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Sexual function and depression in polycystic ovary syndrome: Is it associated with inflammation and neuromodulators?

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ABSTRACT

Numerous studies have been carried out on depression and sexual dysfunction concomitant with polycystic ovary syndrome (PCOS). Increasing evidence has revealed the importance of inflammation in the etiology of PCOS. In addition, it has been known that some neuromodulators affect depression and sexual function. However, their effects on PCOS are not known. This study aimed to evaluate the relationship of depression and sexual function with cytokines and neuromodulators in PCOS patients. The present study included 20 fertile and 30 infertile patients diagnosed with PCOS and 30 healthy volunteers. Metabolic and endocrine parameters, interleukin (IL)-1β, IL-6, TNFα, γ-aminobutyric acid (GABA), Glutamate, Brain-derived neurotrophic factor (BDNF) serum levels, Beck Depression Index (BDI) and Female Sexual Function Index (FSFI) scores of the patients were compared between the groups. TNFα, IL-1β, IL-6, glutamate, GABA, and BDI scores were found to be significantly higher ($p < 0.05$) in the PCOS group ($p < 0.05$). Glutamate, TNFα, IL-1β, and IL-6 values were higher whereas GABA and BDNF values were lower in pateints with moderate and severe depression ($p < 0.05$). There were no statistically significant relationships between these parameters and the FSFI scores ($p > 0.05$). Multivariate logistic regression analysis was conducted with potential factors that may affect sexual dysfunction. The results indicated that high waist-to-hip ratio (WHR) (> 0.80) with an odds ratio of 1.81 in PCOS patients, and body mass index (BMI) with an odds ratio of 2.3 and high WHR (> 0.80) with an odds ratio of 1.97 in all patients were found to be independent risk factors affecting sexual dysfunction. The results of the present study suggested that chronic low-dose inflammation seen in PCOS may interact with some neuromodulators, leading to the development of depression. However, no relationship was found between these parameters and sexual function.

1. Introduction

Polycystic ovary syndrome (PCOS) is a common disease seen in women of reproductive age, and its prevalence varies between 5% and 24% in different populations (De Niet et al., 2010; Hemati et al., 2011). It is characterized by endocrine and gynecological symptoms such as chronic anovulation and hyperandrogenism (Eshre, 2004). Excessive central fat and insulin resistance are key features of PCOS. Inflammatory processes, particularly increased proinflammatory cytokine production and activation of the innate immune system are associated with obesity. This was also thought to be related to the pathophysiology of atherosclerosis, metabolic syndrome, insulin resistance and diabetes mellitus (Bray, 2004; Pickup, 2004). However, inflammatory markers are high in non-obese PCOS patients. Therefore, rather than obesity, inflammation may be the main pathophysiological mechanism in PCOS.

Other than metabolic disorders, the common pathologies known to be associated with PCOS are depression and sexual dysfunction. This raises the question: 'Is depression an inflammatory disease?' Many studies conducted over the last decade have shown that the main underlying cause of depression is inflammation-related processes (Raison and Miller, 2011). In addition to depressive symptoms, sleep disorders, fatigue, and individual dysfunctions were also associated with increased interleukin (IL)-6 and Nuclear Kappa Factor Beta (Bower et al., 2002; Irwin et al., 2008; Meyers et al., 2005; Motivala et al., 2005). The effect of inflammation on sexual function remains unknown. However, many metabolic diseases known to affect sexual function are associated with

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chronic low-dose inflammations (Maiorino et al., 2018). Furthermore, mood and sexual function are regulated by some neuromodulators that affect the central and peripheral nervous system (Gołyszny and Obuchowicz, 2019; Quinn, 2013).

Glutamate is the main excitatory neurotransmitter (Brann and Mahesh, 1997). It is very effective in initiating and maintaining reproductive activity (Meza-Herrera, 2012). Glutamate also regulates sexual function (Dominguez, 2009; Will et al., 2014). Similarly, γ-aminobutyric acid (GABA), one of the most common neurotransmitters of the central nervous system, is a molecule associated with sexual function and depression ("Gamma-aminobutyric acid (GABA), Monograph,", 2007). Brain-derived neurotrophic factor (BDNF) is an important neurotrophin for the formation of healthy neuron functions. High levels of BDNF yield a protective effect against depression (Aicardi et al., 2004).

There are no studies evaluating the association of these neurotransmitters with concomitant symptoms in patients with PCOS. This study aimed to evaluate the relationship between depression and sexual dysfunction seen in patients with PCOS and serum GABA, glutamate, BDNF, and inflammatory markers and to contribute to the determination of the etiopathogenesis of PCOS.

