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Relationship Between Estradiol Level and Sleep Quality in Healthy Women

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ABSTRACT

Objective: The effect of sex hormones on sleep quality was studied mostly in postmenopausal women. In our study we aimed to investigate the effects of estradiol level on sleep quality in premenopausal healthy women.

Materials and Methods: One hundred healthy women without any psychiatric, gynecologic or systemic disease and assessed their sleep quality by Pittsburg Sleep Quality Index (PSQI) were enrolled to the study and their estradiol levels were obtained on the third day of their menstrueal cycles.

Results: Mean serum estradiol level was 208.12±82.028. The mean of global PSQI scores was 5.40±4.357. The mean estradiol level in "good sleepers" (PSQI score < 5) was 243.80±76.07 while the mean estradiol level in "poor sleepers" (PSQI score≥5) was 154.60±58.55, thus estradiol level was significantly higher in "good sleepers" group (t= –6.276; p<0.001).

Conclusion: We found that in normally cycling healthy women, estrogen level in normal range is also important in determining subjective sleep quality.

***Key words*:** *Sleep, estradiol, women*

ÖZET

Sağlıklı Kadınlarda Serum Estradiol Düzeyleri ile Uyku Kalitesi Arasındaki İlişki

Amaç: Uyku kalitesi üzerinde seks hormonlarının etkisi genellikle postmenopozal kadınlarda çalışılmıştır. Çalışmamızda, menapozda olmayan kadınlarda serum estradiol düzeyleri ile uyku kalitesi arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmamıza psikiyatrik, jinekolojik yada sistemik hastalığı olmayan, 100 sağlıklı kadın dahil edilmiştir. Uyku kalitelerini değerlendirmek için Pittsburg Uyku Kailite İndeksi (PSQI) uygulanmıştır ve menstrüel peryodun 3.gününde serum estradiol düzeylerine bakılmıştır.

Bulgular: Ortalama serum estradiol düzeyleri 208.12±82.028 pg/ml'dir. Ortalama PSQI skoru 5.40±4.357 'dir. Ortalama serum estradiol düzeyleri 'iyi uyuyanlar' olarak adlandırılan gurupta (PSQI skoru<5) 243.80±76.07 pg/ml, 'kötü uyuyanlar' olarak adlandırılan gurupta (PSQI score≥5) 154.60±58.55 pg/ml olarak bulunmuştur. Estradiol düzeyleri 'iyi uyuyanlar' da anlamlı olarak daha yüksektir (t= -6.276; p<0.001).

Sonuç: Sağlıklı siklik kadınlarda normal sınırlar içindeki serum estradiol düzeylerindeki değişimin de, subjektif uyku kalitesini belirlemede önemli olduğu bulunmuştur.

Anahtar Sözcükler: *Uyku, estradiol, kadın*

The effect of sex hormones on sleep quality was studied mostly in postmenopausal women. In postmenopausal women, sleep quality was related to hot flashes, mood changes, effects on ventilation, change in core temperature, and it was shown that estrogen replacement therapy improved sleep quality (1). The symptoms that have been linked to worsening of sleep quality are related to decrease in estrogen level; therefore, it is suggested that estrogen replacement would have an improving effect on sleep quality. But on the other hand, estrogen receptors found on hypothalamic neurons prove that estrogen may affect sleep not only with postmenopausal symptoms, but with direct effects on brain as well (2). To find a connection with estrogen level and sleep apart from postmenopausal period, in our study we investigated the effects of estradiol level on sleep quality in premenopausal healthy women who do not have any postmenopausal symptoms like hot flashes or ventilation changes.

MATERIALS AND METHODS

Subjects

For our study, our aim was to evaluate healthy women, so we evaluated 117 women who were female relatives of patients with psychiatric and gynecologic diseases referred to Dumlupinar University Research Hospital. Those women were asked if they would have liked to participate to our study and 112 of them agreed.

Upon agreement of participation, subjects were approved for further screening. After signing informed consent documents, subjects gave a medical history and underwent physical and laboratory tests assessing psychiatric,medical and hormonal state.

