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# Platelet and Plasma Serotonin Levels and Platelet Monoamine Oxidase Activity in Patients with Major Depression: Effects of Sertraline Treatment

## [Major Depresyon Hastalarında Trombosit, Plazma Serotonin Düzeyleri ve Trombosit Monoamin Oksidaz Aktivitesi : Sertralin Tedavisinin Etkileri]

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**ABSTRACT**

**Objectives:** The purpose of this study was to investigate platelet and plasma serotonin levels and platelet monoamine oxidase activity in patients with major depression and the influence of sertraline treatment on these biochemical measures.

**Methods:** Twenty-one patients with major depression and 21 healthy controls matched for age, sex, and smoking status were recruited. Platelet and plasma serotonin levels and platelet monoamine oxidase activity were assessed after a one-week drug-free interval (baseline) and six weeks after the initiation of sertraline treatment.

**Results:** At baseline, the plasma serotonin levels were lower and platelet serotonin and monoamine oxidase levels were higher in the patient group compared to the controls. After six weeks of sertraline treatment, platelet serotonin and monoamine oxidase levels had decreased and plasma serotonin levels had increased, all approaching the levels in the controls.

**Conclusions:** Our results support some earlier findings indicating that major depressive patients have higher platelet serotonin levels and monoamine oxidase activity and lower plasma serotonin levels as compared with healthy subjects. Additionally, these abnormal parameters seem to normalize during sertraline treatment. However, in contrast to the results of some previous studies, our findings suggest that these biochemical parameters are not useful for predicting the clinical response rate or time (*i.e.* early and late responder) to a selective serotonin reuptake inhibitor, sertraline.

**Key Words:** Major depression, MAO, platelet, serotonin, sertraline

**ÖZET**

**Amaç:** Bu çalışmanın amacı; majör depresyon hastalarında plazma, trombosit serotonin düzeyleri ile trombosit monoamin oksidaz aktivitesini araştırmak ve sertralin tedavisinin bu biyokimyasal ölçütler üzerine olan etkisini saptamaktır.

**Yöntem:** Majör depresyonu olan 21 hasta ve yaş, cinsiyet özelliklerin bakımından eşleştirilmiş 21 sağlıklı kişi çalışmaya dahil edilmiştir. Trombosit ve plazma serotonin düzeyleri ve trombosit monoamin oksidaz aktivitesi bir haftalık ilaçsız dönem sonrasında ve sertralin tedavisine başlandıktan 6 hafta sonra değerlendirilmiştir.

**Bulgular:** Başlangıçta, kontrollerle kıyaslandığında, hasta grubunun plazma serotonin düzeyleri daha düşük, trombosit serotonin ve monoamin oksidaz düzeyleri daha yüksek olarak bulunmuştur. 6 haftalık sertralin tedavisi sonrasında trombosit serotonin ve monoamin oksidaz düzeyleri azalırken, plazma serotonin düzeyleri artmış ve kontrol grubunun düzeylerine yaklaşmıştır.

**Sonuçlar:** Bulgularımız depresyon hastalarında sağlıklı kontrollerle karşılaştırıldığında daha yüksek trombosit serotonin düzeyleri ve monoamin oksidaz aktivitesi ile düşük plazma serotonin düzeyleri bildiren diğer araştırma bulgularını destekler niteliktedir. Bununla birlikte, daha önceki bazı araştırma sonuçlarının aksine, bu biyokimyasal değişkenlerin bir seçici serotonin geri alımı inhibitörü olan sertralin ile yapılan tedaviye klinik yanıt oranını ve zamanını (erken ve geç cevap) kestirmede faydalı olmayacağı saptanmıştır.

**Anahtar Kelimeler**: Major depresyon, monoaminoksidaz, trombosit, sertralin

## Introduction

Several studies have suggested an important role for the serotonin (5-hydroxytryptamine, 5-HT) system in the pathophysiology of affective disorders (1). The serotonin parameters in platelets are frequently used as an indirect way to understand changes in the brain serotonin (2,3). The reuptake, storage, and release of platelet serotonin have important similarities with the same processes in serotonergic neurons in the brain (4). Some molecular genetic data also display structural similarities between the components of neuronal and platelet serotonergic systems (5-8). In light of these findings, platelet 5-HT reuptake regions, 5-HT2 receptors, serotonin and monoamine oxidase (MAO) levels are supposed to be peripheral models that provide knowledge about central serotonin activity.

