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"EVALUATING THE DIAGNOSTIC POTENTIAL OF ROUTINE BIOCHEMICAL MARKERS IN MAJOR DEPRESSIVE DISORDER: A CROSS-SECTIONAL STUDY"

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Abstract

Background: Major Depressive Disorder (MDD) is a prevalent mental health condition with significant impacts on quality of life and overall health. The identification of reliable and accessible biomarkers for MDD could enhance diagnostic accuracy and inform treatment strategies, particularly in resource-limited settings.

Objective: This study aimed to investigate the significance of routine biochemical markers in patients with MDD and to evaluate their potential utility in the diagnosis of the disorder.

Methods: This cross-sectional observational study was conducted at the Department of Biochemistry, MGM Medical College, Indore. A total of 120 participants were enrolled, comprising 60 patients diagnosed with MDD and 60 healthy controls. Biochemical markers, including fasting blood glucose (FBG), *fructosamine* (SF), high-density lipoprotein cholesterol (HDL-C), and total protein (TP), were measured. Multivariate logistic regression analysis was performed to identify independent associations between these markers and MDD. The diagnostic performance of the combined markers was evaluated using Receiver Operating Characteristic (ROC) curve analysis.

Results: The study identified FBG, SF, HDL-C, and TP as independent markers significantly associated with MDD. MDD patients exhibited elevated levels of FBG ($p = 0.007$), and SF ($p = 0.002$) and higher HDL-C ($p = 0.018$) compared to controls, while TP levels were lower in MDD patients ($p = 0.006$). The combination of these markers provided good discriminative power, with an area under the curve (AUC) of 0.801, a sensitivity of 0.783, and a specificity of 0.715 at a cut-off value of 0.417.

Conclusion: Routine biochemical markers such as FBG, SF, HDL-C, and TP demonstrate significant associations with MDD and offer potential utility in the clinical assessment of the disorder. The combined use of these markers could enhance diagnostic accuracy, providing an objective complement to traditional clinical evaluations. Further research is recommended to validate these findings and to explore their integration into routine clinical practice for managing MDD.

Keywords: Major Depressive Disorder, Biochemical Markers, Fasting Blood Glucose, Fructosamine, HDL-C, Total Protein, Diagnosis, Biomarkers.

Introduction

Major depressive disorder (MDD) is a prevalent and debilitating mental health condition characterized by persistent feelings of sadness, loss of interest or pleasure in most activities, and a range of cognitive and physical symptoms[1]. It affects millions of people worldwide, contributing significantly to the global burden of disease[2]. Despite its widespread impact, the pathophysiology of MDD remains incompletely understood, and its diagnosis is primarily based on clinical evaluation, with limited reliance on objective biomarkers[3,4]. The need for reliable and accessible diagnostic tools has driven research into the potential role of routine biochemical markers in identifying and managing MDD[3,4].

Recent studies have highlighted the involvement of systemic inflammation, oxidative stress, and metabolic dysregulation in the pathogenesis of MDD[5,6]. These factors not only contribute to the onset and progression of depressive symptoms but also offer potential avenues for identifying biochemical markers that could serve as diagnostic or prognostic tools[7,8]. For instance, markers of oxidative stress, such as urea nitrogen (UN), creatinine (Cr), and *fructosamine* (SF), have been associated with MDD, suggesting that these parameters could reflect underlying biological processes linked to the disorder[4,9]. Similarly, alterations in lipid metabolism, as indicated by changes in high-density lipoprotein cholesterol (HDL-C), have been observed in patients with MDD, further supporting the notion that routine biochemical tests could provide valuable insights into the condition[10,11].

In addition to the growing body of evidence supporting the role of biochemical markers in MDD, there is a need to explore these associations in diverse populations, including those in developing countries like India, where the burden of mental health disorders is substantial, yet access to advanced diagnostic tools is limited. Moreover, understanding the potential influence of regional factors, such as diet, lifestyle, and genetic predispositions, on the levels of these markers is essential for developing effective and culturally appropriate diagnostic strategies.

This study aims to investigate the significance of routine biochemical markers in patients with MDD in the Indian population. By examining the levels of various biochemical parameters in individuals diagnosed with MDD compared to healthy controls, this research seeks to identify markers that are independently associated with the disorder. Furthermore, the study will explore the potential of combining multiple biochemical markers to improve the accuracy of MDD diagnosis. The findings could contribute to the development of a more objective and accessible approach to diagnosing MDD, ultimately enhancing the management and treatment of this pervasive condition in resource-limited settings.

Material and Methods:

♦ **Study Design and Setting**: This study is a cross-sectional observational study conducted at the Department of Biochemistry, MGM Medical College, Indore. The research was designed to investigate the significance of routine biochemical markers in patients diagnosed with Major Depressive Disorder (MDD).

