulinemi ve lipid bozuklukları ile ilişkilidir.*

Anahtar kelimeler: *CRP, inflamasyon, insulin, postmenopozal, seks hormonları, uyku*
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INTRODUCTION

Nearly 50% of postmenopausal (PM) women were reported to have sleep complaints, disturbances as difficulty in maintaining sleep, prolonged sleep latency and decreased sleep efficiency and/or insufficient sleep duration[1,2]. Most women were reported to experience the changes in sleep quality mentioned above during the menopausal transition, this suggested a role for sex-steroids in sleep disturbances[3]. Changes occuring during sleep are important to buffer the daily activities of the body. Thus sleep disturbances may affect the performance of daily tasks and may have metabolic consequences. An increase in mortality with either short (<7 hours/night) and long (≥9 hours/night) sleep duration have been reported[4,5]. The increase in sleep problems seem to parallel the increasing rate of cardiovascular diseases in PM women. Metabolic syndrome (MS) is a constellation of cardiovascular risk factors as hypertension, glucose dysregulation, hyperlipidemia and an increased abdominal girth which act additively to increase the consequences of each other. The aim of this study was to understand the relationship among sleep duration and quality and sex hormones, components of MS and markers of inflammation. Pittsburgh Sleep Quality Index (PSQI), a well-validated measure of sleep disturbances was used to investigate subjective sleep quality[6].

MATERIAL AND METHODS

This was a prospective study in postmenopausal women that presented to our gynecology clinic for their routine gynecological examination. Patients using hormone replacement therapy (HRT), those with systemic diseases as major neurologic disorders, schizophrenia, other pscyhotic disorders, uncontrolled diabetes mellitus (fasting serum glucose>150mg/dl), ischemic heart disease, cerebrovascular accidents, chronic renal failure, malignancy, Cushing syndrome and congenital adrenal hyperplasia were excluded. Patients with MS were not excluded. Postmenopausal status was defined as the absence of menses for more than twelve months in the presence of natural menopause or at the time of bilateral salpingoophorectomy with FSH levels ≥30mIU/ml. The women who had undergone hysterectomy without salpingoophorectomy were not included in the study. The study protocol was in confirmation with the ethical guidelines of the Declaration of Helsinki. All of the participants gave their written informed consent.

All of the patients underwent a physical examination and appropriate laboratory tests were performed as a part of their annual follow-up visit. Weight, height, hip circumference (HC) and waist circumference (WC) were measured. WC was obtained with a measuring tape as the smallest circumference at the level of the umbilicus. Body mass index (BMI) was calculated as body weight in kilograms divided by height in metre squared (kg/m^2). Patients filled a validated Turkish version of PSQI. Participants with a PSQI score ≤5 were considered as good sleepers and >5 were considered as poor sleepers. Serum samples were obtained from all of the women after an overnight fasting. Levels of fasting blood glucose, insulin, total cholesterol (TC), high-density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG), luteinizing hormone (LH), follicle stimulating hormone (FSH), free testosterone, dihydroepiandrosteronesulfate (DHEAS), thyroid stimulating hormone (TSH), estradiol (E2), sex-hormone binding globulin (SHBG), homocysteine were measured. As a marker of inflammation C-reactive protein (CRP), interleukin-6 (IL-6) and interleukin-1beta (IL-1beta) were measured. All parameters were measured immediately after collection of blood samples. Insulin resistance (IR) was determined by homeostasis model assessment (HOMA) of insulin resistance with the formula: HOMA-IR= fasting insulin (mU/ml)x fasting glucose (mg/dl)/405.

Statistical Analysis

Statistical analyses were performed using the NCSS 2007 and PASS 2008 statistical software (Utah, USA). Data showing anthropometric parameters were presented as mean(standard deviation. Parameters showing normal distribution were compared with student t test, other parameters were compared with Mann Whitney U test. The relationship between parameters were studied by using Spearman's correlation analysis.