Among 112 subjects four of them had recent oral contraceptive usage, so they were excluded from the study.

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In psychiatric evaluation, a psychiatrist assessed subjects for psychotic disorders, mood disorders and anxiety disorders. Three subjects had major depression and two had anxiety disorders (one had generalized anxiety disorder, one had panic disorder), so those were also excluded from study. 103 subjects were evaluated for any medical disease, for this purpose physical examination was done, medical history was taken and for subjects who were suspected for any endocrine disorder were assessed by hormonal laboratory evaluations. In that assessments one subject was diagnosed as thyroiditis and another was diagnosed as diabetes and both were excluded from the study.

After those evaluations rest of the subjects were assessed with gynecologic examination, ultrasound examination and their Follicular Stimulating Hormone(FSH) and Estradiol (E2) levels were assessed. In that assessments one of the patients was diagnosed as polycystic ovaries disease so she was also excluded from the study. None of those women were in menopause period (FSH<30 IU/L).

Other 100 subjects were approved for our study and their subjective sleep quality and E2 levels were evaluated in order to find any relation between two variables in healthy women.

Asessment of Serum Estradiol Level

Serum E2 levels of subjects who were approved for our study were taken on third day of their menstruation period in order to make comparison. Laboratory assessments were done by Beckman Coulter Access 2 Immunoassay System, Access Estradiol, USA.

Subjective Sleep Quality Assesment

For assessment of subjective sleep quality we used Pittsburg Sleep Quality Index (PSQI) (Agargun et al,1996). PSQI assessed subjective sleep quality of the past 4 weeks and was administered during the personal interview. A global PSQI≥5 has a diagnostic sensitivity of 89.6 and specificity of 86.5 in distinguishing "poor sleepers" (PSQI≥5) from "good sleepers" (PSQI<5).

Statistical Analysis

After obtaining PSQI scores and estradiol levels of participants, we statistically evaluated those data using SPSS 11.0. In statistical analysis, relationship between two variables was evaluated with Pearson correlation test. To compare "good sleepers" and "poor sleepers" according to estradiol levels, we used independent samples *t*-test.

RESULTS

In our study, the mean age of the 100 participants was 28.50±5.80 (Mean serum estradiol level was 208.12±82.00 pq/ml. The mean of global PSQI scores was 5.40±4.357 (Table 1). In Pearson correlation test, we found that there was negative correlation between estradiol level and sleep quality score of the participants (r=-0.534; p<0.01). To compare "good sleepers" and "poor sleepers," in independent samples *t*-test, we took PSQI cut-off score as 5 and did statistical analysis for estradiol level. In our sample, 60 women had PSQI score below 5 (good sleepers) and 40 women got more than 5 (poor sleepers) as PSQI score, and there was a statistically significant relationship between PQSI score and estradiol level. The mean estradiol level in "good sleepers" (PSQI score<5) was 243.80±76.07 while the mean estradiol level in "poor sleepers" (PSQI score≥5) was 154.60±58.55, thus estradiol level was significantly higher in "good sleepers" group (t= -6.276; p<0.001) (Table 2).

Table 1. *Mean values of variables*

N=100	Mean	Std. Devaition
PSQI†	5.40	4.357
E2‡	208.12	82.028
Age	28.5	5.8

† PSQI: Pittsburg Sleep Quality Index
‡E2: Estradiol

Table 2. *Estradiol levels according to PSQI cut-off 5*

PSQI†	N	Mean (pq/ml)	Std Deviation	t	p
E2‡					
≥5	40	154.60	58.55	-6.276	0.000*
<5	60	243.80	76.07		

† PSQI: Pittsburg Sleep Quality Index
‡E2: Estradiol
**p significant at <0.001 level*

DISCUSSION

In many studies, it was repeatedly shown that menopause was related to worsening in sleep quality. Most of the studies suggested a link between estrogen level and sleep quality in postmenopausal period and the approval of this suggestion was thought to be the increase in sleep quality with estrogen replacement in those women (1).

