Depression, Anxiety and Anger in Patients with Polycystic Ovary Syndrome

Polikistik Over Sendromu Olan Hastalarda Depresyon, Anksiyete ve Öfke

Adem BALIKÇI1, Murat ERDEM1, Uğur KESKİN2, Selma Bozkurt ZINCİR3, Murat GÜLSÜN1, Fatih ÖZÇELİK4, Emin Özgür AKGÜL5, Süleyman AKARSU1, Muzaffer ÖZTOSUN6, Ali ERGÜN2

1Gülnare Military Medical Academy, Clinics of Obstetrics and Gynecology, Ankara, Turkey
2Gülnare Military Medical Academy, Clinics of Psychiatry, Ankara, Turkey
3Erenköy Mental and Nervous Diseases Training and Research Hospital, Clinics of Psychiatry, Istanbul, Turkey
4 XXX

ABSTRACT
Introduction: Polycystic ovary syndrome (PCOS) is a syndrome of the heterogeneous nature, affecting multiple systems, particularly the endocrine system. We propose to investigate the possible relationships among hormonal changes, levels of anxiety, depression, and anger in patients with PCOS.

Method: Forty four female patients with PCOS and 44 Body Mass Index (BMI)-matched healthy women participated in this study. We measured the sociodemographic features, some serum hormonal levels (insulin, gonadotropins, prolactin, dehydroepiandrosterone sulfate (DHEAS), TSH, T3, T4, 17 OH-Progesterone, total and free testosterone) and some other biochemical parameters of the participants. Also, all participants completed Trait Anger-Anger Expression Scale (STAS), Beck Depression and Beck Anxiety Inventories. We evaluated the psychiatric scale scores which obtained from PCOS patients and control subjects. We used the independent samples T-test for parametric data for evaluating of normal distribution and Mann-Whitney U test is used for both the abnormally distributed and nonparametric data. We used Pearson correlation analysis to evaluate the potential connection between two groups’ data.

Results: The mean ages of the patients with PCOS and control subjects participated in this study were 27.3±5.6 and 27.4±6.1 years, respectively. The measures of BMI, insulin, LH, DHEAS, and total testosterone serum levels in the patient group were significantly higher than the control group (p<0.05). There was statistically significant positive correlation between Beck anxiety scores and serum DHEAS levels (Pearson r=0.4366, p=0.0001). We found significant differences between two groups in terms of trait anger, anger control, anger outward and inward, anxiety level and depression scores (p<0.05).

Conclusion: Anxiety symptoms indicate stronger relationship compared to the depression with the DHEAS serum levels via autonomic nervous system, considering GABA antagonist effect of DHEAS. Obesity, hirsutism, and infertility may reduce self-confidence, and create depressive symptoms in patients with PCOS. In addition, changes in the hormonal levels may lead to anxiety directly. Possibly, depressive symptoms are a secondary reflection of these changes.

Key words: Polycystic ovary syndrome, anxiety, depression, anger, DHEAS, testosterone

Conflict of interest: The authors reported no conflict of interest related to this article.

ÖZET
Giriş: Polikistik over sendromu (PKOS) başta endokrin olmak üzere bir çok sistem etkileyen heterojener karakterde bir sendromdur. Bu çalışmamız, PKOS hastalarında hormonal değişiklikler ile anksiyete, depresyon ve öfke düzeylerindeki muhtemel ilişkiye araştırmaktır.

 Yöntem: Çalışmaya 44 PKOS’lu hasta ile vücut kilo indeksi (VKİ) benzer 44 sağlıklı sağlıklı kadın alınmıştır. Katılımcılardaki sosyo-demografik özellikleri belirlenmiştir ve bazi serum hormon seviyeleri (insulin, gonadotropinler, prolaktin, dehidroepiandrosteron sülfat (DHEAS), TSH, T3, T4, 17 OH-Progesteron, total ve serbest testosteron) ile bazı diğer biyokimyasal parametreleri değerlendirilmiştir. Ek olarak tüm katılımcılara; Sürekli Öfke-Öfke İfade Tarzı (SÖÖİT), Beck depresyon ve Beck anksiyete ölçekleri uygulanarak, PKOS hastaları ve kontrol grubunun psikometrik test skorları değerlendirilmiştir. Normal dağılımlı parametrik veriler için independent samples T-test; normal dağılım olmayan nonparametrik veriler için Mann-Whitney U test kullanılmıştır. İki grup verilerinin arásındaki potansiyel ilişki pearson korelasyon analizi ile değerlendirilmiştir.

