Depression and Anxiety in Relation with Hormonal and Metabolic Profile in Women with Polycystic Ovarian Syndrome

Polikistik Over Sendromlu Kadınlarda Depresyon ile Anksiyetenin Metabolik ve Hormonal Profil ile İlişkileri

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ABSTRACT Objective: Polycystic ovary syndrome (PCOS) is a common hyperandrogenic endocrine disorder which is also associated with psychological and metabolic disturbances. The aim of the present study was to determine whether depression and anxiety were more common in women with PCOS and whether were associated with metabolic and hormonal status. **Material and Methods:** A total of 50 women with PCOS and 50 age-matched controls were eligible for the study. All participants completed standardized questionnaires assessing depression (Beck Depression Inventory) and anxiety (Beck Anxiety Inventory). Hirsutism scores, hormonal and metabolic profile were also evaluated. **Results:** Depression and anxiety scores were found higher in women with PCOS compared to controls. Both scores were significantly correlated with body mass index, insulin resistance and lipid parameters as well as hirsutism scores. **Conclusion:** Data of the present study suggested that depression and anxiety scores were higher in women with PCOS compared to controls. Both depression and anxiety in PCOS is associated with obesity, hirsutism and metabolic abnormalities such as insulin resistance, dyslipidemia and hyperandrogenemia. Clinicians treating women with PCOS should be aware that these women are a high risk group for common mood and anxiety disorders. Management should focus on support, education and strongly emphasizing healthy lifestyle changes.

Key Words: Depression; anxiety; polycystic ovary syndrome

ÖZET Amaç: Polikistik over sendromu (PKOS) metabolik ve psikolojik bozuklukların da eşlik ettiği sık görülen bir hiperandrojenik endokrin hastalıktır. Bu çalışmanın amacı PKOS'lu hastalarda depresyon ve anksiyeteyi ölçekler vasıtasıyla değerlendirip, bu ölçeklerin metabolik ve hormonal profil ile ilişkisini incelenmiştir. **Gereç ve Yöntemler:** PKOS tanısı almış 50 hastaya ve 50 sağlıklı gönüllüye Beck depresyon ve Beck anksiyete ölçekleri anket yöntemiyle doldurtuldu. Hasta ve ve kontrol gruplarının fizik muayene bulguları, hirsutizm skorları (modifiye Ferriman Gallwey) not edildi. Hormonal ve metabolik profilleri de değerlendirildi. **Bulgular:** Depresyon ve anksiyete skorları PKOS grubunda kontrol grubuna göre daha yüksek bulundu. Hem depresyon hem de anksiyete skorları vücut kitle indeksi, insülin resistansı, lipid profili ve hirsutizm skorları ile pozitif korelasyon gösterdi. **Sonuç:** Depresyon ve anksiyete skorları PKOS'lu hastalarda sağlıklı kontrollere göre daha yüksektir. Bu skorlar obezite ve hirsutizm ile ve aynı zamanda dislipidemi, insülin rezistansı ve hiperandrojenizm gibi hormonal ve metabolik bozukluklar ile de ilişkilidir. Klinisyenler, PKOS'lu hastaların anksiyete ve duygu durum bozuklukları için yüksek risk grubunda oldukları konusunda bilinçli olmalıdır. Bu hastaların yönetimi, destek, eğitim ve sağlıklı yaşam tarzı değişikliklerinin özendirilmesi konularına odaklanmalıdır.

Anahtar Kelimeler: Depresyon; anksiyete; polikistik over sendromu

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Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women, with a prevalence of 6-12% in women of reproductive age.[1] It is characterized by androgen excess, chronic oligo-anovulation and polycystic ovaries (PCO) on ultrasound. Clinically, the androgen excess presents as hirsutism and acne, whereas anovulation presents as subfertility and menstrual irregularity. In addition, severe physiological (insulin resistance, inflammation, visceral fat, infertility) and psychological (depression, anxiety, body image, social anxieties) abnormalities are common among women with PCOS.[2]

Several studies have shown that women with PCOS were more likely to develop depressive symptoms than healthy women without PCOS.[3-7] Moreover depression rates in women with PCOS were reported to be between 14 and 64%.[3,6,8,9] The wide range of prevalence rates may be attributed to the different sociocultural characteristics and ethnicities of study populations as well as different methodologies used to screen mood disorders.

