Psychiatria Danubina, 2015; Vol. 27, No. 1, pp 25-30 *Original paper*
© Medicinska naklada - Zagreb, Croatia

URINARY NEOPTERINE LEVELS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: ALTERATIONS AFTER TREATMENT WITH PAROXETINE AND COMPARISON WITH HEALTHY CONTROLS

Ibrahim Taymur[1], Kadir Özdel[2], Nurper Erberk Özen[3], Buket Belkiz Güngör[1] & Murad Atmaca[4]

[1]Department of Psychiatry, Şevket Yilmaz Teaching and Research Hospital, Bursa, Turkey
[2]Department of Psychiatry, Yildirim Beyazid Teaching and Research Hospital, Ankara, Turkey
[3]Department of Psychiatry, School of Medicine, Ufuk University, Ankara, Turkey
[4]Department of Psychiatry, School of Medicine, Firat University, Elazığ, Turkey

received: 14.11.2014; revised: 3.2.2015; accepted: 16.2.2015

SUMMARY

Background: *A close relationship has been shown between mood disorders and pteridine levels. The aim of this study was to examine alterations in the urine neopterine levels of patients with major depressive disorder (MDD) who responded to paroxetine during the initial treatment and to compare their levels to those of healthy controls.*

Subjects and methods*: Sixteen patients with major depression and 19 healthy controls were enrolled in the study. In order to assess depression severity levels, the Beck Depression Inventory, the Beck Anxiety Inventory, and the State-Trait Anxiety Inventory were administered. Urinary neopterine values that were measured using high pressure liquid chromatography (HPLC) were compared using non-parametric tests for the MDD patients before and after treatment. Urine neopterine levels in MDD patients before and after treatment were compared to those of the healthy control group.*

Results: *Urinary neopterine levels were recorded as follows: For the MDD group before treatment the mean level was 187.92±54.79 µmol/creatinine. The same group under treatment at 4 to 8 weeks was at 188.53±4962 µmol/creatinine, and the healthy control group showed 150.57±152.98 µmol/creatinine levels. There was no statistically significant difference in the urinary neopterine levels among the MDD patients before and after treatment (p=0.938). When urine neopterine levels in MDD patients before and after treatment were compared to those of the healthy control group, levels in the MDD group were found to be significantly higher (p=0.004 and p=0.005, respectively).*

Conclusions: *Findings from the current study suggest that despite treatment response, depression is related to higher levels of urine neopterine. Paroxetine treatment has no significant effect on urine levels of neopterine in MDD patients.*

Key words: *neopterine – depression – MDD - immune system - paroxetine*

* * * * *

INTRODUCTION

Humoral and cellular immune functions play an important role in the pathophysiology of depressive disorders (Maes et al. 1994). A close relationship has been shown between mood disorders and pteridine levels. Consistently, increased immune system activity during depression may lead to increase pteridine levels (Maes et al. 1994, Dunbar 1992). Increased production of pro-inflammatory cytokines is known to have an important role in the underlying pathophysiology and symptomatology of depression (Sluzewska et al. 1996). Neopterine which is involved in the formation of monoamines serves as a marker of such cellular immune system activation. In recent years, neopterine levels have been involved among the candidates for immune markers related to major depression (Müller 2013, 2014).

Measurements of biopterin and neopterine may indicate changes in the metabolism of tetrahydrobiopterin (BH4) which acts as a cofactor for tyrosine and tryptophan hydroxylases in the initial step of dopamine, serotonin and norepinephrine biosynthesis (Barford et al. 1984, Thony et al. 2000). Since neopterine and biopterin are end products of pterin metabolism, changes in the metabolism of BH4 can be assessed (using various approaches) by measuring total biopterin and neopterine levels (Barford et al. 1984, Thony et al. 2000).

Research pertaining to pteridine clearly demonstrated that there is a relationship between pteridine, the immune system, and chronic diseases affecting the immune system (Daito et al. 1994, Fuchs et al. 1989). Increased urinary neopterine levels related to many malignant and chronic conditions, such as inflammatory diseases, have also been found (Reibnegger et al. 1986). The activation of the immune system in chronic diseases is associated with an increase in tryptophan catabolism and neopterine levels (Murr et al. 2000, Huang et al. 2002, Widner et al. 2002). BH4 is responsible for the release of several neurotransmitters related to mood disorders (Hoekstra & Fekkes 2002).