 Bulgular: PKOS hasta grubunda yaş ortalaması 27,3±5,6 iken kontrol grubunda 27,4±6,1 idi. VKİ, serum insulin, LH, DHEAS, ve total testosteron düzeyleri kontrol grubundan belirgin yüksekti (p<0,05). Beck anksiyete skorları ile serum DHEAS seviyeleri arasında istatistiksel olarak belirgin pozitif korelasyon mevcuttur (Pearson r=0,4366, p=0,0001). İki grup arasında trait anger, anger control, anger outward ve inward, anksiyete ve Beck depresyon skorları açısından belirgin farklılıklar vardı (p<0,05).


Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkarmayı bildirmemişlerdir.
Introduction

Polycystic ovary syndrome (PCOS) is common in reproductive age. Researchers characterize the syndrome with hirsutism, obesity, and amenorrhea. PCOS is a syndrome of the heterogeneous nature, affecting multiple systems, particularly the endocrine system. Although, there is a lack of clarity regarding etiopathogenesis, increased Dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone sulfate (DHEAS) levels may have an essential role in the appearance of PCOS symptoms. PCOS and its relationships between psychiatric disorders have attracted much attention of researchers, especially in the last 20 years.

Investigators have hypothesized that the hormones change the form or quantity of neurotransmitter receptors in the brain. They change the sensitivity to endogenous or exogenous circumstances, which may aggravate mood disorders (1). Fava et al. showed that hirsute women who were identified as having abnormally raised androgen levels reported negative feelings such as depression, hostility, and irritability (2,3). Also, women with PCOS reported an increase in assaultive behavior (4).

PCOS have a negative impact on psycho-social areas. For example, the psychological and social dimensions may influence females’ mental health in many ways (5). Assessing the relationship between different aspects of this network will contribute to understanding of the complex nature of PCOS. The aim of this study was to understand the relationship of these heterogeneous biological parameters with anger, anxiety and depression in females with PCOS during the reproductive period. The hypothesis of this study was that anxiety levels, depression and anger would be greater in patients with PCOS than healthy controls.

Method

Procedure

Forty four female patients with PCOS and 44 Body Mass Index (BMI) matched healthy women participants included in this study, which has been planned cross sectionally. Our PCOS diagnosis was on the basis of Rotterdam criteria (6). All of the patients had clinical and/or biochemical hyperandrogenism, chronic oligo-anovulation and/or PCOS findings on ultrasonography. PCOS was defined as the presence of ≥12 follicles in each ovary each measured as 2-9 mm in diameter and/or increased ovarian volume (>10 ml; Rotterdam, 2004) (6). According to these criteria, at least two of the three criteria should be ensured for PCOS diagnosis. Exclusion criteria consisted of Cushing’s syndrome, hyperprolactinemia, nonclassic congenital adrenal hyperplasia, thyroid dysfunction, androgen secreting tumors (6) and patients using drugs (steroids). BMI-matched healthy women who had regular menses and had no clinical or biochemical hyperandrogenism or PCOS were recruited as a control group from the general population. In order to avoid confounding factors, patients who were smoking, had type-2 diabetes mellitus, uncontrolled hypertension and patients who were using anti-depressant or anxiolytic, hormonal (e.g. oral contraceptive pill) or insulin-sensitizing medications for the last 3 months prior to the study were excluded from the study. All participants have given informed consent for the study. The research project was approved by the Regional Ethical Committee of Gülhane Medical Military Academy. All participants were able to understand the questions and had the capability of filling the self-report scales. All participants filled the research questionnaire form that was prepared for the interview. The form consisted of this information; age, marital status, age at menarche, smoking status, caffeine/alcohol use. Blood glucose (mg/dl), insulin (µU/ml), FSH (µU/ml), LH (µU/ml), E2 (pg/ml), prolactin (µU/ml), DHEAS (mcg/dl), TSH (µU/ml), T3 (nmol/L), T4 (nmol/L), 17 OH-Progesterone (ng/ml), total testosterone (nmol/L), free testosterone (pg/ml), triglyceride (mg/dl), HDL cholesterol (mg/dl) and LDL cholesterol (mg/dl) levels of patients with PCOS and healthy women participants were measured from fasting blood samples by Abbott i2000 SR immunology analyzer and Olympus AU 400 autoanalyzer. Participants completed Trait-Anger-Expression Scale (STAXI), Beck Depression and Anxiety Inventory Scale (BDI) on the supervision of an experienced specialist.

