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High PLC-C level in major depressive disorder and its relationship with disease severity: a different perspective on coagulation in major depressive disorder

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Abstract

Introduction: Large platelets are an important risk factor for the development of thrombosis. In this study, we aimed to measure the presence of large cell platelets and its relationship with disease severity in major depressive disorder (MDD).

Material and methods: In this study, platelet volume indices were analyzed from the complete blood count (CBC) results of 103 cases (51 MDD and 52 controls) analyzed retrospectively. For the experimental group of MDD patients, the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) were applied and compared to platelet parameters.

Results: The study found that platelet large cell ratio (PLC-R) and platelet large cell count (PLC-C) values were higher in the MDD group compared to healthy controls. ROC analysis showed that PLC-C > 91.24 had 70.6% sensitivity and 80.8% specificity for MDD. Pearson correlation analysis showed that PLC-C values and HAM-D scores correlated positively in MDD patients.

Conclusions: A simple CBC analysis detects PLC-R and PLC-C. Indices that give the ratio (PLC-R) and number (PLC-C) of larger and more active platelets in terms of coagulation should be emphasized. Our study found higher PLC-R and PLC-C values in patients with MDD compared to the control group, and increased PLC-C values with increased severity of depression. Thus PLC-C may be a useful marker for the increased coagulation activity observed in MDD patients and MDD patients with high PLC-R and PLC-C values may benefit from preventive antithrombotic therapy.

Key words: major depressive disorder, coagulation, PLC-C, PLC-R.

Introduction

Major depressive disorder (MDD) is the most common mood disorder of psychiatry and significantly impacts quality of life (Aydemir *et al*. 2009). It is observed as a single episode or recurrent episodes. Acute depressive episodes may progress well in many MDD patients, but for one in three patients recurrences continue throughout life and residual symptoms may appear in the period between episodes (Çelik and Hocaoğlu 2016). The diagnosis of MDD requires symptoms that include depressed mood and psychophysiological changes such as slowness in speech and action; sleep, appetite or sexual desire disorders; anhedonia; and suicidal thoughts. To confirm the diagnosis, these changes should persist at least 2 weeks and significantly impair work and family relationships (Belmaker and Agam 2008).

An important cause of morbidity and poor quality of life, depression is an independent risk factor for major cardiovascular events (Amadio *et al*. 2020) and is more prevalent in those with cardiovascular disease (CVD). The incidence of depression in patients with coronary heart disease is 16-23%. Depressed patients have a much higher risk of developing cardiovascular complications compared to nondepressed ones. Depression is a poor prognostic factor for patients who have had a heart attack (Kostanjsak and

Zdunic 2017). There is an increased prevalence of depression in those with cardiovascular disease (CVD). A causal relationship is likely, such as CVD causing more depression or depression causing more CVD (Hare *et al*. 2014). Depression may be a risk factor for adverse outcomes in acute coronary syndrome (Lichtman *et al*. 2014; Gan *et al*. 2014).

Although CVD risk in MDD patients has been shown in various studies, we considered that there are no clear and practical data that can warn clinicians about this risk. For this reason, we aimed to approach the studies on platelets from a different perspective.

Platelets are key factors in the physiology of hemostasis and in recent years have become important tools for understanding psychiatric conditions, psychological stress and the pharmacological properties of some psychotropics (Camacho and Dimsdale 2000). Classical platelet parameters have been associated with many specific symptoms of depression, and they may be suitable biomarkers to predict the onset of depression (Wang *et al*. 2022). In fact, platelets may link depression and cardiac events (Kooy *et al*. 2007). Serotonin plays an important role in the pathophysiology of depressive disorders (Meltzer 1990) and in platelet aggregation. Platelet membranes contain serotonin (5-HT) receptors, such as 5-HT2A, 5-HT3 and a 5-HT transporter (5-HTT), and platelet serotonin reflects plasma serotonin levels, as platelets contain approximately 99% of total circulating serotonin (Ortiz *et al*. 1988). Because peripheral platelets reflect central serotonergic function, they are considered markers of central serotonin (5-HT) metabolism (Mercado and Kilic 2010). Increased platelet volume indices (PVI) are associated with thrombotic events, particularly ischemic cardiovascular diseases and stroke (Kokacya *et al*. 2015; Gregg and Goldschmidt-Clermont 2003). Thus platelet serotonin appears to link coronary heart disease and depression. In addition, especially larger platelets are an important risk factor for the development of thrombosis (Khandekar *et al*. 2006).