Women with PCOS were also found vulnerable to psychological disorders other than depression such as anxiety, social phobia, decreased quality of life, negative body image and eating disorders. Although anxiety appears to be the most common psychiatric diagnosis among patients with endocrine diseases and PCOS is the most common endocrinopathy in women, there are limited data addressing the anxiety status in women with PCOS.[10] Yet, elevations in anxiety scales have also been reported in some studies with a prevalence of 34% to 57%.[3,11-13] However, there are controversial data on the relationship between hirsutism, acne or obesity and anxiety in women with PCOS.[8-14]

PCOS is also known to be associated with increased insulin resistance and other metabolic disorders such as dyslipidemia, hypertension, endothelial dysfunction and reduced vascular compliance and atherosclerosis.[6] Some studies have shown significant association between depression and hormonal and metabolic status in non-PCOS populations.[15,16] There are limited data about the effect of hormonal and metabolic factors of PCOS on the development of psychological disorders.

The aim of the present study was to determine whether depression and anxiety were more common in women with PCOS and to establish if metabolic and hormonal profiles are in relation with mood and anxiety disorders.

MATERIAL AND METHODS

The design of the present study was approved by the Ethical Committee and Institutional Review Board of Adnan Menderes University, Faculty of Medicine, where the study was conducted. Written informed consents were obtained from all participants. As the article was involving human experimental investigations of any kind, it has been carried out in accordance with The Code of Ethics of the Declaration of Helsinki.

The study compromised 50 women with PCOS. The Rotterdam classification (Rotterdam, 2004) was used to define PCOS in the event of: (1) menstrual abnormalities like amenorrhea (no cycles in the past 6 months), oligomenorrhea (cycles lasting longer than 35 days), (2) clinical and/or biochemical hyperandrogenism, (3) ultrasound appearance of PCO (multiple cysts >12 in number of 2-9 mm size). The presence of two of these three criteria was required to define PCOS once other diagnosis, like congenital adrenal hyperplasia, virilising tumor, Cushing syndrome and prolactinoma were ruled out. Clinical hyperandrogenism was defined as hypertrichosis with modified Ferriman-Gallwey (mFG) score >7 and/or acne, and/or androgenic pattern of alopecia. Biochemical hyperandrogenemia was defined by elevated testosterone.[17] As controls 50 age matched women who had regular menses and no clinical or biochemical hyperandrogenism or PCO were eligible. Subjects taking any medication for at least three months prior to the study were excluded.

Detailed clinical history was taken and physical examination was performed for all participants. Body mass index (BMI) was also calculated. Laboratory investigations included fasting blood glucose, fasting insulin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), luteinizing hormone (LH), folli-

cle stimulating hormone (FSH), estradiol (E2), thyroid stimulating hormone (TSH), free thyroxine levels (free T3 and free T4), dehydroepiandrosterone sulphate (DHEA-SO4) and free testosterone (fT) levels. Insulin resistance (IR) was determined by the Homeostasis Model Assessment (HOMA) index (fasting glucose(mg/dl) x fasting insulin (μU/mL)/ 405).[18] All sampling procedures were performed in the early follicular phase (day 2-5 of the menstrual cycle) in the morning after an overnight fast.

All participants completed the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). BDI, created by Dr. Beck, is a 21 question multiple choice self report inventory for measuring the severity of depression. The most current version of the questionnaire is composed if items relating to depression symptoms such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss and lack of interest in sex. The BDI has a maximum score of 63 (0-9: indicates minimal depression, 10-16: indicates mild depression, 17-29: indicates moderate depression, 30-63: indicates severe depression).[19] Similarly BAI, also created by Dr. Beck, is a 21-question multiple-choice self-report inventory that is used for measuring the severity of an individual's anxiety. The BAI consists of 21 questions about how the subject has been feeling in the last month, expressed as common symptoms of anxiety such as numbness and tingling, sweating not due to heat, and fear of the worst happening. The BAI has a maximum score of 63. (0-7: minimal level of anxiety 8-15: mild anxiety 16-25: moderate anxiety 26-63: severe anxiety).[20]

Statistical analysis was done by using Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL, United States). Distribution of continuous and discrete variables were tested by Kolmogorov Smirnov test while homogeneity of variances was tested by Levene's test. Numerical data were shown as mean ± standard deviation or median (minimum-maximum) where appropriate and qualitative data were presented as percentages. Student's t and Mann Whitney U tests were used to determine differences between two independent groups with regard to mean and me-

dian values, respectively. When more than two groups were compared one way ANOVA and Kruskal Wallis tests were used with regard to mean and median values, respectively. When one way ANOVA and Kruskal Wallis tests yielded statistically significant results, post hoc Tukey HSD or non parametic Conover's multiple comparison tests were used to specify which group differs from the others. Categorical changes were evaluated by Pearson's chi square or Fisher's exact tests. Spearman's correlation test was used to determine the correlation between continuous variables and a level of p<0.05 was considered statistically significant.