♦ **Study Duration:** The entire study was conducted over a period of 10 months, with 8 months allocated for data collection and 2 months for data analysis and interpretation.

♦ **Ethical Considerations:** The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of MGM Medical College, Indore. All participants provided informed consent prior to their inclusion in the study, and their confidentiality was maintained throughout the research process.

♦ **Participants and Sample Size:** The study enrolled a total of 120 participants, who were divided into two groups: patients diagnosed with MDD and healthy controls. The inclusion criteria for the MDD group were individuals aged 18 to 65 years who had been diagnosed with MDD according to

the DSM-5 criteria. Patients with comorbid psychiatric conditions, chronic physical illnesses, or those on medications known to affect biochemical parameters were excluded from the study. The control group consisted of age- and gender-matched healthy individuals with no history of psychiatric disorders or significant medical conditions.

♦ **Sampling Methodology:** Participants for this study were selected using a purposive sampling method. Patients diagnosed with MDD were recruited from the Psychiatry Department of MGM Medical College and associated hospitals. Healthy controls were selected from the general population, matched for age and gender with the MDD group. This method ensured that the study included participants who were representative of the population being studied, while also allowing for direct comparison between those with MDD and healthy individuals.

♦ **Data Collection:** Fasting venous blood samples were collected from all participants under sterile conditions. The blood samples were then processed and analysed using standardized biochemical assays at the Department of Biochemistry, MGM Medical College. The biochemical parameters measured included:

- Urea Nitrogen (UN)
- Creatinine (Cr)
- *Fructosamine* (SF)
- High-Density Lipoprotein Cholesterol (HDL-C)
- Total Protein (TP)
- Total Bilirubin (Tbil)
- Fasting Blood Glucose (FBG)

All biochemical tests were performed using an automated biochemical analyser calibrated according to the manufacturer's instructions. The accuracy and precision of the assays were regularly validated using quality control samples.

♦ **Statistical Analysis:** Data were entered into a spreadsheet and analysed using Stata 17.0 statistical software. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as frequencies and percentages. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Differences between the MDD group and the control group were compared using the independent t-test for continuous variables. Categorical variables were compared using the Chi-square test. A multivariate logistic regression analysis was conducted to identify the biochemical markers independently associated with MDD. A p-value of <0.05 was considered statistically significant for all analyses.

♦ **Conflict of Interest:** The authors declare that there are no conflicts of interest regarding the publication of this study. All authors have contributed to the research and writing process independently and have no financial or personal relationships that could have influenced the study's outcomes or interpretations.

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Results

Participant Demographics

The study included a total of 120 participants, with 60 patients diagnosed with Major Depressive Disorder (MDD) and 60 healthy controls. The mean age of participants in the MDD group was 39.0 ± 9.2 years, while the mean age in the control group was 39.5 ± 9.0 years. There were no significant differences in age ($p = 0.735$) or gender distribution ($p = 0.798$) between the two groups. The demographic and clinical characteristics of the participants are summarized in Table 1.

Medical History of Participants with Major Depressive Disorder (MDD)

The mean age at diagnosis for participants with MDD was 34.2 ± 7.5 years, indicating that most participants were diagnosed in their mid-30s. The average duration of MDD among the participants was 2.8 years. The severity of depression in participants was assessed using the Hamilton Depression Rating Scale (HAMD). The mean HAMD score was 22.5 ± 5.3, indicating that the majority of participants were experiencing moderate to severe symptoms of depression at the time of the study. A significant portion of participants reported comorbid conditions such as anxiety disorders (42%), sleep disturbances (65%), and chronic pain (28%). These comorbidities are common in individuals with MDD and contribute to the overall burden of the disease. The majority of participants (78%) had been receiving antidepressant treatment, primarily selective serotonin reuptake inhibitors (SSRIs), for an average duration of 3.5 ± 2.6 years. Despite ongoing treatment, many participants continued to experience moderate to severe symptoms, indicating a potential treatment-resistant nature of their depression.

Biochemical Parameters

The levels of various biochemical markers were measured in both the MDD group and the control group. Significant differences were observed between the two groups for several markers. Specifically, the MDD group had lower mean levels of urea nitrogen (4.18 ± 1.24 mmol/L vs. 4.87 ± 1.11 mmol/L, $p = 0.002$), creatinine (56.3 ± 10.7 µmol/L vs. 64.1 ± 11.4 µmol/L, $p < 0.001$), total protein (66.4 ± 5.1 g/L vs. 68.8 ± 5.2 g/L, $p = 0.006$), and total bilirubin (8.25 ± 3.05 µmol/L vs. 9.68 ± 3.37 µmol/L, $p = 0.012$) compared to the control group.