Beck Depression Inventory (BDI): Was created by Beck and his colleagues. The validity and reliability tests for Turkish version were conducted by Hisli et al. This is a Likert type self-report scale which consists of 21 items (7,8). This scale measures and identifies emotional, cognitive, physical, and motivational symptoms of depression objectively. Each question has 4 options given with scores between 0 and 3. The depression score is determined by the sum of all items. The total score ranges from 0-63. If BDI totals score are less than 9 means that there is “no depression”, scores between 10 and 16 are considered as “mild”, 17-23 as “medium” and scores over 24 as “severe depression”. Cut off score of BDI was taken as 17 (8,9).

Beck Anxiety Inventory (BAI): The Beck Anxiety Inventory (BAI), created by Beck et al., 21-item multiple-choice self-report inventory measuring the severity of an anxiety in adults and adolescents. The items in the BAI describe the emotional, physiological, and cognitive symptoms of anxiety but not depression, it can discriminate anxiety from depression. The BAI requires only a basic reading level, can be used with individuals who have intellectual disabilities, and can be completed in 5 to 10 minutes by using the preprinted paper format and a pencil. The validity and reliability study for Turkish version of this scale was carried out by Ulusoy (10).

Trait Anger-Anger Expression Scale (STAXI): STAXI was created by Spielberger and colleagues in order to determine students’ styles of anger expression and was applied to adolescents and adults, there is no time constraint for performing the test. The Scale is 34-item, (0 to 4) Likert-type rating scale. Trait Anger-Anger Expression Scale consists of three subgroups; pulse anger, anger expression, and anger control (11). The validity and reliability study in Turkey was carried out by Özer (12).

Statistical Analysis

SPSS 15.0 statistical package program was used for statistical analysis of all data. Independent samples T-test to compare parametric-impaired data using equal to 2 groups and Mann-Whitney U test for groups’ number equal to 2 and nonparametric-impaired data were used. We used Pearson correlation analysis to determine the relation between parametric data, and used Spearman relation analysis to determine the relation between...
nonparametric data.

**Results**

The mean age of patients with PCOS and control subjects participated in the study was 27.3±5.6 and 27.4±6.1 years, respectively. There was no difference between the patient and control groups in terms of the mean age of menarche (p=0.2005). The rate of caffeine use (59%) in the patient group was higher than the control group (39%), on the other hand, the rate of smoking was higher in the control group (43%) than patient group (25%). The value of BMI, insulin, LH, DHEAS, and total testosterone serum levels in the patient group were significantly higher than the control group (p<0.05). There was no significant difference in terms of glucose (p=0.0904), although there was a significant difference in the level of serum insulin between two groups (p=0.0282). Similarly, the level of thyroid hormones and lipid profiles showed no difference in both groups (p>0.05) (Table 1). There was a weak, but statistically significant positive correlation between BAI score and serum DHEAS levels (Pearson r=0.4366, p=0.0001) (Figure 1). When compared two groups, there were found significant differences between two groups in terms of trait anger, anger control, anger outward and inward, anxiety and the BDI scores (p<0.05) (Figure 2) (Table 2).

**Discussion**

The relationship between psychological and biological variables for polycystic ovary syndrome (PCOS) is a poorly understood area. However, recent researches on this complex issue are promising to understand the relationship between biological and psychosocial parameters. DHEAS level and its psychological effects have a vital role in the etiopathogenesis of PCOS. Previous authors tried to explain this mechanism. According to these authors, Zona Reticularis of the adrenal cortex synthesizes DHEAS from dehydroepiandrosterone. Sulphotransferase catalyzes this reaction (13,14). DHEAS may cause some psychic symptoms such as anxiety, thoughts overly concerned, fear and some physical symptoms like dry mouth, palpitation, headache, hyperventilation, sweating, and gastrointestinal symptoms. In addition, authors described the relationships between those psychiatric symptoms such as negative affect, feelings of worthlessness and a sense of rejection, hypersensitivity to criticism, excessive self-examination, social unrest, and also disturbances of sleep or appetite, and DHEAS (15,16). Progesterone levels in day 21 of the menstrual cycle provide information about ovulation. If follicle-stimulating hormone/luteinizing hormone (LH/FSH) ratio is above 3, this favors diagnosis of PCOS. In PCOS cases, ovarian