The results of studies on the levels of plasma 5-HT, platelet 5-HT, and MAO in patients with depression and the influence of SSRIs on these parameters are contradictory (9-25). The aim of the present study was to measure the levels of platelet and plasma 5-HT and platelet MAO in a group of patients with major depression, and to examine the effects of a selective serotonin reuptake inhibitor, sertraline hydrochloride [(1S)-cis-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine)] on these parameters. We also aimed to determine whether the response rate or time (early or late response) to sertraline treatment can be predicted by the baseline levels of these biochemical measures or changes in their levels during the treatment.

## Materials and Methods

### *Patient and control population*

The patient group was recruited in the Outpatient Clinic of the Department of Psychiatry in Hacettepe University. Subjects diagnosed with major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and whose treating psychiatrist decided to initiate sertraline treatment were evaluated for participation in the study. While the patients with HAMD scores higher than 17 were considered eligible, those with a history of alcohol or substance abuse, or another psychiatric diagnosis, or a neurological or medical disease that might affect these biochemical parameters, and those using another psychiatric medication were excluded. As a result, 21 patients were included in the study.

Twenty-one healthy controls matched for age, sex, and smoking status were recruited for the study via local advertisements. Subjects who had a psychiatric, neurologic, or chronic medical disease and those who were taking medication for any reason were excluded. The study was approved by the Ethics Committee of the University. All participants were informed about the study and gave consent to participate in it.

Both patient and control groups included 15 female and 6 male subjects. The mean (±SD) age of the patient group was 32.48±10.66 and of the control group was 32.24±10.34, and the difference between the groups was not statistically significant. The number of smokers was the same in the two groups (7/21, 33.3 %).

### *Study design*

Sertraline treatment 50 mg/day was initiated for depressive patients after a one-week drug-free interval. The sertraline dose was increased to 100 mg/day at the 4th week assessment according to the decision of the clinician. After the initial psychiatric interview to confirm the presence of major depression diagnosis, patients were evaluated with SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders). The severity of depressive symptoms of patients was evaluated with HAMD every two weeks during the six-week follow-up period.

In the patient group, plasma 5-HT, platelet 5-HT, and MAO levels were determined at baseline before sertraline was initiated, and after 6 weeks of sertraline treatment. Biochemical parameters were also evaluated in the healthy control group.

### *Assessment instruments*

***Hamilton Depression Rating Scale (HAMD):*** This is a standard scale developed to evaluate the severity of depressive symptoms in patients diagnosed with major depression (26). In our study, the 17-question form of the scale was used. The Turkish version of the scale was shown to be valid and reliable in the assessment of clinical depression (27).

***Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I):*** This is a semistructured interview that provides information for the diagnosis of major DSM-IV Axis 1 psychiatric disorders (28,29). SCID-I was translated into Turkish and its reliability and validity were confirmed (30).

### *Reagents and equipment*

All chemicals were obtained from Sigma Chemical Co. (Germany). Spectrophotometric measurements were obtained using a Shimadzu UV 1700 PC spectrophotometer and HPLC measurements using the HPLC system of Dionex, USA.

### *Determination of plasma and platelet MAO activity*

Platelet MAO-B activity was measured in platelet rich plasma (PRP) samples as described by Holt (31). A chromogenic solution, consisting of 1 mM vanillic acid, 500 µM 4-aminoantipyrine, and 4 $U.ml^{-1}$ peroxidase in 0.2 M potassium phosphate buffer, pH 7.6, was prepared daily. The assay mixture contained 167 µl of chromogenic solution, 667 µl of 500 µM benzylamine, and 133 µl of KP buffer, pH 7.6. The mixture was preincubated at 37 °C for 10 min before the addition of the sample

containing enzyme. The reaction was initiated by the addition of the sample (plasma or PRP, 100 µl) and absorbance increase was monitored at 498 nm at 37 °C for 60 min. Molar absorption coefficient of 4654 $M^{-1}.cm^{-1}$ was used to calculate the initial velocity of the reaction. The results were expressed as nmol/$10^9$ platelets.

