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Brief communication

Platelet serotonin as a biomarker for depression diagnosis in untreated patients

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Abstract

Background: Major depressive disorder is a common mental mood condition that can be challenging to diagnose objectively. The pathophysiology of depression has been linked to impaired serotonergic neurotransmission, and there is strong evidence that serotonin may be crucial in determining a person's susceptibility to depression or mania. This study aimed to investigate the clinical usefulness of platelet count and platelet serotonin concentration for diagnosing and determining the severity of depression.

Methods: A case-control study was conducted from August 2022 to November 2022. Sixty healthy control subjects were enrolled, most of whom were volunteers from the laboratory in Ibn-Rushed Hospital Training, Baghdad, Iraq, and medical students. Subjects were considered controls if they did not have a personal psychiatric history and were not receiving psychoactive medication. Patients were sixty depressive inpatients, age and gender-matched, with an age range of 25-60 years. The enzyme-linked immunosorbent assay technique was used to assess platelet serotonin concentrations.

Results: The mean ranks of platelet serotonin in the cases and controls were 30.55 ng/ml and 90.45 ng/ml, respectively. The platelet serotonin in the cases group was significantly lower than that of the control group (P-value=0.001). The mean ranks of platelet count in the cases and control were 49.3 ng/ml and 71.7 ng/ml, respectively. The platelet count in the cases group was significantly lower than that of the control group (P-value=0.001). An inverse correlation was established between platelet serotonin concentration and depressive symptoms, where more severe symptoms were associated with lower platelet serotonin concentrations (P-value=0.001).

Conclusions: This study found that low platelet serotonin concentrations may be implicated in the diagnosis and severity of major depressive disorder. Assessing platelet serotonin concentration may be a clinically useful tool for diagnosing and determining the severity of depression. Further research is needed to confirm these findings and evaluate their clinical implications.

Keywords: depression; major depressive disorder; platelet count; platelet serotonin; severity

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1. Introduction

Depression is a highly prevalent and debilitating mental health condition that affects millions of people worldwide [1–3]. Despite the availability of various treatments, including medication and psychotherapy, a significant proportion of individuals with depression do not receive appropriate care, either due to lack of access to healthcare or inadequate diagnosis [4–6]. Therefore, there is a need for reliable biomarkers that can aid in the accurate and timely diagnosis of depression, particularly in patients who have not yet received treatment.

Platelet serotonin has emerged as a promising biomarker for depression, due to its role in regulating mood and its potential to reflect central nervous system (CNS) serotonergic function [7, 8]. Serotonin is a monoamine neurotransmitter that is synthesized from the amino acid tryptophan and stored in platelets, which are small blood cells that play a crucial role in hemostasis [9, 10]. Platelet serotonin has been shown to be a valid marker of CNS serotonin function, as platelets and neurons share a common biosynthetic pathway for serotonin [11].

Several studies have investigated the relationship between platelet serotonin concentration and depression, with some studies reporting lower platelet serotonin levels in individuals with depression compared to healthy controls [12–18]. Other studies have found that platelet serotonin levels are negatively correlated with depression severity and that they increase following treatment with antidepressant medication [19]. Furthermore, platelet serotonin has been associated with other depressive symptoms, such as suicidality and cognitive impairment [20–22].

Despite these promising findings, the use of platelet serotonin as a biomarker for depression is still a topic of debate. Some studies have reported inconsistent results, and there are several methodological challenges that need to be addressed, such as the influence of medication use, comorbidities, and age. Nonetheless, the potential of platelet serotonin as a biomarker for depression warrants further exploration, as it may provide a non-invasive and cost-effective method for the diagnosis and monitoring of depression [23].

2. Methods

A case-control study with a total of 120 participants, consisting of 60 patients with depression and 60 healthy controls, was conducted. Control subjects were recruited from the laboratory in Ibn Rushed Training Hospital (Baghdad, Iraq), and from among medical students, with age and gender-matched to the patient group. To be considered as controls, subjects were required to have no personal history of psychiatric illness and not be receiving psychoactive medication. Additionally, those with a family history of psychiatric illness were excluded. Patients were recruited from the same hospital and were all inpatients, aged between 25 and 60 years. They were drug-free when blood was sampled, as antidepressants are known to interfere with serotonin metabolism.

Inclusion criteria for patients were based on the Beck Depression Inventory (BDI) to assess the status and severity of depression [24]. Exclusion criteria for subjects in both groups included any current or past history of other psychiatric illnesses such as schizophrenia and Alzheimer's disease, physical illnesses including diabetes, liver disease, or renal disease, brain trauma, or organic diseases of the brain. Subjects with a history of alcohol or other drug abuse, use of psychoactive substances, or electroconvulsive therapy (ECT) were also excluded, as were those who were pregnant or lactating.

Blood samples were collected from each participant by drawing 5 milliliters from the cubital vein after a 12-hour fast at 9 am. The samples were collected into an EDTA tube to prevent clotting. The platelet serotonin concentration was determined using an enzyme-linked immunosorbent assay (ELISA) technique. Platelet count was determined using an Automated Hematology Analyzer.