In this study, we aimed to measure the levels of larger platelets in MDD and its relationship with disease severity, and thus to determine a marker for coagulation risk.

Material and methods

Inclusion and exclusion criteria

This study retrospectively included 51 patients between the ages of 18 and 65 who were diagnosed according to DSM-V criteria with MDD and who presented to Elazığ Mental Health and Diseases Hospital between June 1, 2020 and December 1, 2020. In addition, the study included 52 healthy individuals without any psychiatric diagnosis who presented between the same dates as controls. The study excluded candidates with mental retardation; organic disease; hematological disease; cognitive or neurological disorders; drug use or alcohol or substance abuse; and those who were pregnant, breastfeeding, or smokers, as these conditions would affect platelet activity. Of all the candidates, 5 were excluded from the study due to pregnancy, 17 due to chronic diseases, 16 due to smoking, 5 due to thrombolytic drug use, 8 due to alcohol or substance abuse, 9 due to age (over 65 years) and 20 due to lack of data. In the control group, 20 people were excluded from the study due to smoking, 9 due to chronic diseases, 2 due to pregnancy and 12 due to lack of data. The Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D) were used to retrospectively evaluate scanned data from the study group with MDD.

The study was approved by Elazığ Fırat University Clinical Research Ethics Committee (No: 2021/08-48).

Hematological analysis

After patients had fasted 12 hours, antecubital blood samples were drawn into vacuum tubes containing 15% K3 ethylene diamine tetraacetic acid (EDTA)-anticoagulant tubes (Sarstedt, Essen, Belgium) and analyzed. Complete blood count (CBC) parameters were evaluated using the Sysmex XN-450 hematology analyzer (Sysmex Corporation, Kobe, Japan) according to the manufacturer's instructions. PLT (platelet count), MPV (mean platelet volume), PLC-R (platelet large cell ratio), PCT (plateletcrit), PDW (platelet distribution width) and PLC-C (platelet large cell count) were evaluated as platelet parameters.

Data collection tools

1) **Hamilton Depression Rating Scale:** Developed by Hamilton (1960) to measure the severity of depression in the patient, this scale consists of 17 questions. The maximum possible score is 53 points. The score increases with depression severity (Güleç *et al*. 2005). The validity and reliability of the Turkish version were determined by Akdemir *et al*. (1996).

Table 1. Intergroup comparison of demographic data

Variables	MDD (*n*) mean ±SD	Control (*n*) mean ±SD	*P*-values
Age (years)	37.274 ±12.88	36.269 ±13.09	0.695
Gender (male/female)	11/40	13/39	0.858
Platelets (10^3/mm^3)	289.490 ±62.08	253.192 ±47.53	0.001
PLC-C (10^3/mm^3)	100.536 ±14.71	78.363 ±17.07	< 0.0001
PDW (fl)	16.002 ±0.32	12.594 ±2.07	< 0.0001
PCT	2.933 ±0.66	0.298 ±0.04	< 0.0001
Hemoglobin (g/dl)	13.421 ±1.52	13.486 ±1.416	0.822
White blood cells (10^3/mm^3)	7.718 ±2.15	7.638 ±2.04	0.847
Hematocrit (%)	41.031 ±4.05	41.139 ±3.95	0.891
PLC-R (%)	35.486 ±4.87	31.561 ±6.93	0.001
Mean platelet volume (fl)	10.372 ±0.93	10.576 ±0.83	0.243

MDD – major depressive disorder, PDW – platelet distribution width, PLC-R – platelet large cell ratio, PLC-C – platelet large cell count, PCT – plateletcrit. Data presented as mean ±SD or medians with 25th-75th percentiles.

2) **Hamilton Anxiety Rating Scale:** Developed by Hamilton to determine anxiety level and symptom distribution and to measure changes in depression severity, this scale assesses both somatic and cognitive anxiety symptoms. Total score ranges from zero to 56 (Eroğlu *et al*. 2012). Yazıcı *et al*. (1998) confirmed the validity and reliability of the Turkish version of the scale.