Though antidepressants used in the treatment of depressive disorders affect tyrosine hydroxylase and tryptophan hydroxylase activities (Miura et al. 2005), mixed results have been obtained from the studies of the relationship between pteridines and depressive disorders (Cryan & Leonard 2010). These results mainly indicate increased total biopterin and neopterine levels in depressed patients (Abou-Saleh et al. 1995, Hashimoto et al. 1987, Duch et al. 1984). One study indicated decreased biopterin levels in depressed patients as compared to healthy controls (Hoekstra et al. 2001). Some studies found increased BH4 levels (Coppen et al. 1989, Knapp et al. 1989) whereas others found reduced BH4 levels in depressed patients (Hashimoto et al. 1990, O'Toole 1998). Another study of patients diagnosed with seasonal depressive disorder observed they showed increased neopterine and decreased biopterin levels when compared with a control group (Hoekstra et al. 2003).

Biological amines such as serotonin, noradrenaline, and dopamine have an important role in the development of major depressive disorder. Many studies have demonstrated the role of these amines (Owens & Nemeroff 1994). However, studies of the role of neopterine, which is involved in the production stage of these amines, do not show the same degree of consistency. Our knowledge is limited about the relationship between neopterine and the results of treatment in specific individuals.

When we look at studies in this area, urine neopterine levels in individuals with depressive disorder have consistently been found to be higher than those in healthy controls. However, two studies that evaluated pre and post treatment changes in urinary neopterine levels did not find any significant alteration in urinary neopterine levels after treatment. These studies examined results related to antidepressants with various mechanisms of action (i.e., rolipram, tricyclic antidepressants, and selective serotonin reuptake inhibitors) and electroconvulsive therapy rather than testing a single antidepressant (Abou-Saleh et al. 1995, Hashimoto et al. 1994, Celik 2010). Therefore, these studies cannot offer a conclusion about the effects of specific antidepressant medications on urine neopterine levels.

Another issue is to choose urinary samples to examine the neopterine levels instead of cerebrospinal fluid (CSF) or serum. Several studies preferred to use urinary neopterine levels because of two reasons. First, the urine samples might easily be collected and tested, and second, the levels of urine and serum neopterine measured by HPLC give very consistent results to each other (Fuchs et al. 1989, Werner et al. 1987).

The aim of the current study was to evaluate alterations of urine neopterine levels in patients with MDD who are under treatment and responsive to paroxetine, a Selective Serotonin Reuptake Inhibitor (SSRI).

SUBJECTS AND METHODS

Subjects

The study sample consisted of 16 patents with MDD diagnoses according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV). Subjects were under treatment at the psychiatric outpatient unit of Kirikkale University in the study period. Their age range was between 20 and 52. Participants had been using no other psychotropic medication within 1 month of the current treatment. All participants had responded to 4-5 weeks of paroxetine treatment. The control group was recruited from employees working at the same university hospital. People included in the control group did not have any currently diagnosed psychiatric disorder or any history of psychiatric treatment or previous psychiatric diagnosis.

To avoid conditions that might affect levels of urine neopterine, all individuals participating in the study underwent an interview including a detailed medical history, a physical examination and laboratory tests. Routine biochemical tests (e.g., liver and kidney function tests), a complete blood count (CBC), Antistreptolysin O (ASO), C-reactive protein (CRP), erythrocyte sedimentation rate, and urinalysis were conducted for every participant. Exclusion criteria were: any general medical condition that could affect psychiatric diagnosis, any acute or chronic disease, any recent anti-inflammatory or oral contraceptive medication use, substance use/abuse, pregnancy, mental/ intellectual problems (e.g., mental retardation, dementia, illiteracy) and any other limitations that could prevent accurate responses on the assessment scales.

The Kirikkale University, School of Medicine Ethics Committee approved the study protocol. This project was conducted in accord with the Helsinki Declaration. A written informed consent was obtained from each participant in the study.