RESULTS

A total of 50 women with PCOS and 50 controls participated in this study and completed the questionnaires. Demographic, clinical, biochemical, hormonal and psychological characteristics of women with PCOS and controls were summarized in Table 1.

BDI and BAI were all higher in women with PCOS compared to controls (p=0.002 and p<0.001, respectively). There was no patient in both study and control groups with severe depression however, 15 (30%) women with PCOS and three (6%) women in control group had scores ≥17 on the BDI indicating clinically significant depression that needs to be treated (Table 2, Figure 1). Of the women with PCOS 17 (34%) showed elevated BAI scores, whereas four (8%) women in control group showed moderate anxiety (Table 2, Figure 2).

Table 3 shows the significant correlations between depression, anxiety and metabolic and androgen excess parameters. Subjects with higher BMI, higher insulin, TG and fT and lower HDL levels, higher HOMA-IR and mFG scores had both higher depression and anxiety scores. BMI, IR, lipid profile and androgen excess remained independently associated with BDI and BAI scores. Table 4 shows the metabolic and androgen excess parameters according to the varying degrees of anxiety and depression. A parallel rise can be seen in BMI, HOMA-IR, fT levels and mFG scores as the BDI and BAI scores increase from minimal to mild and from mild to moderate.

TABLE 1: Demographic, clinical, biochemical, hormonal and psychologic characteristics of women with PCOS and controls.

	PCOS (n: 50)	Control (n: 50)	p
Age (years)	23.7±5.3	24.4±5.7	0.527
BMI (kg/m²)	25.1±3.7	22.1±2.7	**<0.001**
FPG (mg/dl)	90.0 (68-119)	87.5 (70-99)	0.078
Fasting insulin (µIU/ml)	10.5 (3-95)	8.0 (2.6-14)	**<0.001**
HOMA-IR	2.3 (0.5-24.6)	1.7 (0.5-3)	**<0.001**
Total cholesterol (mg/dl)	182.0 (127-306)	165.5 (121-240)	**0.043**
HDL (mg/dl)	47.0 (27-82)	53.0 (33-81)	0.070
LDL (mg/dl)	113.2±23.9	99.8±22.2	**0.005**
TG (mg/dl)	95.5 (31-330)	83.0 (32-190)	**0.042**
fT(pg/ml)	3.0 (1.5-4.7)	1.2 (0.5-2.8)	**<0.001**
DHEA-SO4 (µg/dl)	317.0 (147-712)	254.0 (74-457)	**0.002**
fT3 (pg/ml)	3.1±0.5	3.0±0.4	0.156
fT4 (pg/ml)	1.1 (0.8-1.8)	1.1 (0.8-1.3)	0.273
TSH (µIU/ml)	1.7 (0.41-3.9)	1.7 (0.6-4.6)	0.926
FSH (mIU/ml)	4.2 (2.14-9)	4.6 (1.2-10)	0.084
LH (mIU/ml)	7.0 (2-40)	4.8 (0.8-10)	**<0.001**
E2 (pg/ml)	50.6±23.6	59.4±23.0	0.062
PRL (mIU/ml)	15.3±4.1	15.5±4.3	0.865
mFG score	9.5 (2-15)	3.5 (2-6)	**<0.001**
BDI	8.5 (4-20)	6.0 (2-20)	**<0.001**
BAI	8.0 (3-26)	5.0 (4-18)	**<0.001**

BMI: body mass index; FPG: fasting plasma glucose; HOMA-IR: Homeostasis Model Assessment-Insulin resistence; HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglycerides; fT: Free testosterone; DHEA-SO4: Dehydroepiandrosterone sulphate; fT3-fT4: Free thyroxine levels; TSH: Thyroid stimulating hormone; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; PRL: Prolactin; mFG: Modified Ferriman-Gallwey score; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory.

**TABLE 2:** Distribution of subjects regarding depression and anxiety scores

|	PCOS (n: 50)	Control (n: 50)	p
Depression			**0.002**
Minimal	31 (62.0%)	45 (90.0%)	
Mild	4 (8.0%)	2 (4.0%)	
Moderate	15 (30.0%)	3 (6.0%)	
Severe	-	-	
Anxiety			**<0.001**
Minimal	24 (48.0%)	45 (90.0%)	
Mild	9 (18.0%)	1 (2.0%)	
Moderate	15 (30.0%)	4 (8.0%)	
Severe	2 (4.0%)	-	

DISCUSSION

The data of the present study suggested that women with PCOS may exhibit significantly higher depression and anxiety scores compared to women without PCOS. Despite the fact that women with psychiatric disorders/psychotropic medication were excluded, a relatively large proportion of the women with PCOS had depression (30%) and anxiety (34%) of potential clinical relevance.