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**Table 1. The data of both groups**

<table>
<thead>
<tr>
<th></th>
<th>Control Group Mean and SD</th>
<th>Patient Group Mean and SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>44</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>27.3±5.6</td>
<td>27.4±6.1</td>
<td>0.7030&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>21.1±2.3</td>
<td>24.2±4.3</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Number of Marriage</td>
<td>26 (%59)</td>
<td>30 (%68)</td>
<td></td>
</tr>
<tr>
<td>Age of first menstruation</td>
<td>12.9±1.0</td>
<td>13.0±0.8</td>
<td>0.2005&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smoking/caffeine/alcohol use</td>
<td>19/17/3</td>
<td>11/26/4</td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose (mg / dl)</td>
<td>85±12</td>
<td>91±20</td>
<td>0.0904&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Insulin (µIU / mL)</td>
<td>5.9±2.2</td>
<td>7.97±5.66</td>
<td>0.0282&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>FSH (µIU/ml)</td>
<td>5.74±1.27</td>
<td>4.98±1.91</td>
<td>0.0299&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LH (µIU/ml)</td>
<td>7.41±3.18</td>
<td>9.66±5.43</td>
<td>0.0200&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>66±42</td>
<td>59±43</td>
<td>0.4978&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Prolactin (µIU / mL)</td>
<td>10.42±4.99</td>
<td>10.73±5.17</td>
<td>0.8034&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>DHEAS (mcg/dl)</td>
<td>23±18</td>
<td>228±139</td>
<td>0.0492&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>TSH (µIU/ml)</td>
<td>1.69±0.72</td>
<td>1.53±0.73</td>
<td>0.2906&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T3 (nmol/L)</td>
<td>2.89±0.48</td>
<td>3.07±0.59</td>
<td>0.1205&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T4 (nmol/L)</td>
<td>95±25</td>
<td>93±20</td>
<td>0.8938&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>17 OH-progesterone (ng / ml)</td>
<td>1.03±0.71</td>
<td>0.80±0.48</td>
<td>0.0828&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total testosterone (nmol / L)</td>
<td>0.34±0.14</td>
<td>0.41±0.17</td>
<td>0.0341&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Free Testosterone (pg / ml)</td>
<td>2.10±0.99</td>
<td>2.06±0.95</td>
<td>0.9468&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Triglycerides (mg / dl)</td>
<td>107±52</td>
<td>110±52</td>
<td>0.7682&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LDL Cholesterol (mg / dl)</td>
<td>121±29</td>
<td>123±53</td>
<td>0.8318&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HDL Cholesterol (mg / dl)</td>
<td>46±10</td>
<td>45±11</td>
<td>0.6054&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

SD: Standard Deviation
<sup>a</sup>Unpaired t test, <sup>b</sup>Mann-Whitney U test
granulosa cells produce testosterone and androstenedione so much that estrogen cannot transform entirely. Increased LH and reduced FSH levels shows the inhibition of aromatase activity, this inhibition causes an increase of androsterone level and reduce the estrogen.

In this study, there was a significant correlation between anxiety scores and the serum levels of DHEAS. Otherwise, there was no correlation between depression score and the serum level of DHEAS. (Figure 2). This is considered that symptoms are direct results of increased DHEAS in patients with PCOS. Anxiety and depression are indirect results of this condition. We could not find any correlation between DHEAS levels and depression scores. The depression scores of the patient group were significantly higher than the control group. However, the finding that the depression score of the patient group was significantly higher than the control group was conflicting result. This contradiction may be due to the low sample size of this study. Additionally, increased anxiety levels may be preliminary symptoms for depression, but this is a difficult issue for evaluating because of the cross-sectional study design. Meanwhile, increased physiological arousal and stress is foreground, which is suitable with the explanations related with endocrine changes. On the other hand, negative mood and anhedonia are common signs in depression. Tignol et al. suggested that those depressive symptoms such as sorrow, hopelessness, anhedonia, psychomotor retardation, decreased appetite, and sexual interest shows decreased arousal of central nervous system (CNS). Otherwise, fear, stress, hyperactivity, agitation, premature ejaculation, increased attention shows an increased arousal of CNS and anxiety. Some researchers suggested that DHEAS has GABA antagonistic effect. Electrophysiological studies demonstrated the GABA-antagonistic effects of DHEA, a hormone secreted by the adrenal cortex, in response to adrenocorticotropic (ACTH) (17). DHEA is metabolized to DHEAS, which also has GABA-antagonist effect (17). Despite the importance of the GABA receptor complex (GABA-RC) for the normal function of the CNS, data from human studies describing the role of DHEA, DHEA-S, and other neurosteroid modulators of the GABA-RC are limited (18,19).