2. Materials and method

2.1. Study design and participants

This study was performed prospectively in a tertiary center between February 2019 and October 2019. The present study included 20 fertile and 30 infertile patients diagnosed with PCOS according to the Rotterdam criteria and 30 healthy volunteers. The local ethical committee approved the present study (2017-KAEK-189_2019.01.23_06) and informed consent was obtained from all participants.

A power analysis was conducted using the G*Power software version 3.1.7 and based on findings of comparable studies (Benson et al., 2008; Hollinrake et al., 2007; Jedel et al., 2009). An effect size of 0.427 was used with power set at 0.80 and alpha at 0.05 to determine that a sample size of $n = 19$ was required in each group to conduct the One-Way ANOVA analyses. Patients were divided into three groups: 30 healthy fertile women, 20 fertile PCOS patiens and 30 infertile PCOS patients. According to the Rotterdam criteria, patients were diagnosed with PCOS in cases where at least two of the following criteria exist: oligo/amenorrhea, clinical or biochemical hyperandrogenism and PCO in ultrasonography (Eshre, 2004). Healthy women with regular menstrual cycles and without evidence of hyperandrogenism or PCOS were included in the control group.

Using appropriate tests, we excluded all patients in whom secondary etiologies were clinically suspected, including hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, and virilizing tumors. The exclusion criteria were: (i) history of any exogenous hormonal agent use in the last 3 months; (ii) chronic systemic diseases (e.g. chronic renal failure, chronic heart failure, chronic liver disease); (iii) use of antidepressants and anti-inflammatory agents (e.g. steroids); (iv) (iv) hormonal therapies and insulin sensitizers related to PCOS, or history of antiandrogen drug use in the last 3 months; (v) any antioxidant supportive therapy (e.g. vitamin C, etc.); and (vi) smoking. Furthermore, after a general psychiatric evaluation conducted by a psychiatrist, patients with bipolar disorder, psychotic symptoms during the current major depressive episode, a history of psychosis other than the mood disorder episode, any eating disorders, post-traumatic stress disorder, or a history of substance use were excluded from the study.

2.2. Anthropometric and clinical assessments

The patients' demographic information, menstrual cycle history, personal and family medical history, previous and current drug use, anthropometric parameters, acne and hirsutism were evaluated by a single researcher (DAK).

Body weight was measured with patients minimally clothed using a digital scale (Seca 707, Hanover, Md., USA) and rounded to the nearest 100 g. Similarly, height was measured using a tape measurer while patients were standing without shoes and with shoulders in normal alignment. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters squared (m^2). Waist circumference was measured at the narrowest point between the costal margin and the iliac crest during normal breathing, and hip circumference was measured at the widest point on the hips. Waist-to-hip ratio (WHR) was calculated. Clinical hyperandrogenism was defined as the presence of hirsutism (Ferriman-Galwey score [FGS $\geq$ 8]) (Hatch et al., 1981) and/or acne and/or alopecia. The standardized FGS system covers nine different areas of the body, including the upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, and thigh; a total score of 8 was accepted as hirsutism (Escobar-Morreale et al., 2012). To increase the accuracy of the measurement, patients who had not shaved or used other hair removal methods one month prior to the assessment were included. Menstrual cycle durations of less than 24 days and longer than 35 days were regarded as abnormal. Cycles lasting more than 35 days were defined as oligomenorrhea while menstrual absence in the last 6 months was defined as amenorrhea. Anovulation was defined as a serum progesterone level $<$ 3 ng/ml on days 21–24 of the menstrual cycle.

2.3. Ultrasonography assessment

We performed an ultrasound examination of the uterus and ovaries using a 7.5-MHz transvaginal transducer, or a 5-MHz transabdominal transducer for patients for whom sociocultural constraints precluded transvaginal ultrasounds (E8, GE Healthcare, Milwaukee, WI, USA). Sonography was performed on the day the blood samples were taken, which was the 2nd or 3rd day of the menstrual cycle. Polycystic ovarian morphology was defined as having ten or more peripheral follicular cysts of 8 mm or less in one plane with increased central ovarian stroma (Eshre, 2004). Antral follicles were measured in three dimensions, and those with an average diameter of 2–9 mm were counted.