RESULTS

Mean sleep duration of participants was 7.2±1.27 (3-10) and mean PSQI score was 9.86±7.27 (0-32). PSQI score was detected as good sleepers (≤5) in 18 (31%) of participants and as poor sleepers (>5) in 40 (69%) of participants. A sleep duration of less than 7 hours (short sleep duration) was reported by 17 participants (29.3%), a sleep duration of 7-8 hours (normal sleep duration) was reported by 34 participants (58.6%) and a sleep duration of more than 8 hours (long sleep duration) was reported by 7 participants (12.1%).

Participants with a poor sleep quality as asssessed by PSQI were older (p=0.022), had a higher HC (0.03) and had a longer duration of menopause (p=0.012) when compared to participants with a good PSQI. Other demographic characteristics were not related to sleep quality as shown in Table I. Participants with a poor PSQI had lower HDL (p=0.008) and higher insulin (p=0.027) when compared to participants with a good PSQI. Other hormonal and biochemical parameters were not related to sleep quality as shown in Table II. HOMA-IR was higher in participants with a poor PSQI, but it did not reach statistical significance (2.19±1.01 and 1.69± 0.69 respectively, p=0.051).

There was no correlation between sleep duration and age (r=-0.026, p=0,846), height (r=0.215, p=0.105), weight (r=0.042, p=0.755), WC (r=0.032, p=0.812), HC (r=0.012, p=0.930), BMI (r=-0.079, p=0.556), WHR (r=0.052, p=0.7), SBP (r=0.172, p=0.193), DBP

Table I: *Demographic characteristics of participants with good and poor sleep quality.*

Sleep Quality n=58	**Good (n=18) Mean±SD (range)(Median)**	**Poor (n=40) Mean±SD (range)(Median)**	**p**
Age (years)	55±3.6 (48-61) (56)	58.1±6.1 (47-74) (57)	**0.022***
Height (cm)	160.3±6.5 (150-175) (159.5)	158.9±4.8 (150-168) (159.5)	**0.141**
Weight (kg)	66.2±11.97 (47-92.9) (66)	71.6±11.6 (52-116)(63.9)	**0.105**
Waist Circumference (cm)	89.97±12.4 (70-115)(88)	94.7±9 (78-119)(95)	**0.112**
Hip Circumference (cm)	102.7±10.7 (86-127)(101)	108.5±8.2 (90-132)(107)	**0.030***
Body Mass Index (kg/m2)	25.7±5.2 (19.8-41.3)(24.42)	28.4±4.6 (22-44)(27.32)	**0.056**
[a]Waist-to-Hip Ratio	0.87±0.08 (0.6-1)(0.89)	0.87±0.07 (0.7-1)(0.87)	**0.814**
Systolic BP (mmHg)	115±16.5 (80-160)(120)	123.8±16.8 (100-180)(120)	**0.070**
Diastolic BP (mmHg)	75.6±10.97 (50-100)(80)	78.9±10.5 (60-100)(80)	**0.276**
[a]Duration of Menopause (years)	5.94±3.8 (1-15)(4)	10.1±6.2 (1-24)(9.5)	**0.012***

Student t Test *[a]Mann Whitney U Test* **p<0.05*

Table II: *Hormonal and biochemical parameters of participants with good and poor sleep quality.*