Statistical evaluation

Statistical analyses were performed using SPSS software, version 26.0 for Windows (IBM SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate distribution of the variables, all of which showed normal distribution; Student's *t*-test was used to determine means and standard deviations (SD). Pearson's chi-square test was used to evaluate categorical variables. Pearson's correlation test was used for correlation analyses. Receiver operating characteristics (ROC) analysis was used to evaluate specificity and sensitivity of PLC-C levels in detecting major depressive disorder. All p-values were two-tailed, and values < 0.05 were considered statistically significant.

Results

This cross-sectional study compared 51 MDD patients and 52 healthy controls on the basis of some demographical and laboratory parameters. Values for PLT, PLC-C, PDW, PCT, PLC-R were found to be significantly higher in MDD patients compared to the control group ($p = 0.001$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.001$, respectively) (Table 1, Fig. 1). On the other hand, there was no difference between the two groups with respect to MPV, WBC (white blood cell), Hg (hemoglobin) and HTC (hematocrit), gender and age (Table 1).

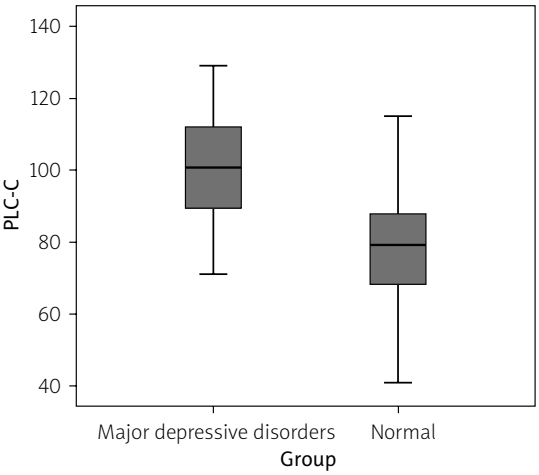

Fig. 1. Comparison for platelet large cell count (PLC-C) between the major depressive disorders and the normal group

Pearson correlation analysis showed PCT, PLT, PLC-C values and HAM-D score to be positively correlated in MDD patients (Table 2, Fig. 2). No correlation was found between other platelet indices and HAM-D and HAM-A scores (Table 2).

The ROC curve analysis demonstrated that the specificity of a PLC-C > 91.24 cut-off value in predicting MDD cases was 80.8% and the sensitivity was 70.6% (Fig. 3).

Discussion

We found significant platelet volume indices in MDD and a positive correlation between the depression severity and PLC-C levels.

Table 2. Pearson correlation analysis

	Age *r, p*	PLC-C *r, p*	PLC-R *r, p*	PDW *r, p*	PLT *r, p*	MPV *r, p*	PCT *r, p*
HAM-A	0.307, 0.028	0.066, 0.645	0.204, 0.150	0.106, 0.461	–0.064, 0.657	0.122, 0.392	–0.015, 0.917
HAM-D	–0.094, 0.512	0.592, 0.000	0.166, 0.246	–0.124, 0.386	0.300, 0.032	–0.036, 0.801	0.324, 0.020

PLC-C – platelet large cell count, PLC-R – platelet large cell ratio, PDW – platelet distribution width, PLT – platelet, MPV – mean platelet volume, PCT – plateletcrit, HAM-A – Hamilton Anxiety Rating Scale, HAM-D – Hamilton Depression Rating Scale

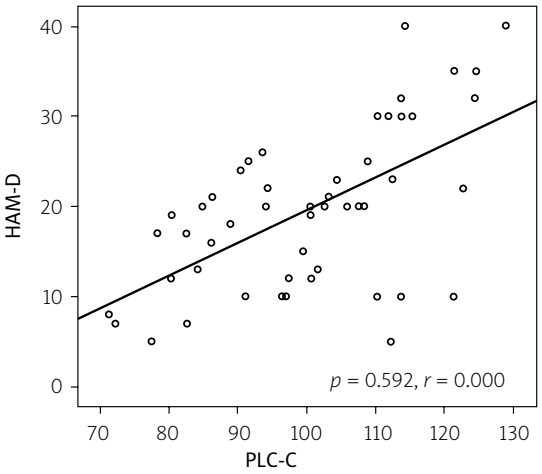

Fig. 2. Correlation analysis between Hamilton Depression Rating Scale (HAM-D) and platelet large cell count (PLC-C)