2.4. Biochemical measurements

All blood samples were obtained in the morning between 8 AM and 9 AM, after overnight fasting and during the early follicular phase of a spontaneous or progesterone-induced menstrual cycle. Endocrine profile (including pituitary hormones, ovarian and adrenal steroids), serum lipids, fasting glucose and insulin levels were measured. Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, insulin, and thyroid-stimulating hormone (TSH) levels were determined with chemiluminescent immunometric assays using a Cobas 6000 analyzer (Roche, Swiss) method. Fasting glucose, total cholesterol, high-density lipoprotein (HDL—C) cholesterol and triglyceride levels (TG) were measured spectrophotometrically using an enzymatic colorimetric assay (Roche Integrated system, Mannheim, Germany). Low-density lipoprotein (LDL-C) cholesterol was calculated using the Friedewald formula. Insulin resistance was calculated using the homeostatic model assessment for insulin resistance index (HOMA-IR). The HOMA-IR formula is: fasting plasma glucose (mg/dl) $\times$ fasting serum insulin (mU/ml)/405 (Legro et al., 2004).

Blood samples were collected from each patient after a 12-h fasting period for BDNF, Glutamate, GABA, TNFα, IL-1β, IL-6. Whole blood samples were centrifuged for 10 min at 4000 rpm, and the supernatants were kept at −80 °C until the assays were performed by an investigator who was blind to each patient's status. Commercial enzyme-linked immunosorbent assay (ELISA) kits were used for the measurement of human BDNF, Glutamate, GABA, TNFα, IL-1β, and IL-6 (Bioassay technologies, China) levels using appropriate wavelengths on a microplate reader (BioTek Instruments, EL $\times$ 800 TM, USA) following the assay instructions. Concentrations were calculated over the standard curves.

Inter-assay coefficients of variation were, respectively: 4.2% for LH (≤0.8, ≤2.1), FSH (≤1.5, ≤4.0), insulin (≤3.7, ≤4.7), prolactin (≤0.9, ≤2.0), glucose (≤1.0, ≤1.3), total cholesterol (≤1.1, ≤1.6), HDL cholesterol (≤0.6, ≤1.1), triglycerides (≤ 0.9, ≤2.0), BDNF (≤6.3, ≤8.1), Glutamate (≤3.8, ≤5.1), GABA (≤5.5, ≤7.4), TNFα (≤6, ≤8), IL-1β (≤8, ≤10.1) and IL-6 (≤6, ≤8).

Beck Depression Inventory (BDI) was used to assess the depression status of the patients. This scale, which was developed by Beck et al. to measure the physical, emotional, cognitive and motivational symptoms of depression, was adapted into Turkish by Hisli (Hisli, 1989). For BDI, the scores are classified as: 1 to 10 = normal, 11 to 16 = slight mental distress, 17 to 30 = moderate depression, 31 to 40 = severe depression, 40 or more = very severe depression, and clinical help is recommended for those whose score is above 17.

The sexual function of women were assessed using the Turkish version of the Female Sexual Function Index (FSFI), which has been previously validated in the Turkish language by the Turkish Society of Andrology (Çayan et al., 2004; Rosen et al., 2000). The total-scale score range was from 2 to 36. The cutoff value was 26.55, and scores equal to or below this point were classified as sexual dysfunction (Rosen et al., 2000).

2.5. Statistical analysis

Statistical package program SPSS 20 (IBM Corp. released 2011. IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) was used to evaluate the data. Data were expressed as mean ± SD and in percentages. Continuous variables were investigated using analytical methods (Kolmogorov-Simirnov / Shapiro-Wilk's test) to determine whether or not they were normally distributed. If the numerical data were not normally distributed, the (non-parametric) Kruskal Wallis test was conducted; if data were normally distributed, a (parametric) one-way ANOVA test was carried out and Bonferroni correction was used for the post-hoc assessment. For double comparison, the (non-parametric) Mann–Whitney *U* test was utilized for numerical data that were not normally distributed, while the (parametric) Student *t*-test was adopted for normally distributed numerical data. Relationships between categorical variables were analyzed using Chi-square tests. Bivariate correlations were investigated using Spearman's correlation analysis. For the multivariate analysis, the possible factors identified with univariate analyses were entered into the logistic regression analysis to determine further independent predictors of sexual dysfunction. $p < 0.05$ were accepted as statistically significant.

3. Results

A total of 80 women admitted to gynecology outpatient clinics were included in this study. The control group consisted of 30 healthy fertile women (37.5%), and the treatment group consisted of 20 fertile (25%) and 30 infertile (37.5%) patients with PCOS. Group characteristics are shown in Table 1.

3.1. Group comparisons

Statistically significant differences were determined between the three groups in terms of age, WHR, gravidity, parity, FGS, fasting blood glucose, insulin, and HOMA-IR (Table 1). WHR, FGS and fasting blood glucose values in the control group were significantly lower than those of the two PCOS groups ($p < 0.001$, $p = 0.004$, $p = 0.011$, respectively). Fasting insulin and HOMA-IR levels in the PCOS fertile group were significantly higher than those of the control group ($p = 0.033$, $p = 0.017$, respectively). The other metabolic values were similar between the groups ($p > 0.050$).

