Plasma Indolamine 2,3 Dioxygenase and Serum Neopterin Levels in Patients with First Episode Major Depressive Disorder and Recurrent Major Depressive Disorder

Emin Ozgur Akgul1, Murat Erdem2, Adem Balikci3, Emre Aydemir3, Gazi Unlu4, Tevfik Honca5, Abdullah Bolu6, Mehtap Honca7, Tuncer Cayci1

ABSTRACT:
Plasma Indolamine 2,3 dioxygenase and serum neopterin levels in patients with first episode major depressive disorder and recurrent major depressive disorder

Objective: The aims of this study were to determine whether the plasma Indolamine 2,3 dioxygenase and neopterin levels in patients with major depression differ from a healthy control group and to investigate the relationship between previous major depression episodes and plasma indolamine 2,3 dioxygenase and serum neopterin levels.

Methods: Thirty-eight first episode major depression patients, sixty-four recurrent major depression patients and forty-one healthy control participant included the study. Plasma indolamine 2,3 dioxygenase and serum neopterin levels compared in these three groups.

Results: Plasma indolamine 2,3 dioxygenase and serum neopterin levels in recurrent major depression group were statistically higher than first episode major depression and healthy control group. There was a positive correlation between plasma IDO levels and number of depressive episodes in major depression group (rho=0.36, p<0.001).

Conclusion: According to these findings previous major depression episodes can promote response of the immune system associated with proinflammatuar cytokine activity. This sensitizing effect of previous depressive episodes may increase the recurrence risk of depression.

Keywords: major depressive disorder, indolamine 2,3 dioxygenase, neopterin

INTRODUCTION
Neuroimmune factors play an important role in etiopathogenesis of depression. In mammals, indoleamine 2,3-dioxygenase (IDO) is a heme-containing rate-limiting enzyme that catalysis the initial step in the major metabolic pathway of tryptophan (Trp). The activity of IDO plays a role in the cytokine cascade. IDO activity increases in existence of inflammatory activation. Proinflammatory cytokines such as Interferon γ, Interleukin 1β and tumor necrosis factor-α (TNFα) rise during inflammatory activation1-2. IDO is expressed in fibroblasts, macrophages, dendritic cells, trophoblasts, and epithelial cells3. Increased IDO activity reduces the serotonin levels and also increases tryptophan catabolits (TRYCATs) such as kynurenine, quinolinic acid which contribute to neurotoxicity and nociception via the interaction with glutamate receptors4. Kynurenine may induce
Plasma Indolamine 2,3 dioxygenase and serum neopterin levels in patients with first episode major depressive disorder and recurrent major...

depressive and anxiety symptoms and has additional excitotoxic and neurotoxic effects\textsuperscript{5,6}. IDO appears to be a biological mediator of inflammation related depressive disorders\textsuperscript{1,7,8}. There was a positive correlation between IDO activity and depression severity in many studies\textsuperscript{9-13}. O’connor et al. showed that direct inhibition of IDO prevented depressive symptoms without affecting cytokines\textsuperscript{7}. Prolinflammatory cytokines also cause to increased serum neopterin levels. Neopterin is one of the important indicators of the cellular immune response which is synthesized from guanosine triphosphate in macrophages and monocytes, when guanosine triphosphate chlohydrolase I is activated by IFN-gamma and other proinflammatory cytokines\textsuperscript{14,15}. Several studies have found high serum neopterin levels in MDD patients compared to controls\textsuperscript{16-19}.

There were a few studies about the biological differences between the first episode and recurrent major depression. A recent electrophysiological study demonstrated that the recurrence of depressive episodes can lead to the impaired pre-attentive information processing, causing an impairment of the subsequent orienting process as the neurophysiological transmission travels from mismatch negativity (MMN) to $P_3a$\textsuperscript{20}. Many biochemical studies indicated that previous depressive episodes may increase cellular immunity\textsuperscript{18,19} and acute phase response\textsuperscript{21}. Yang et al. found that Serum S-100 B levels is higher in recurrent MDD group than first episode MDD and healthy control group\textsuperscript{22}. The effect of previous depressive episodes on IDO activity was not evaluated. The aims of this study were to determine whether the plasma IDO and neopterin levels in patients with MDD differ from a healthy control group and to examine the relationship between previous MDD episodes and plasma IDO and serum neopterin levels.

**MATERIALS AND METHODS**

One hundred forty five patients with Major Depressive Disorder according to DSM-IV who gave written informed consents to be enrolled in the study at the Gulhane Military Medical Academy Psychiatry Clinic were included in the study. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was performed by two psychiatrists. Thirty eight patients had experienced only one MD episode, while sixty four patients had two or more MDD episodes in the study group. Twenty three patients with psychotic, atypical, catatonic features, and with postpartum depression and thirteen patients with a history of psychotropic drug or alcohol/ substance use within the last 6 weeks were excluded from the study. Other exclusion criteria were any additional axis I DSM-IV diagnosis, current pregnancy, acute (within the past month) or chronic infections, autoimmune, allergic, neoplastic, or endocrine diseases (thyroid and other endocrine dysfunctions) and other acute physical disorders, including surgery or myocardial or cerebral infarction within the past 3 months. Individuals exposed to any drug including nonsteroidal antiinflammatory drugs and oral contraceptives in the past 6 weeks were also excluded from the study.