Procedure

Participants completed a form consisting of questions about socio-demographic characteristics, drugs, and diseases that might affect neopterine. Diagnoses of major depressive disorder were determined using a semi-structured clinical interview (i.e., Structured Clinical Interview for DSM-IV Axis I Disorders-SCID-I) (First et al. 1995). Urine samples were obtained from all individuals who participated in the study to assess baseline levels of neopterine. At the same time a set of paper and pencil self-measurements including the Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI), the State and Trait Anxiety Inventory (STAI-ST) were administered to the participants. Urine samples were collected again from patients diagnosed with MDD who responded to paroxetine treatment by the fourth to the eighth week of the study (response was defined as at

least a 50 percent reduction in the Beck Depression Inventory scores). At that point, the BDI, BAI, and STAI-S/T were filled out a second time by the patients.

All patients were treated with paroxetine. The initial dose of paroxetine was adjusted to 20 mg/day. Every other week, the dose of paroxetine was increased by 10 mg/day until a therapeutic response was achieved (defined as at least a 50% reduction in the BDI score). Daily paroxetine doses were taken in the morning after breakfast. At the study baseline 26 patients with MDD were included. Sixteen patients who responded to treatment by the eighth week completed the study. Ten patients who did not respond to treatment during the study period were excluded from the study.

Measurement of neopterine

In our study, high pressure liquid chromatography (HPLC) was used to measure urine neopterine levels. Samples were stored, protected from light, up to 24 hours at 2-8º C and up to 6 months at -20º C. The normal range of urinary neopterine values in adults is 100-200 mmol/creatinine. Urinary neopterine levels can vary slightly depending on age and gender (Hausen et al 1982). For this study, urine samples were studied in the Biochemistry laboratory of Gülhane Military Medical Academy/Ankara.

Self-report measures

The Beck Depression Inventory (BDI) is a 21-item scale which measures emotional, somatic, cognitive and motivational symptoms related to depression and is based on clinical data obtained from observations. It was created by Beck (1961). The Beck depression inventory is used to measure severity and variations in the intensity of depressive symptoms. The Turkish validity and reliability of the scale was established by Hisli (1989).

The Beck Anxiety Inventory (BAI) measures the frequency of anxiety symptoms experienced by individuals. It is a self-rated Likert-type scale scored between 0-3 and consisting of 21 items. The total score refers to the rate of elevated anxiety experienced by an individual. The Inventory was developed by Beck et al (1988), and its reliability and validity in Turkey was established by Ulusoy et al. (1998).

The State-Trait Anxiety Inventory includes two different paper and pencil scales each including 20 questions. One of the sub-scales the Trait Anxiety Inventory (STAI-T) rates the feelings of individuals independent of circumstances and conditions. The other State Anxiety Inventory (STAI-S) measures an individual's anxiety level at the time it is evaluated. This scale was developed by Spielberger (Spielberg 1970). This test was translated to Turkish by Öner and A. Le Compte (1985).

Statistical Analyses

The data obtained were analyzed with SPSS 13.0 for Windows. Chi-square tests were used to compare the Socio-demographic data. Mann-Whitney U tests were used to compare the scale scores and neopterine values between the groups. A Wilcoxon test was used to compare pre and post treatment urine levels of neopterine. Statistical significance was set at $p<0.005$.

RESULTS

In the study, the 16 patients with major depressive disorder had a mean (± Standard Deviation) age of 37.5±10.5 years, while the average age of the 19 people in the healthy control group was 33.1±9.3 years. The sociodemographic characteristics of individuals participating in the study are shown in Table 1.

Table 1. Socio-demographic data of the patients with MDD and healthy controls

	MDD Group (Pre-Treatment)		Control Group	
	N	%	N	%
Gender				
Male	2	87.50	13	68.40
Female	14	12.50	6	31.60
Education				
Elementary school	9	56.25	1	5.26
Secondary school	2	12.50	2	10.52
High school	3	18.75	10	52.63
College +	2	12.50	6	31.57
Marital status				
Single	3	18.75	7	36.80
Married	13	81.25	12	63.20
Occupation status				
Officer	2	12.5	7	36.84
Worker	1	6.25	7	36.84
Un-stable	0	0.00	1	5.26
Unemployed	13	81.25	4	21.06

Table 2. Comparison of the BDI, BAI, STAI-S, STAI-T scores, and Neopterin levels between MDD patients (pre-treatment) and healthy controls