FSFI and BDI results are given in Table 3. Lubrication was significantly higher in the PCOS groups compared to those in the control group ($p = 0.040$). There were no statistically significant differences in other

Table 1
Comparison of baseline clinical, endocrine, and metabolic characteristics of the groups.

	Control fertile n: 30	PCOS fertile n: 20	PCOS infertile n: 30	p
Age (years)	31.9 ± 4.73[b,c]	23.8 ± 4.05	26.13 ± 4.66	<0.001[&]
BMI (Kg/m^2)	25.08 ± 4.84	26.72 ± 3.77	26.19 ± 6.02	0.501[μ]
WHR	0.75 ± 0.07[b,c]	0.84 ± 0.06	0.81 ± 0.08	<0.001[&]
Gravidty	1.75 ± 1.32[c]	1.25 ± 1.04	0.42 ± 0.76	<0.001[μ]
Parity	1.36 ± 0.99	1.13 ± 0.83	0.23 ± 0.43[a,b]	<0.001[μ]
Hirsutism, FGS > 8	4 (13.3%) [b,c]	9 (45%)	16 (53.3%)	0.004[γ]
Fasting glucose (mg/dl)	86.79 ± 8.47[b,c]	93.8 ± 7.7	89.87 ± 7.44	0.011[&]
Insulin (μIU/ml)	8.88 ± 4.23[b]	11.78 ± 3.49	15.48 ± 27.31	0.033[μ]
HOMA-IR	1.92 ± 0.98[b]	2.75 ± 0.87	3.40 ± 5.66	0.017[μ]
FSH (mIU/ml)	6.08 ± 1.75	4.95 ± 1.46	4.97 ± 1.73	0.306[μ]
LH (mIU/ml)	5.92 ± 2.21	6.56 ± 3.41	6.77 ± 3.72	0.865[&]
Estrodiol (mIU/ml)	40.07 ± 19.89	44.12 ± 22.74	44.37 ± 23.79	0.927[μ]
LDL-C (mg/dl)	95.35 ± 38.46	104.92 ± 27.9	101.70 ± 25.37	0.552[&]
HDL-C (mg/dl)	54.67 ± 12.41	57.69 ± 13.15	55.42 ± 15.75	0.749[μ]
Cholesterol (mg/dl)	171.94 ± 38.88	179.3 ± 27.35	173.55 ± 28.05	0.725[&]
Trigliserid (mg/dl)	89.64 ± 42.46	97.65 ± 53.31	90.71 ± 46.50	0.826[μ]

&: T-student test, μ: Mann–Whitney U test, γ: Chi-square test.
Data presented as mean ± SD. BMI; body mass index, WHR; waist/hip ratio; FGS; Ferriman-Gallway score, HOMA-IR; homeostatic model assessment insulin resistance index.
[a] There was a significant difference with compared control fertile in post-hoc comparison.
[b] There was a significant difference with compared PCOS fertile in post-hoc comparison.
[c] There was a significant difference with compared PCOS infertile in post-hoc comparison.

FSFI scores between the groups. Although not statistically significant, sexual dysfunction was higher (50%) in the PCOS infertile group. The mean values of the depression scores in both PCOS groups were significantly higher than the control group ($p < 0.001$). Furthermore, BDI scores were divided into two groups as mild and moderate depression. The differences in neuropeptide and inflammatory cytokine values between these groups were also examined. Glutamate, TNFα, IL-1β, and IL-6 values were higher in Group 2, whereas GABA and BDNF values were higher in Group 1, and the differences in these values were statistically significant ($p < 0.050$) (Table 2). In all patients, total FSFI score ($r = -0.287$, $p = 0.027$) and arousal ($r = -0.340$, $p = 0.008$) decreased with increased depression, whereas such a relationship was not determined only in the PCOS group.

3.2. Markers

The results of neuropeptide and inflammatory markers between the

Table 2
Neuromodulator and cytokine levels in Beck Depression Inventory (BDI) score groups.