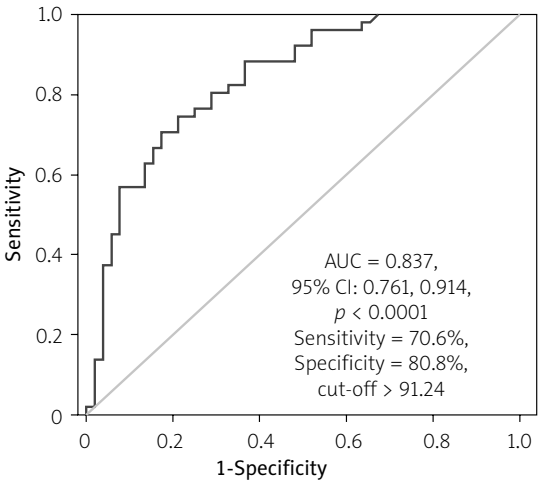

Fig. 3. ROC analysis for platelet large cell count (PLC-C) cut-off predicting major depressive disorder. AUC – area under the curve; CI – confidence interval; ROC – receiver operating characteristics

Serotonin is the most important neurotransmitter in the etiology of MDD; disruption of serotonin release has been associated with depression (Cowen and Browning 2015; Ruhe *et al*. 2007). Serotonin also plays a role in platelet aggregation. Platelet surfaces bear serotonin receptors and peripheral platelets are the indicators for central serotonergic functions (Mercado and Kilic 2010; Kokacya *et al*. 2015). Some studies have found the amount of platelet serotonin to be lower in depressed patients than in healthy people (Takakashi 1976; Quintana 1992). Depressed patients may be at risk for platelet activation (Pollock *et al*. 2000) and increased platelet reactivity and platelet function abnormalities may predispose depressed patients to coagulation, explaining their vulnerability to cardiovascular disease (Nemeroff *et al*. 2000). Increased plasma epinephrine concentrations and impaired serotonin (5-HT) balance may alter platelet function in patients. Impairment in secondary signal transduction and altered intraplatelet monoamine and catecholamine concentrations may cause an imbalance in coagulation diathesis in patients with depression (Musselman *et al*. 1996). Activation of 5-HT2 receptors regulates platelet aggregation and coronary vasoconstriction. Platelets from depressed patients exhibit increased 5-HT2 binding density and decreased 5-HT transporter density (Arora and Meltzer 1989; Paul *et al*. 1982). The serotonin secreted by platelet alpha granules is a highly potent vasoconstrictor that increases the risk of thrombus formation (Levkovits *et al*. 1995). Thus it is clear that serotonin plays a crucial role in both thrombogenesis and the neurobiology of depression (Camacho and Dimsdale 2000).

The inflammatory process may also be significant. Clinical studies have found that inflammation plays a role in the etiology of MDD and that inflammatory biomarkers may reflect the inflammatory response (Dantzer *et al*. 2008). Platelets are activated by inflammation, and many cytokines interact with inflammatory biomarkers during the inflammatory process (Klınger and Jelkmann 2002). Cytokines lower central synaptic serotonin levels by decreasing its synthesis and increasing its reuptake. They may deplete neurotrophic factors and inhibit neurogenesis in the hippocampus (Miller *et al*. 2009; Makhija and Karunakaran 2013). The complex inflammatory process in MDD may be related to platelet activation.

In the whole blood analysis conducted in our study, the number of PLT increased significantly in MDD patients compared to controls. Previous studies found PLT counts to be higher in

patients with depression than in controls (Caı *et al*. 2017; Ataoğlu and Canan 2009), and higher in hospitalized adolescents with suicidality than in non-suicidal inpatients and controls (Ragolsky *et al*. 2013). Regarding coagulation potential, larger platelets have more granules and receptors and a greater tendency to clot than small platelets. Therefore, it would be more accurate to evaluate platelet activity by platelet size than number (Yılmaz *et al*. 2018). Platelet size can be evaluated with platelet volume indices such as PLC-C, PLC-R, MPV, PDW, and PCT (Gasparyan *et al*. 2011).

Platelet distribution width is the distribution width of platelets of different sizes and is indicative of platelet anisocytosis. It is a simple index that is considered a specific marker of platelet activation. It reflects heterogeneity in platelet morphology (Budak *et al*. 2016). PDW may be a potential biomarker for depression (Gialluisi *et al*. 2020). In our study, PDW was significant in the MDD patient group, which supports platelet activation.