The healthy controls have been recruited from the employees of the medical academy. Healthy control group was consisted of forty one participants without any life time psychiatric diagnosis and any life time psychiatric treatment.

Sociodemographic (age, gender, level of education, and marital status) and clinical features of the subjects were assessed using the data query form. Diagnosis of Major Depressive Episode was made with the SCID-I. The SCID-I is a semi-structured interview guide developed by First et al. for the diagnosis of DSM-IV Axis I disorders\textsuperscript{23}. The validity and reliability studies of Turkish version were conducted by Ozkurkcugil et al.\textsuperscript{24}. Depression severity was evaluated with the 17-item Hamilton Depression Rating Scale (HDRS). The validity and reliability studies of Turkish version were conducted by Akdemir et al.\textsuperscript{25}.

Complete blood count, routine biochemistry, and the detection of plasma IDO and serum neopterin levels of the patients and the healthy control group were analyzed at the laboratory of the Gulhane Military Medical Academy

Department of Medical Biochemistry. From fasting subjects (overnight for 12 h) venous blood were drawn into plain tubes with no additives in the morning between 8:00 and 11:00 a.m. All samples were protected from the sun light. We centrifuged the tubes 10 minutes, at 2000 g, 4°C for obtaining serum samples. The serum samples were stored at -80°C until the analyses are performed. Plasma IDO level was assayed by the ELISA method and serum neopterin levels were assayed by High Pressure Liquid Chromatography (Agilent Technologies 1200 Series System, Santa Clara, CA, USA), with a fluorescent detector (Ex: 353 nm; Em: 438 nm) as reported by Alrashed et al.26. The neopterin results were given as nmol/L. The study was approved by the local Research Ethics Committee. The patients and healthy controls provided written informed consents. The funding of this study was provided by an internal grant at the Gulhane Military Medical Academy.

Statistical Analysis

The continuous variables were presented as the median (min-max) and mean±standard deviation (SD). The qualitative variables were presented as number and percent. For comparison of qualitative data between MDD patients and healthy control group Chi-Square test was used. If the parametric conditions were not met, the Mann–Whitney U test was used for the comparison of two group means. The Kruskal–Wallis test was used for the comparison of more than two groups. The correlation coefficients and their significance were calculated using the Spearman’s rank-order correlation test. The rate was set to \( \alpha = 0.05 \) and \( p \)-values equal to or lower than this value were considered as statistically significant.

RESULTS

In MDD group, 38 patients (37.3%) had experienced the 1st episode of MDD, 30 patients (29.4%) had second episode, 34 patients (33.3%) had third or more episode of MDD.

The comparison of Hamilton Depression Rating Scale and healthy control group according to sociodemographic features, plasma IDO, and neopterin levels are shown in Table 1.

Serum neopterin levels were statistically higher in MD group than healthy control groups. Plasma IDO level, age, and gender ratio were not different in MD group and healthy control group. The education levels were statistically higher in healthy control group than major depression group.

![Figure 1: Plasma IDO levels in first episode, recurrent major depression, and healthy groups.](image-url)

Table 1: The comparison of sociodemographic features, plasma IDO, and neopterin level of MD and healthy control groups.

<table>
<thead>
<tr>
<th></th>
<th>Major Depression (n=102)</th>
<th>Healthy Control (n=41)</th>
<th>z/χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neopterin (nmol/L)</td>
<td>6.53 (2.3-25.8)</td>
<td>7.10±3.79</td>
<td>2.9 (1.8-8.7)</td>
<td>3.22±1.28</td>
</tr>
<tr>
<td>IDO (nmol/L)</td>
<td>8.86 (1.23-54.66)</td>
<td>15.98±14.56</td>
<td>8.96 (1.09-24.57)</td>
<td>10.48±7.06</td>
</tr>
<tr>
<td>Age (year)</td>
<td>34.00 (20-63)</td>
<td>36.53±11.82</td>
<td>32.00 (20-48)</td>
<td>32.27±7.40</td>
</tr>
<tr>
<td>Education level (year)</td>
<td>11.00 (5-16)</td>
<td>9.76±3.63</td>
<td>13.00 (5-15)</td>
<td>11.81±3.50</td>
</tr>
<tr>
<td>Gender (male)(n,%)</td>
<td>62 (60.78)</td>
<td>27 (65.85)</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>HDRS score</td>
<td>22.00 (12-35)</td>
<td>21.94±5.30</td>
<td>.</td>
<td></td>
</tr>
</tbody>
</table>

z: Mann-Whitney U test value, χ²: Chi-Square test value, HDRS: Hamilton Depression Rating Scale.
The comparison of plasma IDO and serum neopterin levels between first episode, recurrent depression, and healthy control groups are shown in Figure 1 and Figure 2.