	Group 1 (mild depression)	Group 2 (Moderate and severe depression)	p
Glutamat (ng/ml)	42.77 ± 3.9	51.62 ± 6.82	<0.001[μ]
GABA (ng/ml)	15.01 ± 3.9	14.7 ± 2.82	<0.001[&]
BDNF (pg/ml)	111.01 ± 25.85	99.91 ± 21.58	0.015[μ]
TNF-α (pg/ml)	29.7 ± 9.63	40.92 ± 8.56	<0.001[&]
IL-1β (pg/ml)	39.33 ± 9.94	47.54 ± 10.35	0.001[&]
IL-6 (pg/ml)	1.52 ± 0.76	2.57 ± 0.99	<0.001[μ]

&: T-student test, μ: Mann–Whitney U test. Data presented as mean ± SD.

Table 3
Female sexual function index (FSFI) and Beck Depression Inventory (BDI) scores in all patients.

	Control fertile	PCOS fertile	PCOS infertile	p
Desire	3.69 ± 0.92	3.86 ± 1.34	4.2 ± 1.05	0.162[μ]
Arousal	4.09 ± 0.97	4.07 ± 1.31	4.14 ± 0.82	0.960[μ]
Lubrication	5.07 ± 0.76[b,c]	4.5 ± 1.04	4.49 ± 0.82	0.040[μ]
Orgasm	4.41 ± 1.05	4.06 ± 1.45	4.35 ± 0.98	0.826[μ]
Satisfaction	4.93 ± 1.5	4.1 ± 1.91	4.94 ± 1.25	0.349[μ]
Pain	4.43 ± 1.54	4.11 ± 1.08	4.26 ± 1.58	0.643[μ]
Total FSFI score	26.8 ± 4.58	25.29 ± 6.58	26.57 ± 4.22	0.748[&]
Sexual dysfunction (%)	11 (36.7%)	9 (45.0%)	15 (50.0%)	0.576[γ]
BDI score	8.3 ± 5.57[b,c]	17 ± 8.91	15.63 ± 5.53	<0.001[&]

&: T-student test, μ: Mann–Whitney U test, γ: Chi-square test.
Note: Unless otherwise specified, results are presented as mean ± SD. BDI, Beck Depression Inventory score, FSFI;female sexual function index.
[b] There was a significant difference with compared PCOS fertile in post-hoc comparison.
[c] There was a significant difference with compared PCOS infertile in post-hoc comparison.

Table 4
Neuromodulator and cytokine levels in all patients.[b]

	Control fertile	PCOS fertile	PCOS infertile	p
Glutamat (ng/ml)	42.63 ± 3.36 [c]	46.49 ± 6.03	48.7 ± 8.03	0.003[μ]
GABA (ng/ml)	13.22 ± 3.72 [c]	15.26 ± 3.05	16.34 ± 3.03	0.002[&]
BDNF (pg/ml)	114.37 ± 30.24	100.62 ± 16.48	104.21 ± 22.39	0.116[μ]
TNF-α (pg/ml)	26.43 ± 7.17 [b.c]	36.35 ± 10.6	39.02 ± 9.83	<0.001[&]
IL-1β (pg/ml)	35.15 ± 8.86 [b.c]	48.12 ± 9.38	45.31 ± 9.7	<0.001[&]
IL-6 (pg/ml)	1.3 ± 0.74 [b.c]	2.5 ± 0.75	2.07 ± 1.02	<0.001[μ]

&: T-student test, μ: Mann–Whitney *U* test. Data presented as mean ± SD.
[b] There was a significant difference with compared PCOS fertile in post-hoc comparison.
[c] There was a significant difference with compared PCOS infertile in post-hoc comparison.

groups are given in Table 4. Glutamate, GABA, TNFα, IL-1β, and IL-6 levels were significantly higher in PCOS patients compared to those in the control group ($p < 0.005$). BDNF values were higher in the control group, although no statistically significant differences were found between the groups ($p = 0.116$).

3.3. Correlations between groups

There was a positive correlation between BMI and IL-1β ($r = 0.249$, $p = 0.026$); WHR and TNFα ($r = 0.269$, $p = 0.016$), IL-1β ($r = 0.348$, $p = 0.002$) and IL-6 ($r = 0.222$, $p = 0.048$); and HOMA-IR and TNFα ($r = 0.322$, $p = 0.004$) and IL-1B ($r = 0.378$, $p = 0.001$) in all patients. Furthermore, there was a positive correlation between HOMA-IR and IL-1β in all patients with PCOS ($r = 0.332$, $p = 0.019$). No significant correlation was found between other inflammatory markers. While there were no significant correlations between BMI and inflammatory markers in patients with PCOS, there was a positive correlation only between BMI and TNFα ($r = 0.364$, p = 0.048) and IL-1β ($r = 0.374$, $p = 0.042$) in the infertile POCS group.