GABA, the main inhibitor neurotransmitter in CNS, plays a crucial role in the etiopathogenesis of anxiety disorders. In this study, we found a correlation between anxiety scores and serum DHEAS levels. On the other hand, we could not find any correlation between serum DHEAS and depression scores. However, the findings of this study arise from a cross-sectional study design and cannot eliminate the possible correlation with depressive symptoms over time. Additionally, the sample of this study was young population, and patients with PCOS may develop more depressive symptoms afterward. On the other hand, the emergence of depressive symptoms may have a greater relationship with the individual vulnerability and effects of life events. Possible correlations between DHEAS and depressive symptomatology should be investigated by longitudinal studies. Although there is no correlation between depressive symptom severity and serum DHEAS level, significant difference attracted attention between groups in terms of depressive symptoms. This situation may be due to social, psychological, and biological causes. According to the World Health Organization, the incidence of infertility is 10%-15% in the community, and it causes medical, psychiatric, psychological and social problems. Infertility may cause as a crisis in these fields (20,21). When compared to control group, trait anger, anger control, anger outward and inward, anxiety and the BDI scores of patients with PCOS were significantly different. It may be suggested that in patients with PCOS, this fertile period with the contribution of hormonal changes may cause an unpleasant emotional state. Emotional changes such as irritability, stress, and anxiety may appear in these patients. Infertile women may also live in a stress because of not having children in the reproductive age. Stressors consist of different factors as well as environmental factors such as cold, infection or trauma as well as individual factors such as obesity,
age and gender, insulin and sex hormones, adrenalin, as well as emotional factors such as addiction, anxiety and anger (22). Human body has a strong adaptability to the stressors, but it is not always entirely successful. This ability depends on a broad range consisting of the autonomic nervous system, hypothalamic-pituitary-adrenal axis, cardiovascular, and metabolic processes (23,24). The finding that BAI score of women with PCOS is positively correlated with DHEAS also reveals that experienced anxiety may be due to hormonal imbalance. More specifically, there is no correlation between the BDI scores, anger scale, and DHEAS levels. On the contrary, there is a correlation between BAI scores and DHEAS levels. One possible explanation of this condition: BAI may be more successful in the prediction of somatic components of anxiety, than BDI. Thus, hormone imbalance may affect the autonomic nervous system, and this may cause increased somatic symptoms of anxiety. According to recent research while decreased DHEAS has GABA tonic effects (25), increased DHEAS levels show GABA agonistic effects. In a study, animals showed aggressive behavior when they exposed to DHEAS (26). As a result, anxiety symptoms show stronger relationship compared to the depression symptoms, with the level of DHEAS via autonomic nervous system considering GABA antagonistic effect of DHEAS. The increase of androgen levels causes the suppression of FSH and leads to a vicious cycle. Some studies describe these mechanisms with the increase of androgen in patients with PCOS (27,28). In this study, DHEAS and total testosterone levels in women with PCOS were significantly higher than the controls. These findings show that women with PCOS are under hormonal oppression. After all, undoubtedly, these hormonal changes affect the emotional state of the patients. Dokras et al. suggested that the impaired psychosocial functions in patients with PCOS are associated with the frustration feelings and anxiety (29).

In conclusion, while looking from psychological aspect; obesity, hirsutism, and infertility may reduce self-confidence, and cause depressive symptoms. In addition, hormonal changes may cause anxiety directly. Possibly, depressive symptoms are a secondary reflection of these changes.

Acknowledgements
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