Plateletcrit is the ratio of platelet volume to whole blood volume and gives an idea of acceptable total platelet mass, similar to hematocrit. PCT is an effective screening tool to detect quantitative abnormalities of platelets (Akpınar *et al*. 2014). In a study of MDD patients, PCT was found to be significantly higher compared to healthy controls (Caı *et al*. 2017); our study also found PCT to be significant higher in MDD patients.

Mean platelet volume reflects the average platelet size (7.5 fl to 10.5 fl). In people with MDD, especially MPV may be a potential biomarker for inflammation (Caı *et al*. 2017). In one study, MPV values detected at admission were correlated with the development of poststroke depression 1 month after stroke (Qiu *et al*. 2018). Some previous studies have found MDD patients to have higher MPV levels than patients without depression, and increased MPV has been associated with major depression (Canan *et al*. 2012; Bondade *et al*. 2018). After the escitalopram treatment in depressed patients whose MPV levels were higher than the control group, there was a significant decrease in MPV levels (Ataoglu and Canan 2009). In a study examining platelet parameters in patients with schizophrenia, unipolar depression and bipolar depression, the highest platelet count and relatively the highest MPV were found in patients with unipolar depression (Wysokiński and Szczepocka 2016). Our study found no significant difference for MPV between the two groups.

Though platelet count and other indices are important for quantifying coagulation, we think indices that give the ratio (PLC-R) and number (PLC-C) of larger and more active platelets should be emphasized. PLC-R is a platelet ratio greater than 12 fl and PLC-C is a platelet count greater than 12 fl. PLC-C is the product of PLT and PLC-R. PLC-R indicates risk for thromboembolic ischemic events (Grotto and Noronha 2004). Our study found higher PLC-R and PLC-C levels compared to controls and a positive correlation between HAM-D scores and PLC-C levels. A large-sample study has observed that the risk of developing ischemic heart disease increases with increased severity of depressed affect and hopelessness (Anda *et al*. 1993). Increased depressive symptoms are associated with mortality and risk of MI (Barefoot and Schroll 1996). Depression may indicate poor prognosis for CVD. The patient's depression level may play a role in the worsening of CVD (Amadio *et al*. 2020). The increase in large-cell platelets that correlates with increasing severity of depression may contribute to more severe cardiovascular disease.

Platelet size contributes to hemostatic potential. Large platelets contain more proteins, particularly β-thromboglobulin, fibrinogen, serotonin, and various glycoproteins. The amount of receptors on the platelet surface is proportional to platelet size. With collagen stimulation large platelets aggregate more rapidly, and diffuse more rapidly to surfaces (Handtake and Thiele 2020) and bind more fibrinogen on their surfaces (Mangalpally *et al*. 2010). Larger platelets also have higher ATP and glycogen levels and greater metabolic potential (Karpatkin and Charmatz 1969) and contain greater amounts of mRNA related to prothrombotic hemostatic processes (Clancy *et al*. 2017). They are usually relatively young, containing more granules and so have a greater tendency to coagulate. Platelet turnover rate is determined by platelet size (Gawlita *et al*. 2015).

Although the mechanism of increasing platelet size is not fully understood, cytokines may trigger the production of new and larger platelets following peripheral platelet destruction (Endler *et al*. 2002). The complex inflammatory processes in depression may explain this. In addition, neurotransmitter changes in depression may trigger platelet activation, especially serotonin, and the development of large platelets.

Conclusions

We detected increased PLC-R and PLC-C levels in MDD. Depression is a risk factor for coagu-

lation and CVD (Kostanjsak and Zdunic 2017). Large platelets are an important risk factor for the development of thrombosis (Khandekar *et al*. 2006). Platelet size has been investigated previously; however, platelets greater than 12 fL and platelet indices PLC-R and PLC-C, which carry a higher risk of thrombosis, have not been investigated. A simple CBC analysis can detect high PLC-R and PLC-C values and identify patients who will likely benefit from preventive antithrombotic therapy. Elevated PLC-C levels in MDD show a positive correlation with disease severity. It will be useful to control PLC-C levels in severe depression. In addition, PLC-C may be a useful marker for the increased coagulation activity observed in MDD patients.

Disclosure

The authors declare no conflict of interest.

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