In all patients, Spearman's correlation analysis was performed between FSFI scores and age, BMI, WHR, glutamate, GABA, BDNF, TNFα, IL-1β, IL-6. No significant correlations were found according to these analyses, except for BMI. BMI was significantly negatively correlated with arousal ($r = -0.326$, $p = 0.012$), lubrication ($r = -0.238$, $p = 0.040$) orgasm ($r = -0.381$, $p = 0.003$), satisfaction ($r = -0.288$, $p = 0.027$), pain ($r = -0.275$, $p = 0.035$), and total score ($r = -0.367$, $p = 0.034$). Moreover, in patients with PCOS, Spearman's correlation analysis between FSFI scores and age, BMI, WHR, Glutamate, GABA, BDNF, TNFα, IL-1β, and IL-6 values was performed and no significant correlation was found ($p > 0.050$). While a negative correlation was found between BDI score and age ($r = -0.380$, $p = 0.001$) and BDNF ($r = -0.260$, $p = 0.020$), a positive correlation was found between BDI score and BMI ($r = 0.244$, $p = 0.029$), WHR ($r = 0.223$, $p = 0.047$), Glutamate ($r = 0.516$, $p < 0.001$), TNFα ($r = 0.468$, p < 0.001), IL-1β ($r = 0.371$, p = 0.001), and IL-6 ($r = 0.399$, p < 0.001).

3.4. Multivariate logistic regression analysis

Multivariate logistic regression analysis was conducted with potential factors that may affect sexual dysfunction. The WHR parameters were categorized and included in the analysis as ≤ and > 0.80, in line with a previous publication (Milnerowicz and Madej, 2017). The results indicated that high waist-to-hip ratio (WHR) (> 0.80) in PCOS patients (OR = 1.81, 95% CI = 1.05–2.12), and body mass index (BMI) (OR = 2.3, 95%CI = 1.46–2.58) and high WHR (> 0.80) (OR = 1.97, 95% CI = 1.22–2.36) in all patients were found to be independent risk factors affecting sexual dysfunction (Table 5).

4. Discussion

In PCOS patients, problems such as obesity, insulin resistance, metabolic syndrome and infertility receive a great deal of focus, while depression and sexual dysfunction are often overlooked. However, these two conditions fundamentally affect the appropriateness and process of treatment in PCOS. This study aimed to investigate the complex relationship between metabolic problems and depression and sexual functions in patients with PCOS and to examine the role of inflammation and neuromodulators in this process.

This is the first study to evaluate the effect of chronic inflammation and neuromodulators on sexual function and depression in patients with

Table 5
Multivariate logistic regression model of potential factors affecting sexual dysfunction.

	PCOS patients ($n = 50$)				All patients ($n = 80$)			
	B	p	OR	95% C.I.	B	p	OR	95% C.I.
Age (years)	0.042	0.787	1.04	0.77–1.41	−0.09	0.264	0.91	0.78–1.07
BMI (kg/m^2)	0.339	0.167	1.40	0.87–2.27	0.24	0.012	2.30	1.46–2.58
High WHR (>0.80)	4.240	0.034	1.81	1.05–2.12	2.07	0.034	1.97	1.22–2.36
Fasting glucose (mg/dl)	0.061	0.787	1.06	0.68–1.66	−0.02	0.865	0.98	0.82–1.18
Insulin (μIU/ml)	2.597	0.178	1.30	0.31–58.7	0.29	0.716	1.34	0.28–6.47
HOMA-IR	−10.160	0.223	0.01	0–488.02	−0.98	0.787	0.38	0–450.65
TNF-α (pg/ml)	−0.016	0.793	0.98	0.87–1.11	−0.03	0.397	0.97	0.90–1.04
IL-1β (pg/ml)	−0.134	0.044	0.87	0.77–1.00	−0.03	0.440	0.97	0.91–1.04
IL-6 (pg/ml)	−0.370	0.523	0.69	0.22–2.15	0.03	0.923	1.03	0.52–2.05

BMI: Body mass index, WHR: Waist-hip ratio, OR: odds ratio; CI: confidence interval.

PCOS. The data in this study once more confirmed the presence of chronic inflammation in PCOS. Increased inflammation was found to increase significantly with depression score; however, no relationship was found between sexual function and inflammation. Patients with PCOS had higher levels of sexual dysfunction. Serum glutamate levels were found to be significantly higher whereas serum GABA and BDNF levels were lower in patients with moderate and severe depression. Moreover, glutamate and GABA levels were significantly higher in patients with PCOS, whereas BNDF levels were lower in the PCOS group. No significant relationships were found between sexual dysfunction and serum GABA, glutamate, and BDNF values in patients with PCOS.