### *Determination of plasma and platelet 5-HT levels*

Blood samples were drawn by venipuncture after an overnight fast into tubes containing EDTA as anticoagulant. Then 10 ml of blood was divided into two portions. One portion was centrifuged for 5 min at 1000 x g and the supernatant was kept as plasma. The next portion was centrifuged for 5 min at 10,000 x g and 4 °C, to obtain PRP. Platelet counts were determined on aliquots of pooled PRP diluted in Isotone II and counted twice on a thrombocounter (Coulter Electronics, STKS). After the platelet count, 2 ml of PRP was centrifuged for 10 min at 2000 x g. The supernatant was discarded and the pellet was suspended in 1 ml of a mixture containing 4 % perchloric acid and 0.15 % EDTA. The mixture was centrifuged for 10 min at 2000 x g and 4 °C. The resulting supernatant was filtered through 0.45 µm Millipore filters by centrifugation for 5 min at 2000 x g (Sigma, microcentrifuge filter Ultrafree-CL, Durapore PVDF membrane) and 4 °C. The eluate was divided into two portions: one portion was used for the determination of platelet MAO activity while the rest was used for the determination of platelet 5-HT level. The samples were kept frozen at -80 °C until used. The portions kept for 5-HT determination in plasma and PRP were thawed and centrifuged for 3 min at 2000 x g. Plasma and platelet 5-HT contents were measured as described previously (31). An aliquot of the supernatants was applied to the HPLC system equipped with a 5 µm C18 column. The elution buffer consisted of 50 mM potassium phosphate, pH 5.0 and 12 % methanol, with flow rate of 1 $ml.min^{-1}$ under isocratic conditions. The fluorescence detector was set at 230 nm excitation and 338 nm emission. Plasma and platelet 5-HT contents were expressed as $nmol.l^{-1}$ and nmol.$10^9$ platelets, respectively.

### *Clinical chemistry*

Biochemical parameters were measured in the plasma samples of the subjects in an autoanalyzer (Roche Modular System) and the hematological parameters were determined using an electronic cell counter (Coulter STKS).

### *Statistical analysis*

Results were defined as mean values and standard deviations (mean ± SD). *Independent samples t test* and *paired samples t test* were used for testing the statistical significance of differences between the means of groups, and between the first and last values within the group, respectively. Changes in the severity of depressive symptoms over six weeks were tested with repeated measures *ANOVA*. The relationship between the biochemical parameters and improvement in clinical parameters in the course of treatment was assessed using *Pearson correlation analysis*. After the patients were grouped as treatment responders and nonresponders, the predictive value of baseline biochemical parameters in these groups was investigated with *logistic regression analysis*. Level of significance was set as $P < 0.05$ for all of the statistical analyses.

## RESULTS

### *Demographic and clinical characteristics of the patient group*

All the patients completed the study. The mean number of depressive episodes was 0.71±0.9 (range: 0-3) in the patient group. While 11 subjects in the patient group (52.4 %) were experiencing their first depressive episode, 10 (48.6 %) had had one or more depressive episodes in the past.

The course of the change in HAMD scores of patients is shown in Table 1. According to the repeated measures ANOVA analysis, there was a significant decrease in depression scores after the 2nd week compared to the initial interview ($p < 0.001$). When a 50% or greater decrease in HAMD scores compared to initial scores was regarded as a positive response and HAMD scores ≤ 7 as remission criteria, 15 (71.4 %) of the patients had a positive response to treatment and 12 (57.1 %) were in remission at the end of the study (Table 1). Early response was defined as ≥ 50 % decrease in HAMD scores before the end of the 2nd week. Accordingly, 6 patients (28.5 %) showed an early response to sertraline treatment in this study.

### *Comparison of biochemical parameters between patient and control groups*

The values of biochemical parameters of the patient and control groups are shown in Table 2. The initial plasma serotonin levels of patients were significantly lower than those of the controls, while platelet 5-HT and MAO levels were significantly higher in patients.

### *Comparison of biochemical and clinical parameters at baseline and after six weeks of sertraline treatment in the patient group*

Despite a significant decrease in platelet 5-HT levels and MAO activity with treatment, a significant increase was observed in plasma serotonin levels. Collectively the values of the biochemical parameters approached those of the controls in response to treatment. When the 6th week biochemical values of the patient group were compared to control values, no significant difference was found between the groups.