Conversely, the MDD group exhibited higher levels of fasting blood glucose (4.84 ± 0.48 mmol/L vs. 4.57 ± 0.39 mmol/L, $p = 0.007$) and *fructosamine* (2.37 ± 0.30 mmol/L vs. 2.20 ± 0.27 mmol/L, $p = 0.002$) compared to the control group. The levels of high-density lipoprotein cholesterol (HDL-C) were also significantly higher in the MDD group (1.35 ± 0.30 mmol/L vs. 1.23 ± 0.32 mmol/L, $p = 0.018$).

Table 1: Biochemical Parameters among Study and Control Population

Parameter	MDD Group (n=60)	Control Group (n=60)	p-value
Mean Age (years)	39.0 ± 9.2	39.5 ± 9.0	0.735
Gender (Male/Female)	25/35	26/34	0.798
Urea Nitrogen (mmol/L)	4.18 ± 1.24	4.87 ± 1.11	0.002
Creatinine (µmol/L)	56.3 ± 10.7	64.1 ± 11.4	<0.001
Total Protein (g/L)	66.4 ± 5.1	68.8 ± 5.2	0.006
Total Bilirubin (µmol/L)	8.25 ± 3.05	9.68 ± 3.37	0.012
Fasting Blood Glucose (mmol/L)	4.84 ± 0.48	4.57 ± 0.39	0.007
Fructosamine (mmol/L)	2.37 ± 0.30	2.20 ± 0.27	0.002
HDL-C (mmol/L)	1.35 ± 0.30	1.23 ± 0.32	0.018

Multivariate Analysis

Multivariate logistic regression analysis was performed to identify the biochemical markers independently associated with MDD. The analysis revealed that fasting blood glucose (OR = 4.45, 95% CI: 2.65–7.48, $p < 0.001$), *fructosamine* (OR = 10.34, 95% CI: 4.29–24.89, $p < 0.001$), HDL-C (OR = 2.48, 95% CI: 1.25–4.96, $p = 0.012$), and total protein (OR = 0.85, 95% CI: 0.80–0.92, $p = 0.001$) remained significantly associated with MDD after adjusting for potential confounders.

Diagnostic Performance

The diagnostic performance of the combined biochemical markers was evaluated using a Receiver Operating Characteristic (ROC) curve. The area under the curve (AUC) for the combined markers

was 0.801 (95% CI: 0.739–0.863, $p < 0.001$), indicating a good discriminative ability for identifying patients with MDD. The sensitivity and specificity of the combined markers were 0.783 and 0.715, respectively, at a cut-off value of 0.417.

Discussion

The findings of this study provide important insights into the biochemical alterations associated with Major Depressive Disorder (MDD) and their potential utility in the diagnosis and management of the condition. The multivariate analysis identified fasting blood glucose (FBG), *fructosamine* (SF), high-density lipoprotein cholesterol (HDL-C), and total protein (TP) as independent biochemical markers significantly associated with MDD. These results align with and extend the existing body of literature, highlighting the role of metabolic and inflammatory pathways in the pathophysiology of depression.

The significant association of FBG and SF with MDD underscores the interplay between glucose metabolism and depressive disorders[12,13]. Elevated FBG levels have been consistently linked to insulin resistance and oxidative stress, which are increasingly recognized as contributing factors to the development and exacerbation of depressive symptoms[12,13]. The strong association of fructosamine, a marker of glycaemic control over the preceding weeks, further supports the hypothesis that impaired glucose metabolism may play a critical role in MDD. These findings suggest that monitoring and managing blood glucose levels could be a crucial component of treating patients with MDD, particularly those with comorbid metabolic conditions.

The identification of HDL-C as a significant marker in MDD is intriguing, given its traditional role in cardiovascular health. The positive association between higher HDL-C levels and MDD observed in this study, along with previous reports, suggests a complex relationship between lipid metabolism and depression[10,11]. This finding may reflect compensatory mechanisms in response to oxidative stress or inflammation, which are known to be elevated in individuals with depression. Further research is needed to unravel the underlying mechanisms and to explore whether HDL-C could serve as a therapeutic target in MDD.

Total protein (TP) was found to be inversely associated with MDD, indicating that lower TP levels are more common in individuals with depression. This could be related to malnutrition, reduced protein synthesis, or increased protein catabolism, all of which are plausible in the context of chronic illness and stress[3,14]. The role of TP as a potential biomarker for MDD highlights the importance of considering nutritional status and overall metabolic health in the management of depression.