The high incidence of obesity, insulin resistance, and metabolic syndrome in patients with PCOS has attracted increasing attention in studies on the inflammatory process in these patients. There is evidence in the literature to suggest the presence of chronic low-grade inflammation in these patients. In one study, c-reactive protein (CRP), TNF α, IL-1B, and IL-6 were reported to be high in PCOS patients (Diamanti-Kandarakis et al., 2006). It has been suggested that overexpression of TNF α from adipose and muscle tissues plays an important role in the development of insulin resistance by reducing tyrosine kinase activity at insulin receptors (Hotamisligil et al., 1996; Saghizadeh et al., 1996). Furthermore, an increase in serum IL-6 levels was associated with the insulin effect (Fernandez-Real et al., 2001; Kern et al., 2001; Tarkun et al., 2006). In the present study, serum TNFα, IL1-β and IL-6 levels were significantly higher in PCOS patients compared to those in the control group. There was a positive correlation between HOMA-IR and IL1β in PCOS patients. BMI was not associated with inflammatory markers in PCOS patients; however, serum TNFα and IL-1β values were significantly positively correlated with BMI in infertile PCOS patients. These results once again showed the effect of the inflammatory process on the etiopathogenesis of PCOS. However, the effects of inflammatory processes on mood, behavior, and sexuality are still unclear.

The oldest known theory of depression development is the Monoamine hypothesis. However, evidence shows that this hypothesis is effective in neuromodulators such as serotonin, dopamine and noradrenaline monoamines, as well as various cytokines, GABA, Glutamate and BDNF (Slattery et al., 2004; Tripp et al., 2012). Cytokines have been found to access the brain and interact in almost all the pathophysiological areas related to depression, including neurotransmitter metabolism, neuroendocrine function, and neural plasticity (Dantzer et al., 2008; Raison et al., 2006). The relationship between increased cytokines and depression has brought about the question, 'Is depression an inflammatory disease?'. Previous research has suggested that cytokines are associated with these mediators. The increase in cytokines reduces BDNF expressed from the hippocampus, increases extracellular glutamate, and reduces its re-uptake (Miller et al., 2009). When other inflammatory contributions to depressive symptoms are examined, depressive behaviors have been found to increase in laboratory animals given endotoxin triggers, whereas symptoms improved by blocking pro-inflammatory cycokines. The mediator believed to be most responsible for the relationship between inflammation and depression is glutamate. Inflammation affects the release and transmission of glutamate, and the concentration of extracellular glutamate in the central nervous system increases. Increased glutamate causes the down-regulation of BDNF synthesis through *N*-methyl-D-aspartate (NMDA) receptors (Haroon et al., 2017; Tilleux and Hermans, 2007). However, the mechanism of action of the inflammatory pathways in the central nervous system is still unknown. The cause of depression in patients with PCOS was thought be related to obesity, insulin resistance, hirsutism, and abnormal hypothalamic-pituitary axis (Miller et al., 2009). The number of studies on the relationship between depression and inflammation in these patients is very limited. Benson et al. investigated the relationship between depression and cytokine in patients with PCOS and found that IL-1β, IL-6, and high sensitive CRP did not show an increased relationship with depression (Benson et al., 2008). The data in the present study showed that depression was associated with inflammation in patients with PCOS, and as the depression score increased, TNF-α and IL-6 levels increased significantly. Moreover, GABA and BDNF levels were lower in depressed patients whereas Glutamate was found to be higher in PCOS patients. In the current study, these parameters were evaluated in peripheral blood. Previous studies have shown that serum levels of these neuromodulators correlate with their levels in the central nervous system (Alfredsson et al., 1988; Hashimoto et al., 2005; Karege et al., 2002; McGale et al., 1977).

Classical antidepressant therapies are frequently used to relieve symptoms of depression in patients. These antidepressant therapies affect monoamines. In the general population, 30% of patients show no improvement, even when combinations of these treatments are applied (Miller et al., 2009). Unlike SSRIs (Selective serotin reuptake inhibitor), ketamine, which is being investigated as a new treatment modality, suppresses cytokine release (especially IL-6) and creates an antidepressive effect on NMDA receptors. Confirms the relationship. This confirms the strong relationship between depression-inflammation-glutamate and BDNF (Cui et al., 2019). The findings of the current study may lead to the emergence of such new therapies for patients with PCOS who were given treatment based on the monoamine hypothesis but for whom treatment was not successful.