Plasma IDO levels in recurrent MDD group (median=18.77 nmol/L) were statistically higher than other two groups. Plasma IDO levels were not different in first episode major depression group (median=5.33 nmol/L) and healthy control group (median=8.96 nmol/L).

Serum neopterin levels were the highest in recurrent MDD group (median=6.76 nmol/L). Serum neopterin levels in first episode MDD group (median=5.65 nmol/L) were statistically higher than healthy control group (median=2.90 nmol/L).

In MDD group, the correlation between plasma IDO, serum neopterin levels and number of depressive episode is shown at Table 2.

There was a positive correlation between plasma IDO levels and number of depressive episodes in MD group (rho=0.36, p<0.001). There was positive but weak correlation between serum neopterin levels and number of depression episode in MD group (rho=0.23, p=0.021). There were no statistically significant correlations between HDRS score and number of depression episodes in MD group (rho=0.12, p=0.25).

There were no statistically significant correlations between HDRS score and plasma IDO level (rho=-0.14, p=0.15), serum neopterin level, (rho=-0.06, p=0.55) in MDD group. There were no statistically significant correlations between plasma IDO and serum neopterin levels in MDD group (rho=0.03, p=0.76).

**DISCUSSION**

In this study, we examined plasma IDO and serum neopterin levels in patients with MDD and healthy control group. We tested whether the number of previous depressive episodes have an effect on these markers.

We found no statistically significant between whole MDD and healthy control group in terms of plasma IDO levels. But serum neopterin levels of MDD group were statistically higher than healthy control group. Plasma IDO and serum neopterin levels of recurrent MDD patients were statistically higher than first episode MDD patients and healthy control group. There was a positive correlation both plasma IDO and serum neopterin levels and number of depression episodes in MDD group.

IDO activity (Serum Kynurenine/Tryptophan) was higher in MD patients 11-13 and MDD patients with suicide attempt27 than healthy controls. Gabbay et al. found that IDO activity was higher in melancholic MDD patients than non melancholic MDD and healthy control28. Moreover depressive symptoms were found to be associated with increased IDO activity in patients with coronary atherosclerosis29,30. Gabbay et. al found that IDO activity was positive correlated with anhedon severity in adolescent31. In contrast to these studies

| Table 2: The correlation between number of depressive episode and plasma IDO, serum neopterin levels, HAM-D scores in MD group. |
|-----------------|-----------------|-----------------|-----------------|
| Plasma IDO levels (nmol/L) | Serum Neopterin levels (nmol/L) | HDRS scores |
| Depressive Episode Number | rho=0.36, p<0.001 | rho=0.23, p=0.021 | rho=0.12, p=0.25 |
Quak et al. found that IDO activity was not different in MDD patients than healthy controls in a large sample study32. In Quak’s study, medicating and unmedicating MDD patients were not evaluated and also the previous MDD episodes. For all MDD patients our findings about plasma IDO levels were similar with Quak’s study. Elovanio et al. found no relationship between IDO activity and depressive symptoms in men. They showed that IDO activity predicted depressive symptoms in women only33.

Celik et al. found that the serum neopterin levels in major depression group are higher than the serum neopterin levels of the control groups34. In this present study, serum neopterin level was statistically higher in recurrent MDD patients than first episode MDD patients and healthy control groups as correlated with the previous studies35,36. This finding indicate that previous depressive episodes may cause sensitivity in the cellular immune system. Conversely, Tiemeier et al. did not find any correlations between the neopterin levels of patients with depressive disorder35. However, this study group was heterogeneous consisting of major depression, minor depression, and dysthnia.

The findings of this study indicated that plasma IDO level was statistically higher in second or more depressive episode but not first in MDD episode. Conversely serum neopterin levels was statistically higher in first and subsequent MD episodes. Additionally depressive episode numbers were found positively correlated with plasma IDO and serum neopterin levels in MDD group. According to these findings previous MDD episodes can promote response of the immune system associated with proinflammatory cytokine activity. This sensitizing effect of previous depressive episodes may increase the recurrence risk of depression. The recurrence of major depression may be mediated by immune system.

There are few limitations in this study. Proinflammatory cytokines levels were not determined. Also suicidality and stressor life events before index depressive episode were not evaluated.

**Acknowledgement:** This study is supported by Gulhane Military Medical Academy Scientific Research Board (AR-2011/51)

**References:**


6. Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new ‘5-HT’ hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Prog Neuropsychopharmacol Biol Psychiatry 2011;35(3):702-21. [CrossRef]