To assess the platelet count, whole blood collected in EDTA tubes was used. The remaining EDTA blood samples were centrifuged for 10 minutes at room temperature at 800 xg to separate the platelet pellet. The pellet was then washed with 800 microliters of physiological saline to obtain platelet-rich plasma (PRP) containing between 350,000 and 500,000 platelets per liter. The supernatant was discarded, and the pellet was mixed with 200 microliters of deionized, distilled water on a vortex mixer. The mixture was then frozen at -20 °C and analyzed quantitatively using the competitive ELISA method by following the manufacturers instructions provided in commercial kit.

The collected data was initially entered into Microsoft Excel and then imported into GraphPad Prism (GraphPad Software, USA) for statistical analysis. After testing for normality using the Shapiro-Wilk test, it was determined that the data did not follow a normal distribution, leading to the use of Mann-Whitney and Kruskal Wallis tests to compare means. The Chi-square test was employed to investigate the significance of relationships between nominal and categorical variables. In all statistical analyses, a P-value of 0.05 or less was considered statistically significant. Additionally, ROC curve analysis was performed by using Medcalc software to evaluate the diagnostic accuracy of using platelet serotonin levels in the detection of depression.

3. Results & discussion

In this case-control study, a total of 120 subjects were enrolled, including 60 patients with depression (cases), who were further divided into mild, moderate, and severe subgroups, and 60 apparently healthy subjects with no signs or symptoms of depression (control). The demographic and clinical characteristics of the subjects are presented in Table 1. Statistical analysis using chi-square test revealed that gender, occupation, and education were not significantly associated with the studied groups (P-value >0.05) in all cases. Interestingly, the prevalence of depression was found to be more common among individuals who were divorced or widowed compared to other marital status categories (P-value= 0.04).

Table 2 displays the results of statistical analyses conducted on the data collected. The mean rank of platelet serotonin in the case group was significantly lower than that of the control group (P-value= 0.001), as was the mean rank of platelet count (P-value= 0.001). The study also found a significant association between BMI and depression, with obese patients having a higher prevalence of depression (P-value= 0.022).

The figure 1 indicate that the levels of platelet serotonin and platelet count were significantly lower in severe depression compared to moderate and mild depression (p-value <0.05). However, there was no significant difference between age and severity of depression (P-value =0.739), nor was there a significant difference between BMI and severity of depression (P-value = 0.732).

Based on ROC curve analysis (figure 2), a cut-off value of ≤217 for platelet serotonin was found to have a high diagnostic accuracy for detecting depression in untreated patients, with an overall accuracy of 96%. The sensitivity of the test was 100% (95% CI, 94.0 – 100), and the specificity was 96.67% (95% CI, 88.5 – 99.6).

In the present case-control study, the relationship between depression and platelet serotonin levels, platelet count, and body mass index (BMI) was investigated in a sample of 120 participants. Our findings revealed a higher prevalence of depression among divorced or widowed individuals compared to other marital statuses. Additionally, the case group exhibited significantly lower mean platelet serotonin levels and platelet counts compared to the control group. A significant association between BMI and depression was also observed, with a higher prevalence of depression among obese patients. Furthermore, platelet serotonin levels and platelet counts were significantly lower in patients with severe depression compared to those with moderate or mild depression.

Table 1 · The association between studied variables according to the group of study.

		Control		Cases		**P-value**
		n	%	n	%	
Gender	Male	32	53.3	28	46.7	0.465
	Female	28	46.7	32	53.3	
Marital status	Single	20	66.7	10	33.3	0.04
	Married	38	46.9	43	53.1	
	Other	2	22.2	7	77.8	
Education	Primary	12	54.5	10	45.5	0.170
	Secondary	19	39.6	29	60.4	
	University	29	58.0	21	42.0	
Occupation	Unemployed	35	56.5	27	43.5	0.144
	Employed	25	43.1	33	56.9	

P-value computed using Chi-square test.

Table 2 ▪ Differences of BMI, platelet serotonin and platelet count between patients and healthy controls.

	BMI (kg/m2)	Platelet count (×103/µl)	Platelet serotonin (pg/ml)
Control (n=60)	26.12 (23.96 – 27.92)	263 (236 – 308)	334.0 (282.3 – 427.5)
Patients (n= 60)	28.16 (24.53 – 31.34)	233 (190 – 269)	81.50 (64.75 – 93.00)
P-value	0.004	<0.001	<0.001

Mann Whitney test was used. BMI= body mass index, n= number of participants.