	MDD (pre-treatment), N=16 X±SD	Control, N=19 X±SD	U	P
BDI	24.50±12.58	3±2.70	17.00	0.000
BAI	26.43±11.11	4.94±4.14	2.50	0.000
STAI-S	47.43±12.69	31.36±5.37	33.00	0.000
STAI-T	57.56±7.77	38.84±6.09	8.50	0.000
Neopterin (µmol/creatine)	187.92±54.79	150.57±152.98	65.00	0.004

BDI - Beck Depression Inventory; BAI - Beck Anxiety Inventory; STAI-S/STAI-T - State-Trait Anxiety Inventory

Table 3. Comparison of the BDI, BAI, STAI-S, STAI-T scores, and Neopterin levels between MDD patients (post-treatment) and healthy controls

	MDD (pre-treatment), N=16 X±SD	Control, N=19 X±SD	U	P
BDI	11.87±10.91	3±2.70	63.00	0.003
BAI	17.31±9.28	4.94±4.14	30.50	0.000
STAI-S	37.62±11.09	31.36±5.37	98.50	0.075
STAI-T	45.75±11.79	38.84±6.09	109.00	0.154
Neopterin (µmol/creatine)	188.53±49.62	150.57±152.98	68.00	0.005

BDI - Beck Depression Inventory; BAI - Beck Anxiety Inventory; STAI-S/STAI-T - State-Trait Anxiety Inventory

Table 4. Alterations in the BDI, BAI, STAI-S, STAI-S, and STAI-T scores and Neopterin levels pre- to post-treatment

	Pre-Treatment Values (N=16) Mean±SD	Post-Treatment Values (N=16) Mean±SD	Z	P
BDI	24.50±12.58	11.87±10.91	-3.315	0.001
BAI	26.43±11.11	17.31±9.28	-2.330	0.020
STAI-S	47.43±12.69	37.62±11.09	-2.406	0.016
STAI-T	57.56±7.77	45.75±11.79	-3.440	0.001
Neopterin (µmol/creatine)	187.92±54.79	188.53±49.62	-0.780	0.938

BDI - Beck Depression Inventory; BAI - Beck Anxiety Inventory; STAI-S/STAI-T - State-Trait Anxiety Inventory

Comparison of the BDI, BAI, and STAI-S/T scores (pre-treatment scores for the patient group) for patients with MDD and healthy controls showed that the scores of the MDD patients were significantly higher than those of healthy controls (Table 2). The urinary neopterine levels of major depressive disorder patients before treatment (187.92±54.79 mmol/creatine) was significantly higher than those of the healthy control group (150.57±152.98 mmol/creatinine) (p=0.004) (Table 2). In addition, comparing patients with MDD and healthy controls in terms of their BDI, BAI, and STAI-S/T scores (this time using post treatment scores for the patient group) revealed that BDI and BAI scores were statistically significantly higher in the MDD group. But the groups' STAI-S and STAI-T scores were not significantly different (see Table 3). Post treatment urinary neopterine levels remained significantly higher in the MDD group in comparison to healthy controls (p=0.005) (188.53±4962 µmol/creatine, 150.57±152.98 µmol/creatine respectively).

BDI, BAI, and STAI-S/T scores all decreased significantly from pre to post treatment but urinary neopterine levels did not alter significantly in the same period (see Table 4).

DISCUSSION

The present study aimed to explore possible changes in urinary neopterine levels for patients with MDD related to response to paroxetine treatment, and to compare urinary neopterine levels between MDD patients and healthy controls. Results from the current study showed that despite the response to the paroxetine treatment, the patients' urine neopterin level, in comparison to those of healthy subjects has continued being higher. Paroxetine treatment has no significant effect on urinary neopterine levels between four to eight weeks period.