Sleep Quality n=58	**Good (n=18) (Mean±SD (range)(Median)**	**Poor (n=40) Mean±SD (range)(Median)**	**P**
Fasting blood glucose (mg/dl)	96.4±7.6 (82-109)(96.5)	97.6±8.1 (78-118)(96)	**0.578**
LDL (mg/dl)	150.2±31.1 (109-205)8146.5)	137±31(66-216)(137)	**0.141**
HDL (mg/dl)	77.1±16.1 (49-107)(72.5)	64.1±16.7 (37-113)(60.5)	**0.008****
Triglyceride (mg/dl)	84.7±28.9 (47-158)(82.5)	97.9±39.8 (45-220)(89)	**0.212**
[a]CRP (mg/l)	0.25±0.3 (0-0.8)(0.19)	0.35±0.4 (0.1-2.3)(0.23)	**0.263**
IL-6 (ng/ml)	11.7±2.9 (8.3-18.9)(10.5)	13±3.5 (8.3-25)(12.65)	**0.212**
IL-1beta (ng/ml)	8.6±0.96 (7.5-10.9)(8.3)	8.9±1.6 (7.6-16.1)(8.42)	**0.418**
[a]TSH (uIU/ml)	2.16±1.64 (0.4-7.8)(1.94)	2.4±1.6 (0.5-9.6)(2.19)	**0.342**
[a]Insulin (uU/ml)	6.97±2.6 (2.2-14.3)(6.41)	9.1±3.8 (4-21.4)(8.51)	**0.027***
Homocysteine (u/ml)	9.97±2.2 (6.4-14.4)(9.73)	10.9±3.3 (5.2-26)(10.55)	**0.272**
Estradiol (pg/ml)	7.2±4.7 (5-22.4)(5)	8.7±5.5 (5.0-28.2)(5.83)	**0.124**
FSH (mIU/ml)	79.9±28.8 (42.5-151.7)(80.1)	77.5±28.5 (29.3-163.3)(74.65)	**0.771**
[a]DHEAS (ug/dl)	99.8±44.1 (40.5-192.3)(99.22)	87.1±56.8 (22.3-251.4)(73.17)	**0.201**
F. Testosterone (ng/dl)	0.2±0.13 (0-0.6)(0.16)	0.38±0.9 (0-5.8)(0.2)	**0.317**
SHBG (nmol/l)	54.6±17.9 (20-82)(58.88)	48.94±22.3 (18-100.2)(44.87)	**0.354**
HOMA-IR	1.7±0.7 (0.5-3.6)(1.57)	2.2±1.1 (0.9-5.4)(2.02)	**0.051**
LH (mIU/ml)	27.8±10.5 (15.2-46.8)(27.25)	27.8±12.7 (7.1-63.8)(24.59)	**0.998**

Student t Test *[a]Mann Whitney U Test* **p<0.05* ***p<0.01*

(r=0.957, p=0.669) and duration of menstruation (r=0.110, p=0.411). There was also no correlation among sleep duration and hormonal and biochemical parameters as shown in Table III.

Table III: *Correlation of sleep duration with biochemical and hormonal parameters.*

	Sleep Duration	
	r	p
Fasting blood glucose	0.183	**0.168**
LDL	-0.111	**0.406**
HDL	0.019	**0.888**
Triglyceride	-0.010	**0.939**
CRP	-0.050	**0.708**
IL-6	-0.003	**0.983**
IL-1beta	-0.206	**0.155**
TSH	0.052	**0.701**
Insulin	-0.026	**0.849**
Homocysteine	-0.062	**0.642**
E2	0.030	**0.824**
LH	-0.022	**0.882**
FSH	-0.151	**0.258**
D-HEAS	-0.001	**0.993**
F. Testosterone	0.081	**0.546**
SHBG	0.007	**0.958**
HOMA-IR	0.032	**0.809**

r=Spearman's rho

DISCUSSION

In this study we found increased fasting insulin levels in PM women with a poor sleep quality, but there was no relationship between sleep duration and parameters of glucose metabolism. Jennings linked inadequate sleep assessed by PSQI to increased appetite and IR [7]. Poor sleep quality was reported to impair glucose metabolism[8]. Patients with sleep apnea and loud snoring were also reported to have higher insulin levels [9]. Previous studies demonstrated an increase in appetite and food cravings and an abnormal IR after experimental sleep restriction[10]. The mechanism proposed to explain the increase in appetite after sleep was the change in hormones regulating hunger and satiety (leptin) with sleep restriction[11,12]. Sleep restriction was also reported to lead to hypercortisolemia which triggers IR[13,14]. These findings were proved by investigations showing the importance of sleep duration and quality in glycemic control of patients with type 2 DM[15]. An increased risk of diabetes was reported both in short and long sleepers, but we failed to detect a relationship between sleep duration and impaired glucose metabolism[16-19].