Ventrolateral preoptic nucleus, suprachiasmatic nucleus, lateral and posterior hypothalamus and thalamus are the brain regions thought to be involved in sleep regulation (3, 4). In rats, it was shown that ovariectomy was followed by marked reduction in Fos expression in the ventrolateral preoptic and suprachiasmatic nuclei, indicating that Fos expression is highly estrogen-dependent, which has been implicated in sleep regulation (5). Also, estrogen receptors were shown in hypothalamic neurons proving estrogen's direct effect on brain functions [2]. With these animal studies and studies with postmenopausal women, we concluded that estrogen should have a role in the regulation of sleep and this could not have been restricted to postmenopausal period.

In normally cycling women, estrogen and progesterone levels change during menstrual cycle. Women taking oral contraceptives and therefore changing sex hormone levels during cycle were shown to have more stage-2 non-rapid eye movement sleep in the active phase when compared with that in the naturally cycling women[6]. The naturally cycling women, however, had more slow wave sleep in the luteal phase when compared with that in the contraceptive group of women. In the study of Hollander et al. in 2001, they evaluated 236 women aged 35-49 years and they stated that there was a significant association between FSH levels and sleep duration, and FSH levels were 20% higher in long-time

sleepers than in short-time sleepers, indicating that decrease in FSH level might have decreased sleep duration, but in their study, only in women aged 45-49 years, estradiol level was an important factor in poor sleep (7).

In our study, our aim was to show if there was any relationship between estrogen level and sleep quality in healthy, normally cycling women who had no contraceptive or any hormone use. We found that estradiol level on the third day of cycle was significantly related to subjective sleep quality. According to the literature about estrogen acting on nuclei that are important in sleep regulation, this finding is not surprising. From this point of view, we can suggest that even estradiol in normal range has an effect on sleep so that lower levels of estradiol in normal range cause worsening of sleep quality; this finding is in accordance with the studies which found that replacement therapies with estrogen increased sleep quality. But to our knowledge, replacement therapies have been mostly advised for postmenopausal women; with the present findings, we suggest that estrogen replacement that will keep its level in the highest rank of normal range may have a potential improving effect on sleep quality.

Moreover, sleep disturbances have been related to sleep apnea especially in men; in the study of Rowley et al. in 2006 about apnea threshold and NREM sleep, they stated that hormone replacement improves apnea threshold in NREM sleep, which was shown to be higher in premenopausal women when compared with that in postmenopausal women (8, 9). Thus, apart from its direct effect on sleep regulation centers in the brain, estrogen is important in respiration during sleep, which is an important component of a "good sleep".

In normally cycling healthy women, estradiol level may affect sleep quality; however, our study had no implication about its mechanism. Thus, in our opinion, another question should be asked: Which one comes first? Does the decrease in estradiol level precede sleep changes or changes in sleep composition cause a decrease in estrogen level in healthy women? In an animal study, paradoxical sleep-deprived (PSD) adult female Wistar rats were compared with home-cage control ones on their estrous cyclicity. In this study, the authors stated that PSD rats exhibited lower estrogen than those in the respective control rats (10). From this point of view, sleep deprivation may be a factor for changes in estrogen level even though there have been no studies, to our knowledge, investigated in this issue.

Thus, we can conclude that in normally cycling healthy women, estrogen level in normal range is also important in determining sleep quality as in postmenopausal women, but there is a missing point-whether estrogen decrease comes first or not.

In our study, we selected 100 healthy women and our aim was to define sleep-estradiol level relationship in them, but we did not mention about any causal factor. A higher number of women and a study intended to find any causal relation would give more accurate and satisfying results. On the other hand, in our study we did not consider other hormone levels, which with a more comprehensive study design including other hormones that might have a role in sleep regulation may give a more coherent picture of sleep regulation in women.

In future studies, sleep quality and regulation in healthy women should be evaluated from sex hormones' perspective. To clearly identify the connection between sex steroids and sleep, studies in human and animals should focus on both the function and effects of sex steroids on the brain and clinical appearance of changes in sex hormone level.

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