### *The relationship between changes in biochemical parameters and improvements in symptoms*

Pearson correlation analysis did not show any significant

**Table 1.** The progress of clinical symptoms during follow-up: HAMD scores, response and remission rates of patients for each interview. For 2nd, 3rd and 4th interviews, the response and remission rates were computed on the basis of change of the HAMD scores as compared with the values of the first interview. There was a significant decrease in depression scores after the second week compared to the initial interview ($p < 0.001$).

| | HAMD | RESPONSE(%) | REMISSION (%) |
|---|---|---|---|
| 1st INTERVIEW (Initial) | 24.71±5.58 | 0 (0 %) | 0 (0 %) |
| 2nd INTERVIEW (2nd week) | 15.57±8.77 | 6 (28.5 %) | 3 (14.2 %) |
| 3rd INTERVIEW (4th week) | 10.67±8.92 | 12 (57.1 %) | 9 (42.8 %) |
| 4th INTERVIEW (6th week) | 9.29±8.67 | 15 (71.4 %) | 12 (57.1 %) |

HAMD:Hamilton Depression Rating Scale

**Table 2.** Results of biochemical parameters in patient and control groups (mean ± SD). Independent samples t test and paired samples t test were used for between groups and within group comparisons. The initial plasma serotonin levels were lower, while platelet 5-HT and MAO levels were higher in patients as compared to the control group. A significant decrease in platelet 5-HT levels and MAO activity and an increase in plasma serotonin levels were observed with treatment.

| | Patients Pre-treatment (N=21) | Patients After treatment (6th week) (N=21) | Controls (N=21) | Pre vs. After treatment | Patients (Pre-treatment) vs. Controls |
|---|---|---|---|---|---|
| Plasma serotonin (nmol/L) | 5.19±0.43 | 5.96±0.14 | 5.89±0.31 | t=10.70, df=20* | t=5.98, df=40* |
| Platelet serotonin (nmol/$10^9$ pl.) | 13.52±1.32 | 10.17±0.63 | 9.90±0.52 | t=16.44, df=20* | t=11.61, df=40* |
| Platelet MAO (nmol/$10^9$ pl) | 32.74±1.75 | 29.85±1.13 | 29.60±2.48 | t=8.59, df=20* | t=4.73, df=40* |

MAO: Monoamine oxidase
*P < 0.001

relationship between parameters reflecting improvements in clinical symptoms and changes in biochemical measures. These values were not presented on the tables.

Logistic regression analysis was performed to assess the predictive value of biochemical parameters on the patients' being responders or nonresponders after six weeks of sertraline treatment. Neither initial biochemical measures nor the changes in these parameters during the study were useful for predicting the response rate or time (*i.e.* early and late responder) to sertraline treatment.

## Discussion

In this study, plasma 5-HT levels were lower and platelet 5-HT and MAO levels higher in depression patients compared to normal controls. After six weeks of sertraline treatment, platelet 5-HT and MAO decreased while plasma 5-HT levels increased, all approaching the values in control subjects.

Our finding of higher pretreatment platelet serotonin levels compared to normal controls contradicts the previous data, which suggested lower platelet 5-HT concentrations (9,32,33) or no statistically significant difference (4,10) in depressed patients compared to normal controls. On the other hand, platelet serotonin concentrations were reported to be significantly elevated in patients with bipolar or psychotic depressive disorder, in accordance with our results (1,11,12).

Higher platelet MAO activity in drug-free depression patients compared to controls is in line with the findings of some previous studies (14,15), but contradicts another study indicating no difference between the two groups (13). The decrease in platelet MAO activity after six weeks of sertraline treatment may result from the probable direct effect of sertraline on the expression of MAO (34). Pivac et al. (21) also reported a decrease in platelet MAO after 24 weeks of sertraline treatment, although this result was not repeated with paroxetine, tianeptine, or some other antidepressants (18,35). The significance of the change in MAO activity is not clear yet, and this investigation should be repeated in a larger group of patients.