Blair et al. (1984) found decreased BH4 levels in postmortem brain tissue evaluations of four patients with a history of severe depression. Based on this observation they suggest an association between depressive disorders and low BH4 levels. In their study they emphasize that BH4 is responsible for the synthesis and release of many neurotransmitters and there is a relationship between mood disorders and pteridines (Hoekstra & Fekkes 2002). Recent experimental studies suggest BH4 may have an important role in the pathophysiology of depression (Miura et al. 2005). However, previous studies related to depressive disorders of neopterine and biopterin, which

have a close relationship with BH4, showed conflicting results. In many studies increased levels of urinary neopterine (Maes et al. 1994, Dunbar et al. 1992) and increased plasma levels of biopterin (Knapp & Irwin 1989, Hashimoto et al. 1990, Hashimoto et al. 1994) were demonstrated. But in one study, decreased levels of plasma biopterin were found (Hoekstra et al. 2001). O'Toole and colleagues (1998) did not find a significant difference between plasma neopterine levels in depressed individuals and a healthy control group (O'Toole et al. 1998). A recent study has reported a significant correlation between serum levels of neopterine and the number of depressive episodes (Celik et al. 2010). Another study by Krause et al found that women with postpartum depression had higher levels of prenatal blood neopterine levels in comparison to women without postpartum depressive symptoms (Krause et al. 2014). In our study we found that the urinary neopterine levels of patients with MDD were significantly higher than in healthy controls. This result is consistent with the vast majority of other studies.

Abou-Saleh et al. (1995) examined 48 patients with depressive disorders to determine if their urinary neopterine/biopterin ratios before and after treatment changed. Although the values were higher in the MDD group than in healthy controls before the treatment, there was no significant change in these values after placebo, antidepressant and electro convulsive therapy. In another study with 10 MDD patients, total biopterin levels during the depressed period were significantly higher than in healthy controls, and a decrease in neopterine levels was also detected after remission (Hashimoto et al. 1994). Anderson et al. found a significant reduction in elevated urinary neopterine/biopterin ratios after Electroconvulsive Therapy (ECT) (Anderson et al. 1992).

After surveying this literature, to the best of our knowledge there has been no study examining the effect of a single antidepressant medication on neopterine levels. In the current study we used paroxetine, an SSRI that is widely and successfully used in the treatment of MDD. After a response to paroxetine was achieved, we measured no significant decrease in urinary neopterine levels. Findings from the current study are also in accord with the study by Celik et al. (2010) in which they found that pretreatment neopterine levels were higher in MDD group compared to healthy subjects and neopterine level did not predict the response to sertraline (a selective serotonin reuptake inhibitor like paroxetine).

BH4 has an important role in the syntheses of monoamines, and urine neopterine levels reflect BH4 levels (Thony et al. 2000, Levine 1988). In addition, no previous study has examined neopterine levels after treatment with a specific SSRI in MDD patients with no prior psychotropic medication history. We believe these are the advantages of our study. Results from this study suggest that higher urinary neopterine levels in patients with MDD may be found concurrently with depression but these levels cannot be used as a marker of treatment response. A limitation of this study is that it does not provide insight into the relationship between higher levels of urinary neopterine and remission of MDD. Other limitations include the relatively small sample size, the exclusions of patients in remission and unresponsive patients, evaluation only of urinary levels of neopterine, and possible gender differences between the two groups. Finally, examination of neopterine levels of the control group was performed only once.

CONCLUSIONS

Notwithstanding certain limitations of this study, our findings suggest that despite treatment response, depression is related to higher levels of urine neopterine. Paroxetine treatment has no significant effect on urine levels of neopterine in MDD patients.

Acknowledgements: None.

Conflict of interest: None to declare.