This study confirms previous researches that anxiety and depression were more prevalent in women with PCOS.[3-9,11-13] Furthermore the current study showed that there were significant correlations between depression, anxiety and metabolic and androgen excess parameters. Subjects with higher BMI, higher insulin, TG and fT and lower HDL levels had both higher depression and anxiety scores. Higher HOMA-IR and mFG scores were also in relation with higher BDI and BAI scores.
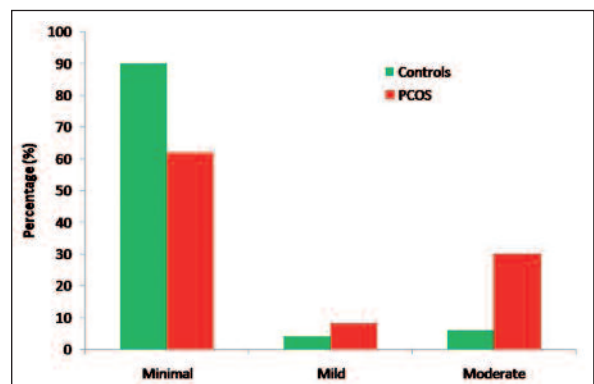
FIGURE 1: BDI (Beck Depression Inventory) scores of the study and control groups.
(See color figure at http://www.turkiyeklinikleri.com/journal/jinekoloji-obstetrik-dergisi/1300-0306/)
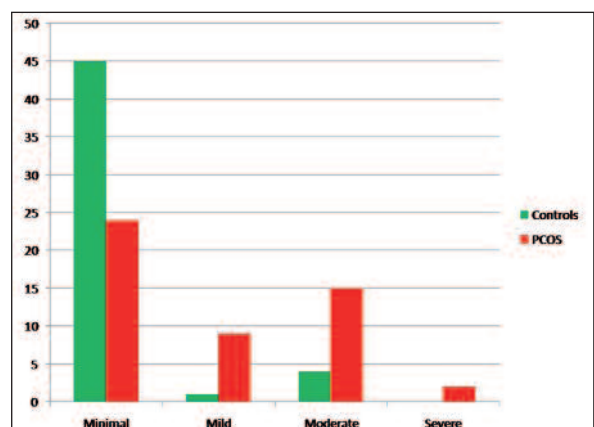
FIGURE 2: BAI (Beck Anxiety Inventory) scores of the study and control groups.
(See color figure at http://www.turkiyeklinikleri.com/journal/jinekoloji-obstetrik-dergisi/1300-0306/)

TABLE 3: Correlations between depression, anxiety and metabolic and androgen excess parameters.

	Depression (BDI)		Anxiety (BAI)	
	r	p	r	p
BMI	0.526	<0.001	0.409	<0.001
Fasting insulin	0.449	<0.001	0.401	<0.001
HOMA-IR	0.453	<0.001	0.440	<0.001
HDL	-0.244	0.014	-0.201	0.045
TG	0.277	0.005	0.239	0.017
fT	0.426	<0.001	0.474	<0.001
mFG score	0.596	<0.001	0.494	<0.001

BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; BMI: Body mass index; HOMA-IR: Homeostasis Model Assessment-Insulin resistence; HDL: High density lipoprotein; TG: Triglycerides; fT: Free testosterone; mFG: Modified Ferriman-Gallwey score; r: Correlation coefficient.

There is a well documented link between mood disorders, particularly depression and obesity, which is a major contributor to IR. Moreover, a linkage between IR with mood and anxiety disorders has been suggested.[6,11,21] There are limited and conflicting data on the association between depression and cardiometabolic risk factors in PCOS. Rasgon et al. reported higher levels of IR and higher BMI were associated with depression in women with PCOS.[22] The data of the present study also suggested that the risk of both depression and anxiety were more prevalent in patients with a higher BMI, HOMA-IR, fasting insulin, TG and lower HDL levels.