The data regarding the influence of antidepressants on plasma and platelet serotonin parameters are also contradictory. Spreux-Varoquaux et al. (22) reported an initial increase in plasma 5-HT after treating drug-free depression patients with clomipramine. Alvarez et al. (23) reported lower platelet 5-HT levels in drug-free depressed patients compared to healthy controls and found that treatment with clomipramine and paroxetine decreased their levels further. Narayan et al. (20) found that patients with depression treated with selective serotonin reuptake inhibitors (SSRIs) had lower platelet 5-HT levels after treatment compared with the pretreatment results. Our results in this study are in accordance with the study by Blardi et al. (24), in which higher platelet serotonin levels and lower plasma 5-HT levels in depressive patients versus controls before fluoxetine treatment decreased and increased, respectively, after fluoxetine treatment. In other words, fluoxetine treatment had a normalizing effect on these parameters in depressed patients. Similar to fluoxetine, citalopram was also found to have an opposite effect on plasma and platelet 5-HT levels, which resulted in lower platelet and higher plasma 5-HT concentrations (25). Paroxetine was also shown to decrease the 5-HT levels in patients with major depression (36). Mück-Seler et al. (18) reported significant decreases in platelet 5-HT levels after paroxetine medication in a study that compared the blood parameters before and after treatment. In another study (21) platelet 5-HT levels in drug-free patients with major depression were lower compared to those in normal controls, and decreased further after sertraline treatment.

Our secondary objective was to determine whether basal measurements of these biochemical parameters could be used to predict the response to sertraline. Although in some studies high pretreatment platelet 5-HT levels were found to be predictive of the both good and poor treatment response of depression patients (16-19), our results are in agreement with studies that suggest no significant importance of these parameters in the prediction of treatment response (20,21). According to our findings, none of these biochemical parameters was useful for estimating the treatment response or determining early and late responders.

Platelet 5-HT levels are the result of the dynamic equilibrium between platelet and plasma 5-HT, and are controlled directly by the platelet 5-HT reuptake mechanisms (37). In contrast to the neurons, platelets do not synthesize 5-HT and their 5-HT content is related to the amount taken from plasma by the transporter mediated mechanism (38). As the primary target of serotonin reuptake inhibitors is the serotonin transporters, our results indicating a decreased platelet 5-HT and an increased plasma 5-HT in depression patients could be attributed to the inhibitory effect of sertraline on transporters, which are localized on the platelet membrane (24).

SSRIs not only affect the levels of 5-HT in platelets and plasma, but also lead to changes in the levels of SERT (serotonin transporter), which might be related to the polymorphism of 5-HTTLPR (39) SSRIs have an acute effect through inhibiting SERT on cell membrane but it is still questionable what kinds of changes occur in the expression of SERT for the chronic therapeutic effects of SSRIs. The results of studies about the effect of antidepressant treatments on SERT expression vary (40). Benmansour et al (41,42) reported that brain SERT was downregulated by chronic administration of SSRIs but decreases in SERT binding densities were not caused by decreased SERT gene expression. Furthermore, fluoxetine was found to reduce the availability of the transporter in the membrane, although levels of total human SERT protein content or human SERT mRNA level did not change significantly (43). In the same study, this effect of fluoxetine on human SERT was suggested to be posttranslational.

Neuroimaging studies about SERT levels in different regions of the brain in drug-free subjects with major depression are rare and contradictory (44). The low serotonin levels in the synaptic cleft may be related to increased levels or activity of SERT in some brain areas, which might be genetically determined (44). On the other hand, the findings about decreased levels of SERT in depressed patients in some studies might be explained as a sign of loss of serotonergic neurons or may be a compensatory down regulation of transporters (44). This down regulation of SERT might be secondary to increased intracellular 5-HT levels.

The discrepancy in the results of studies investigating the baseline serotonin parameters and the effects of antidepressants on them may result from the heterogeneity of the etiology of depression. Other neurotransmitters aside from serotonin also play a role in the neuropathogenesis of depression, and the changes in serotonergic system parameters may vary according to the predominant underlying pathophysiology.

In summary, this study suggests that lower plasma and higher platelet 5-HT levels and higher platelet MAO activity in drug-free depression patients normalize (approach the values in normal controls) during the course of sertraline treatment. On the other hand, biochemical parameters are not predictive of response rate or response time to sertraline. The peripheral serotonergic markers are still attractive targets to investigate, as they may increase our understanding of the mechanism of action of antidepressants.

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