References

1. *Abou-Saleh MT, Anderson DN, Collins J: The role of pterins in depression and the effects of antidepressive therapy. Biol Psychiatry 1995; 38:458–463.*
2. *Anderson DN, Abou-Saleh MT, Collins J: Pterin metabolism in depression: an extension of the amine hypothesis and possible marker of response to ECT. Psychol Med 1992; 22:863–869.*
3. *Barford PA, Blair JA, Eggar C, Hamon C, Morar C, Whitburn SB: Tetrahydrobiopterin metabolism in the temporal lobe of patients dying with senile dementia of Alzheimer type. J Neurol Neurosurg Psychiatry 1984; 47:736–738.*
4. *Beck AT, Epstein N, Brown G: An inventory for measuring clinical anxiety: Psychometric properties. J Consult Clin Psychol 1988; 56:893-897.*
5. *Beck AT: An inventory for measuring depression. Arch Gen Psychiatry 1961; 4:561-571.*
6. *Bell C, Abrams J, Nutt D: Tryptophan depletion and its implications for psychiatry. Br J Psychiatry 2001; 178:399-405.*
7. *Blair JA, Barford PA, Morar C: Tetrahydrobiopterin metabolism in depression. Lancet 1984; 2:163.*
8. *Celik C, Erdem M, Cayci T, Ozdemir B, Ozgur Akgul E, Kurt YG et al.: The association between serum levels of neopterine and number of depressive episodes of major depression. Prog Neuropsychopharmacol Biol Psychiatry 2010; 17:372-375.*
9. *Celik C, Erdem M, Özdemir B, Cayci T, Türker T, Özgen F: Treatment of major depression with sertraline: Relationship between serum neopterin levels and respond to the treatment. Bull Clin Psychopharmacol 2010; 20:134-139*
10. *Coppen A, Swade C, Jones SA, Armstrong RA, Blair JA, Leeming RJ. Depression and tetrahydrobiopterin: the folate connection. J Affect Disord 1989; 16:103-107.*
11. *Cryan JF, Leonard BE: Depression: from psychopathology to pharmacotherapy (Vol. 27). Galway/Cork: Karger Medical and Scientific Publishers, 2010.*
12. *Daito K, Suou T, Kawasaki H: Serum and urinary neopterine levels in patients with chronic active hepatitis B*

treated with interferon. Res Commun Chem Pathol Pharmacol 1994; 83:303–316.