The diagnostic performance of the combined biochemical markers was evaluated using ROC curve analysis, which demonstrated a good discriminative ability with an AUC of 0.801. This suggests that these markers, when used together, could effectively differentiate individuals with MDD from healthy controls. The sensitivity and specificity of 0.783 and 0.715, respectively, indicate a balanced performance, making these markers potentially useful in clinical practice. The cut-off value of 0.417 provides a threshold that could be employed in screening and diagnostic protocols to improve the identification of MDD, especially in settings where traditional psychiatric assessments may be challenging.

Overall, the findings of this study contribute to a growing understanding of the biological underpinnings of MDD. The identification of these biochemical markers provides a foundation for developing more objective, accessible, and cost-effective diagnostic tools for depression. However, it is important to acknowledge the need for further research to validate these findings across different populations and to explore the integration of these markers into routine clinical practice. Future studies should also consider longitudinal designs to assess the predictive value of these markers over time and their response to treatment interventions.

These findings align with previous research conducted by Peng et al. (2016) in a Chinese population, suggesting that these biochemical markers may be robust indicators of MDD across different populations[4]. In the study by Peng et al. (2016), significant differences were observed between MDD patients and controls in several biochemical parameters, including urea nitrogen (UN),

creatinine (Cr), total bilirubin (Tbil), and HDL-C. The study found that these markers, when combined, provided a strong discriminatory power for identifying MDD patients, with an area under the curve (AUC) of 0.810. Similarly, our study found that FBG, SF, HDL-C, and TP were significantly associated with MDD, with the combination of these markers yielding an AUC of 0.801, indicating good diagnostic potential.

Both studies reported lower levels of UN and TP in MDD patients compared to controls, suggesting that these markers may reflect underlying metabolic disturbances commonly associated with depression. The reduction in UN and TP could be attributed to altered protein metabolism and reduced nutritional intake often seen in individuals with depression, as discussed by Peng et al. (2016). Moreover, the decreased creatinine levels observed in both studies could be related to muscle mass reduction and poor nutritional status, further supporting the notion of metabolic dysregulation in MDD[4].

Our study also observed elevated levels of FBG and SF in MDD patients, which is consistent with Peng et al.'s findings of higher FBG levels in depressed individuals. The association between elevated glucose levels and MDD may be linked to the role of oxidative stress and insulin resistance in the pathophysiology of depression. Peng et al. (2016) highlighted the potential role of oxidative stress in contributing to insulin resistance, which may exacerbate depressive symptoms[4]. The increase in SF, a marker of glycaemic control, further supports the link between glucose metabolism and MDD.

Interestingly, both studies reported higher HDL-C levels in MDD patients compared to controls, contrary to the traditional view that lower HDL-C is associated with poor cardiovascular health. This finding may reflect a complex interaction between lipid metabolism and depressive states, where elevated HDL-C could be a compensatory response to oxidative stress or inflammation. Peng et al. (2016) suggested that the increase in HDL-C might be related to alterations in lipid transport and metabolism in MDD patients.

The consistency between our findings and those of Peng et al. (2016) across different populations suggests that routine biochemical markers could serve as valuable tools for the early identification and management of MDD[4]. The use of combined markers, such as FBG, SF, HDL-C, and TP, may enhance the accuracy of MDD diagnosis, providing clinicians with objective data to complement clinical assessments.

Furthermore, these markers may offer insights into the metabolic and inflammatory processes underlying MDD, potentially guiding the development of targeted therapeutic strategies. For instance, interventions aimed at improving glucose metabolism or reducing oxidative stress could be beneficial for MDD patients with elevated FBG and SF levels.

Limitations and Future Directions

While our study corroborates the findings of Peng et al. (2016), it is important to acknowledge the limitations of cross-sectional designs, which preclude the establishment of causal relationships. Additionally, the sample size in our study was smaller than that of Peng et al., which may limit the generalizability of our findings. Future research should focus on longitudinal studies to explore the temporal relationship between biochemical markers and the onset or progression of MDD. Moreover, multicentre studies involving diverse populations are needed to validate the utility of these markers in different clinical settings.

Conclusion

This study highlights the significant role those routine biochemical markers such as fasting blood glucose (FBG), *fructosamine* (SF), high-density lipoprotein cholesterol (HDL-C), and total protein (TP) can play in the diagnosis and management of Major Depressive Disorder (MDD). Our findings demonstrate that these markers are independently associated with MDD and, when combined, provide good discriminative power for identifying individuals with the disorder. This suggests that routine biochemical tests, which are readily available and cost-effective, could be integrated into clinical practice to support the diagnosis and monitoring of MDD, particularly in settings where access to

advanced diagnostic tools is limited. The study's results also underline the importance of considering metabolic and nutritional factors in the management of depression. Elevated levels of FBG and SF point to the need for careful monitoring of glucose metabolism in patients with MDD, while the inverse relationship between TP and MDD highlights the potential impact of nutritional status on mental health.

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