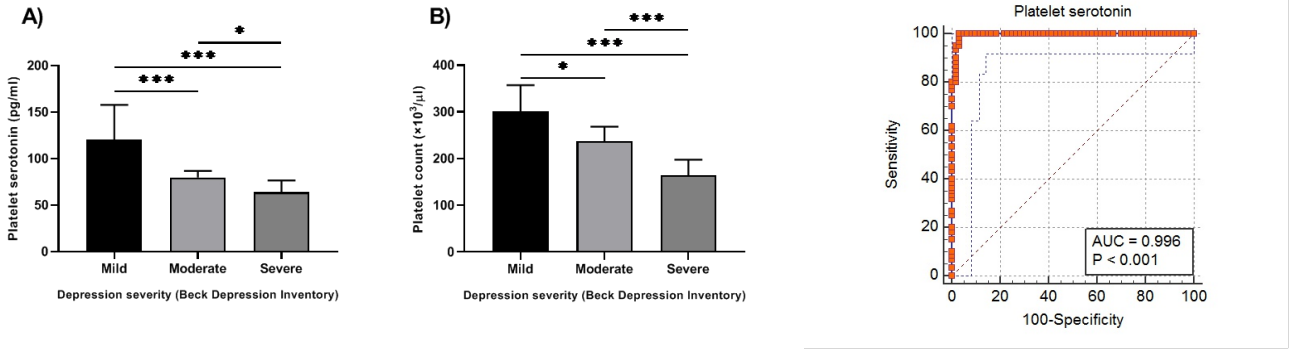

Figure 1 ▪ Difference in mean of A) platelet serotonin and B) platelet count, among patients. Stars denote statistically significant difference, * when P<0.05 and *** when P<0.001

Figure 2 ▪ Receiver operating characteristic (ROC) curve analysis of platelet serotonin in depression.

These results hold significance as they suggest that platelet serotonin levels and platelet count may serve as potential biomarkers for depression. The observed association between BMI and depression also emphasizes the importance of weight management in patients with depression [25]. Interestingly, the findings related to marital status and depression are consistent with existing literature. For instance, a study by Richards and colleagues (1997) reported an association between divorce or separation and a higher risk of depression, supporting our findings [26]. Similar associations between lower platelet serotonin levels and depression have been documented in other studies [15,21].

The underlying mechanisms linking platelet serotonin and untreated depression remain elusive, but several hypotheses have been proposed. Serotonin, a monoamine neurotransmitter, plays a pivotal role in mood regulation and other physiological functions [27]. Alterations in serotonin function have been implicated in depression's pathophysiology, and many antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs), function by increasing serotonin availability in the synaptic cleft [28].

Platelets participate in the storage, uptake, and release of serotonin in the bloodstream [16]. They absorb serotonin from plasma and store it in dense granules, releasing it upon activation [29]. Given that platelets and neurons share a common mechanism for serotonin uptake and storage, platelet serotonin levels have been proposed as a peripheral biomarker for central serotonergic activity [30]. The association between reduced platelet serotonin levels and untreated depression may be attributed to altered serotonin synthesis due to genetic or environmental factors, such as changes in the tryptophan hydroxylase enzyme responsible for converting tryptophan into serotonin [31]. Additionally, impaired serotonin uptake by platelets could result from changes in the expression or function of the serotonin transporter (SERT), responsible for transporting serotonin into platelets and neurons [32]. Moreover, increased serotonin breakdown or metabolism may contribute to the observed decrease in platelet serotonin levels [33]. Furthermore, altered platelet activation and serotonin release may also be involved in the association between platelet serotonin levels and untreated depression [34]. Dysregulation in these processes could lead to an imbalance in serotonin levels, potentially influencing mood and contributing to depression.

Our findings suggest potential biomarkers for depression and underscore the importance of addressing weight management in depressed patients. They also offer a potential diagnostic tool for identifying depression in untreated patients, as the study determined a cut-off value of ≤217 for platelet serotonin to have high diagnostic accuracy for detecting depression in untreated patients.

It is important to acknowledge the limitations of the current study, such as the relatively small sample size and the cross-sectional design, which prevents establishing causal relationships between the examined factors and depression. Future research should include larger and more diverse samples, longitudinal designs, and advanced statistical methods to account for potential confounding factors. Additionally, studies should explore the potential mechanisms underlying the observed associations and investigate the efficacy of interventions targeting these factors in the prevention and treatment of depression.

Conclusions

This study provides insights into the relationship between depression and platelet serotonin levels, platelet count, and BMI. The findings contribute to the understanding of the potential role of these factors in the pathophysiology of depression and highlight the importance of addressing weight management in depressed patients. Moreover, the study identifies a potential diagnostic tool for depression in untreated patients based on a platelet serotonin cut-off value. Further research is needed to confirm and expand upon these findings and explore their clinical implications in depression diagnosis, monitoring, and treatment.

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Declarations

Authors' contributions

Conceptualization: RAJ & OFA. Data curation: RAJ. Formal Analysis: RAJ. Funding acquisition: N/A. Investigation: RAJ & AYM. Methodology: RAJ, HAH OFA. Project administration: RAJ. Resources: RAJ, OFA, HAA. Software: HAA. Supervision: OFA. Validation: RAJ & AYM. Writing – original draft: RAJ & HAH. Writing – review & editing: HAA & OFA.

Ethics approvals

The present study has received ethical approval from the Institutional Review Board of Al-Nahrain University, College of Medicine (2021). The study protocol adhered to the principles outlined in the Helsinki Declaration, and written informed consent was obtained from all participants prior to their enrollment in the study.

Consent for publication

N/A.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declared no conflicts of interest.

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