Sexual problems or sexual dysfunctions refer to a problem that occurs at any stage of the sexual response cycle, preventing the satisfaction of the individual or the couple during sexual activity. This problem can be caused by physical, social and psychological factors (Burri and Spector, 2011). Sexual physiology is regulated by subcortical structures such as the hypothalamus, brainstem, and spinal cord, as well as several cortical brain regions with neurotransmitters and neuromodulators. Sexual disorders such as decreased libido, erectile dysfunction, and anorgasmia have been reported in patients using GABA analogue for the treatment of epilepsy, neuropathic pain, generalized anxiety disorders, fibromyalgia, and the prevention of migraines (Hamed, 2018). Studies on rodents and ewe have shown that consumer sexual behavior increases in males and ovulation and pregnancy rates increase in females with glutamate injections (Calderón-Leyva et al., 2018; Will et al., 2014). It is not yet fully known why and how these mediators create and change the sexual response. There is evidence in the literature that peripheral inflammation causes endogenous changes in neuromodulatory levels. In rats with hepatic encephalopathy, peripheral inflammation as a cause of neuroinflammation has been reported to increase some neuromodulators, especially GABA, and impair cognitive functions (Dadsetan et al., 2016). It is still unknown whether the chronic inflammation that occurs in PCOS creates chronic neuroinflammation; however, there is a strong association between PCOS, inflammation, depression, and sexual dysfunction. This study revealed that sexual dysfunction was higher in patients with PCOS. However, no relationship was found between sexual dysfunction and inflammatory mediators and neuromodulators. Previous studies have found that sexual dysfunctions observed in patients with PCOS were mostly associated with factors such as obesity, WHR, and hyperandrogenemia, which are thought to impair body image and female identity (Bazarganipour et al., 2014; Morotti et al., 2013). In line with this, the regression model in this study found that WHR in patients with PCOS and BMI and WHR in all patients were independent risk factors for sexual dysfunction. These two parameters are known to be factors affecting sexual activity and sexual intercourse. However, we attribute the effect of these risk factors not only to the patients' changing body image, but also to the contribution of increased BMI and WHR to inflammation. Some studies have suggested that mild hirsutism and hyperandrogenism do not decrease female identity, which is supported by the positive correlation between BMI and inflammatory markers found in this study (Battaglia et al., 2008). In the last two decades, endothelial dysfunction has attracted attention as a potential mediator in many metabolic disorders, including chronic low-grade inflammation, obesity, metabolic syndrome, and type 2 diabetes (Esposito and Giugliano, 2004; Libby et al., 2002). Interestingly, these pathological conditions are also considered to be strong risk factors for erectile

dysfunction in men and female sexual dysfunction. A study conducted in men found that increases in IL-6, IL-8, IL-18 and CRP in proportion to increases in visceral fat were associated with erectile dysfunction (Giugliano et al., 2004).

In this study, we hypothesized that inflammation may affect sexual functions by altering neuromodulator levels, but the current results do not directly support such a claim. This might be due to the fact that human sexuality is dependent on complex interactions related to psychological factors as well as biological factors. Factors affecting sexuality may vary for cultures, individuals, and even for the same individual depending on the time, environment and conditions (Clayton and Juarez, 2019).

Evaluating sexual dysfunction in PCOS patients is very difficult due to the wide clinical spectrum of the disease, female psychology, and the ever-changing characteristics of sexuality. The most important limitation of this study was that a one-off procedure with a single scale system was used to evaluate female sexual function. In addition, the number of participant patients was limited, and the sexual functions of patients' partners were not evaluated. Some problems in men such as erectile dysfunction may affect many sexual parameters in women. Increasing the sample size by including the partners in the study might have affected the results of the study. Another important limitation was the lack of continuous monitoring of neuromodulators affecting sexual function.

5. Conclusion

In this study, significant differences were found in the inflammatory markers and neuromodulator levels between PCOS patients and the healthy control group. This study found that in patients with depression and sex dysfunction concomitant with PCOS, inflammatory markers and glutamate increased whereas GABA and BDNF decreased. However, these markers do not seem to have any relationship with sexual dysfunction. Since the definition of PCOS was first developed in 1935, it has remained a challenge for gynecologists. These findings may be helpful in future studies on the treatment of PCOS and concomitant pathologies, particularly depression.

Author contribution

AK Demet: Protocol/project development, Manuscript writing/editing,
B Emre: Data analysis, Manuscript writing/editing,
O Taylan: Data collection or management,
DC Melike: Data collection or management,
K Mustafa: Data analysis,
Y Ethem Serdar: Manuscript writing/editing,
G Yesim: Protocol/project development.

Declaration of Competing Interest

The authors of this manuscript have no conflicts of interest to declare.

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