13. *Duch DS, Woolf JH, Nichol CA, Davidson JR, Garbut JC: Urinary excretion of biopterin and neopterin in psychiatric disorders. Psychiatry Res 1984; 11:83–89.*
14. *Dunbar PR, Hill J, Neale TJ, Mellsop GW: Neopterin measurement provides evidence of altered cell-mediated immunity in patients with depression, but not with schizophrenia. Psychol Med 1992; 22:1051-1057.*
15. *First MB, Spitzer RL, Gibbon M, Williams JBW: Structured Clinical Interview for DSM-IV Axis-I Disorders Patient Edition (SCID-I/P, Version2.0). Biometrics Research Department, New York State Psychiatric Institute, New York, 1995.*
16. *Fuchs D, Spira TJ, Hausen A, Reibnegger G, Werner ER, Felmayer GW: Neopterin as a predictive marker for disease progression in human immunodeficiency virus type 1 infection. Clin Chem 1989; 35:1746–1749.*
17. *Fuchs D, Milstien S, Krämer A, Reibnegger G, Werner ER, Goedert JJ et al.: Urinary neopterin concentrations vs total neopterins for clinical utility. Clin Chem 1989; 35:2305-2307.*
18. *Hashimoto R, Mizutani M, Ohta T, Nakazawa K, Nagatsu T: Changes in plasma tetrahydrobiopterin levels of depressives in depressive and remission phases: reconfirmed by measurement with an internal standard. Neuropsychobiol 1994; 29:57-60.*
19. *Hashimoto R, Ozaki N, Ohta T, Kasahara Y, Kaneda N, Nagatsu T: The plasma tetrahydrobiopterin levels in patients with affective disorders. Biol Psychiatry 1990; 15:526-528.*
20. *Hashimoto R, Ozaki N, Ohta T, Kasahara Y, Kaneda N, Nagatsu T: Total biopterin levels of plasma in patients with depression. Neuropsychobiology 1987; 17:176-177.*
21. *Hausen A, Fuchs D, Konig K, Wachter H: Determination of neopterin in urine by reversed-phase high performance liquid chromatography. J Chromatogr 1982; 8:61-70.*
22. *Hisli N: Beck Depresyon Envanterinin üniversite öğrencileri için geçerliliği, güvenilirliği. Psikoloji Dergisi 1989; 7:3-13.*
23. *Hoekstra R, Fekkes D, van de Wetering BJ, Pepplinkhuizen L, Verhoeven WM: Effect of light therapy on biopterin, neopterin and tryptophan in patients with seasonal affective disorder. Psychiatry Res 2003; 30:37-42.*
24. *Hoekstra R, Fekkes D: Pteridines and affective disorders. Acta Neuropsychiatrica 2002; 14:120–126.*
25. *Hoekstra R, van den Broek WW, Fekkes D, Bruijn JA, Mulder PG, Pepplinkhuizen L: Effect of electroconvulsive therapy on biopterin and large neutral amino acids in severe, medication-resistant depression. Psychiatry Res 2001; 103:115-123.*
26. *Huang A, Fuchs D, Widner B, Glover C, Henderson DC, Allen-Mersh TG: Serum tryptophan decrease correlates with immune activation and impaired quality of life in colorectal cancer. Br J Cancer 2002; 11:1691-1696.*
27. *Knapp S, Irwin M: Plasma levels of tetrahydrobiopterin and folate in major depression. Biol Psychiatry 1989; 26:156-162.*
28. *Krause D, Jobst A, Kirchberg F, Kieper S, Hartl K, Kastner R et al.: Prenatal immunologic predictors of postpartum postpartum depressive symptoms: a prospective study for potential diagnostic markers. Eur Arch Psychiatry Clin Neurosci 2014; 264:615–624*
29. *Levine RA. Tetrahydrobiopterin and biogenic amine metabolism in neuropsychiatry, immunology, and aging. Ann NY Acad Sci 1988; 521:129–139.*
30. *Maes M, Scharpé S, Meltzer HY, Okayli G, Bosmans E, D'Hondt P et al.: Increased neopterine and interferon-gamma secretion and lower availability of L-tryptophan in major depression: further evidence for an immune response. Psychiatry Res 1994; 54:143-160.*
31. *Miura H, Qiao H, Kitagami T, Ohta T, Ozaki N: Fluvoxamine, a selective serotonin reuptake inhibitor, suppresses tetrahydrobiopterin levels and dopamine as well as serotonin turnover in the mesoprefrontal system of mice. Psychopharmacology (Berl) 2005; 177:307-314.*
32. *Murr C, Widner B, Sperner-Unterweger B, Ledochowski M, Schubert C, Fuchs D: Immune reaction links disease progression in cancer patients with depression. Med Hypotheses 2000; 55:137-140.*
33. *Öner N ve Le Compte A: Durumluk- Sürekli Kaygı Envanteri El Kitabı, İstanbul: Boğaziçi Üniversitesi Yayımları, 1985.*
34. *Müller N: Immunology of Major Depression. Neuroimmunomodulation 2014; 21:123–130.*
35. *Müller N: The role of anti-inflammatory treatment in psychiatric disorders. Psychiatr Danub 2013; 25:292-298.*
36. *O'Toole SM, Chiappelli F, Rubin RT: Plasma neopterin in major depression: relationship to basal and stimulated pituitary-adrenal cortical axis function. Psychiatry Res 1998; 2:21-29.*
37. *Owens MJ, Nemeroff CB: Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. Clin Chem 1994; 40:288-295.*
38. *Reibnegger G, Egg D, Fuchs D, Gunther R, Hausen, A, Werner ER: Urinary neopterine reflects clinical activity in patients with rheumatoid arthritis. Arthritis Rheum 1986; 29:1063–1070.*
39. *Ressler KJ, Nemeroff CB: Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress Anxiety 2000; 12:2-19.*
40. *Sluzewska A, Rybakowski J, Bosmans E, Sobieska M, Berghmans R, Maes M et al.: Indicators of immune activation in major depression. Psychiatry Res 1996; 64: 161-7.*
41. *Spielberg CD: Manual for state-trait anxiety inventory. Consulting Psychologists Press, California, 1970.*
42. *Thony B, Auerbach G, Blau N: Tetrahydrobiopterin biosynthesis, regeneration and functions. Biochem J 2000; 347:1–16.*
43. *Ulusoy M, Şahin NH, Erkmen H: Turkish version of the Beck Anxiety Inventory: Psychometric properties. J Cogn Psychother 1998; 12:163-172.*
44. *Werner ER, Bichler A, Daxenbichler G, Fuchs D, Fuith LC, Hausen A et al.: Determination of neopterin in serum and urine. Clinical Chem 1987; 33:62-66.*
45. *Widner B, Laich A, Sperner-Unterweger B, Ledochowski M, Fuchs D: Neopterin production, tryptophan degradation, and mental depression--what is the link? Brain Behav Immun 2002; 16:590-595.*

Correspondence:
Kadir Özdel, MD
Department of Psychiatry, Yildirim Beyazid Teaching and Research Hospital
06110 Ankara, Turkey
E-mail: kadirozdel@gmail.com