A connection between mood and anxiety disorders and androgen excess parameters has been reported in previous studies. The skin manifestations of hyperandrogenism such as hirsutism and acne were found to be strongly associated with body dissatisfaction.[5,6,11] These physical symptoms of PCOS may have made these women more focused on their appearance, implying a need to do something about their appearance, which ultimately may lead to increased depression and anxiety. Considering that both obesity and hirsutism go astray of the modern female ideal, it might also be speculated that this social anxiety is triggered by reactions from other people, and the subjective sense of not being able to fulfill the ideal image of a woman. However, there are controversial data in the literature. Some studies have shown that hirsutism and acne are associated with depression and anxiety, whereas others failed to demonstrate a positive correlation between depression, anxiety and androgen levels or hirsutism scores.[6,14,22,23] Interestingly, Livadas et al. stated that anxiety escalated in parallel with the degree of IR as well as androgen excess while no association was observed between anxiety and mFG scores.[11] In addition, Weiner et al. suggested that the most elevated negative mood scale scores were associated with free testosterone values just beyond the upper limits of normal, whereas lower negative mood levels corresponded to both normal and extremely high levels of fT.[24] Data from the present study also indicated a positive correlation between mFG scores as well as fT levels and added to the prior work and suggested that both clinical and biochemical hyperandrogenism may contribute to mood changes. Discrepant findings may be attributed to methodological bias and differences in study populations. Body perception might show variations in populations with diffe-

TABLE 4: Metabolic and androgen excess parameters according to the varying degrees of anxiety and depression.

	Depression (BDI)				Anxiety (BAI)			
	Minimal (n=76)	Mild (n=6)	Moderate (n=18)	p	Minimal (n=69)	Mild (n=10)	Moderate-Severe (n=21)	p
BMI	22.4±2.4[a]	23.2±2.4[b]	29.0±3.0[a,b]	<0.001	22.3±2.4[c,d]	25.7±3.6[c]	26.9±4.3[d]	<0.001
HOMAIR	1.8 (0.9)[a]	2.2 (1.4)	2.7 (2.5)[a]	0.004	1.8 (0.9)[d]	2.2 (1.4)	2.5 (3.0)[d]	0.007
fT	2.0 (1.5)a	2.2 (1.8)[b]	4.0 (1.4)[a,b]	<0.001	1.8 (1.5)[c,d]	3.0 (2.0)[c]	3.0 (2.2)[d]	<0.001
mFG score	4.0 (2.0)[a,c]	9.0 (6.7)[c]	11.5 (4.2)[a]	<0.001	4.0 (2.0)[c,d]	9.5 (3.7)[c]	10.0 (8.0)[d]	<0.001

BMI: Body mass index; HOMA-IR: Homeostasis Model Assessment-Insulin resistence; fT: Free testosterone; mFG: Modified Ferriman-Gallwey score, r: Correlation coefficient.

[a]: significant difference between minimal and moderate group; [b]: significant difference between mild and moderate group; [c]: significant difference between minimal and mild group; [d]: significant difference between minimal and moderate-severe group.

rent sociocultural characteristics. Thus, available data are inconclusive and the role of androgens in mood and anxiety disorders in women is still a matter of debate.

One of the limitations of the present study was the sample size. Due to small sample size we grouped women by Rotterdam diagnostic criteria with no further subgroup assessment of women within phenotype subgroups. Given the individual effects of the menstrual irregularity, infertility and hirsutism on psychological state in PCOS, larger studies may also aim to detect psychological function in all phenotypes of PCOS. Another limitation of the study is increased body mass index in the PCOS group, but this is expected. Although normal healthy subjects constitutive of the control group may provide some superiority, possible confounding effects of being overweight may be accepted as a limitation. Moreover, the diagnoses were made by questionnaires without clinical interviews performed by physicians specialized in psychiatry which may constitute potential bias of self report assessment tools. Prospective design of the present study may provide

advantages. Furthermore, the current study represented the clinical significance of the metabolic and androgen excess parameters according to the varying degrees of anxiety and depression (mild, moderate, severe) as distinct from aforementioned studies which suggested only higher depression and anxiety scores without indicating clinical significance.

In conclusion, our results suggested increased scores of depression and anxiety in women with PCOS. These symptoms seem to be in relation with obesity, hirsutism and IR. Clinicians treating women with PCOS should be aware that women with PCOS are at high risk for mood and anxiety disorders. Management should focus on support, education, addressing psychological factors and strongly emphasizing healthy lifestyle with targeted medical therapy as required. There is need for increased screening of depression and anxiety in women with PCOS as part of an overall treatment plan. Multidisciplinary approach with a mental health professional for patients with abnormal screening results is optimal to manage the features of PCOS and prevent long term complications.

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