In this study we detected low levels of HDL in participants with a poor sleep quality. Previously loud snouring was reported to predict low HDL[20]. Other studies showed lower HDL levels in long sleepers[21,22]. We did not observe a relationship between sleep duration and HDL. Patients with increased BMI had lesser sleep duration. Increased BMI was associated with both long and shortened sleep duration [4,5,12,16,23]. In this study we did not detect an association between sleep duration-quality and BMI. Another study reported reduced sleep duration in patients with abdominal obesity[21]. Our patients with increased HC had poor sleep quality, but there was no relationship between WC and sleep quality or duration. Aging is a known risk factor for poor sleep quality, our older patients and patients with a longer duration of menopause had poorer sleep quality[24,25].

An increased prevalence of obstructive sleep apnea syndrome (OSAS) has been reported in patients with the MS[27,28]. Reduced sleep duration was associated with MS[10,16]. Our sample was small, therefore we did not search the effects of presence of MS in participants with reduced sleep. Reduced sleep duration was also reported to be independently associated with the components of metabolic syndrome, mostly abdominal obesity and elevated glucose[7,21]. In this study we detected low HDL and impaired glucose metabolism in association with sleep quality. Presence of sleep symptoms as snouring, unrefreshing sleep and difficulty in falling asleep predicted the development of MS within 3 years.

In our study there was no relationship between proinflammatory cytokines and sleep duration or quality. OSAS was reported to lead to low-grade systemic inflammation[29]. Women sleeping longer were reported to have higher CRP and IL-6 levels , in contrast other studies reported increased CRP levels with sleep restriction[22,30-32]. Okun et al reported increased CRP levels in young women with poor sleep quality but there was no association between sleep duration and proinflammatory cytokines[33]. Sleep restriction increased IL-6, white blood cell count and LDL but not CRP in postmenopausal women[34,35]. Others found no significant associations betwee CRP and sleep duration[36]. Episodes of nocturnal hypoxia was related to increased serum CRP levels, while others

rejected CRP as an independet predictor of nocturnal hypoxia and proposed obesity as the main contributor [37-39].

A controversy exists whether the sleep disorders in PM women were related to changes in sex hormones or to aging itself. Sex hormone receptors were detected in the suprachiasmatic nucleus,which regulates the circadian biological rhythms including sleep[40]. Hormonal changes starting in the premenopausal period as decreased follicular E2 were reported to be associated with sleep disorders[41]. Interestingly women of reproductive age whose menses were stopped with GnRH analogues did not experience sleep disorders [42]. In this study we did not find any relationship among sleep quality and duration and gonadotropins and sex steroids.

Limitations of our study include the lack of data related to dietary habits and exercise which may have an influence on sleep. The study group was small, therefore some results may reach statistical significance with larger patient groups. Another limitation is the absence of polysomnography and the dependence of results on self-reported data. We did not explore the presence of factors that may affect sleep as depression, restless legs syndrome, fibromyalgia and postmenopausal symptoms. We also did not search for the presence of OSAS. The study group was composed of Caucasian PM women, so differences related to gender and race could not be assessed. The relatively small study sample enabled us to compare subjects with and without MS. Exclusion of participants with major diseases as uncontrolled diabetes mellitus might have hampered the results.

In conclusion sleep duration was probably not associated with metabolic parameters, but sleep quality might be related to age, insulin concentration and HDL. While the underlying mechanisms contributing to these changes remain unknown, we may suggest treatment of hyperinsulinemia and lipid abnormalities to patients with sleep disturbances after seeing the results of future randomized studies proving such an effect.

Conflicts of interest: The authors report no conflicts of interest

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