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A case-control study of oxidative stress and endogenous antioxidants in major depressive disorder at a tertiary care hospital in Assam

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Abstract

Background: Major depressive disorder (MDD) is a leading cause of disability worldwide. Although its etiopathogenesis remains largely unknown, several studies suggest that major depression is characterized by decreased antioxidant status and increased oxidative stress. This study aims to estimate oxidative stress markers (MDA) and endogenous antioxidants (SOD, Nrf2, uric acid, and albumin) in patients with MDD, compare them with healthy controls, and evaluate the correlation between oxidative stress markers, antioxidant levels, and disease severity.

Methods: A hospital-based case-control study was conducted on 50 patients with MDD and 50 age- and sex-matched healthy controls over a period of one year at a tertiary care center in Assam. MDA, SOD, and Nrf2 levels were measured using ELISA kits. Uric acid and albumin were estimated using a double-beam UV spectrophotometer (Spectrascan UV-2600, Chemito).

Results: MDA levels were significantly increased ($p < 0.0001$), while SOD, Nrf2, uric acid, and albumin levels were significantly decreased ($p < 0.05$) in the test group compared to the control group. Furthermore, MDA levels were positively correlated with the severity of depression, whereas SOD, Nrf2, and uric acid levels decreased significantly with increasing severity.

Conclusion: Oxidative stress may play a key role in the pathophysiology of MDD, MDA, SOD, Nrf2, albumin, and uric acid could potentially serve as biomarkers for depression.

Keywords: malondialdehyde; superoxide dismutase; nuclear factor; major depressive disorder; albumin; uric acid; Assam

Introduction

Major depressive disorder (MDD) is a common mental illness affecting over 300 million people globally, with an annual prevalence rate of approximately 6% [1, 2]. It is projected to become the second most prevalent disease by 2030 [3].

Depression is multifactorial in origin, involving genetic, psychological, environmental, and neuroendocrinological components. Recent studies suggest a strong association between depression and inflammation [4], as well as neuroanatomical changes [1, 5–7]. One of the major contributing factors to these changes is oxidative stress [7–9]. The brain is particularly vulnerable to oxidative stress due to its high metabolic rate and relatively low antioxidant capacity [7, 10]. Consequently, oxidative stress has been implicated in several brain-related disorders, including Alzheimer's disease, schizophrenia, and MDD [8, 9, 11].

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Malondialdehyde (MDA), a byproduct of polyunsaturated fatty acid peroxidation, is elevated during oxidative stress [7]. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key regulator of the body's antioxidant response [12]. Nrf2 plays a critical role in inflammatory processes by reducing the production of free radicals and modulating the macrophage M1 phenotype [13]. It also regulates the expression of antioxidant response element (ARE) genes through its interaction with Keap1 (Kelch-like ECH-associated protein). In neurodegenerative disorders, stimulation of Nrf2 is considered a promising therapeutic strategy and an important target for drug discovery [14].

Additionally, the enzyme superoxide dismutase (SOD) serves as a major defense mechanism against oxidative stress [15, 16]. Non-enzymatic antioxidants such as uric acid and albumin are also found to be altered in patients with MDD. Several studies have reported decreased levels of these antioxidants in individuals with major depression .

The aim of this study was twofold. First, it sought to estimate the serum levels of malondialdehyde (MDA), nuclear factor erythroid 2-related factor 2 (Nrf2), superoxide dismutase (SOD), uric acid, and albumin in patients with major depressive disorder and compare these levels with those in healthy controls. Second, the study aimed to evaluate the correlation between the levels of MDA, Nrf2, SOD, uric acid, and albumin and the severity of major depressive disorder.

Materials and methods

This case–control study was conducted in the Department of Biochemistry in coordination with the Department of Psychiatry at Gauhati Medical College and Hospital from February 2024 to December 2024. The study protocol was approved by the Institutional Ethics Committee. A total of 100 subjects aged between 15 and 58 years were enrolled in the study. Among them, 50 were patients diagnosed with major depressive disorder (MDD), and 50 were age- and gender-matched healthy controls. All participants, including patients and controls, provided written informed consent after the nature and purpose of the study were explained to them.

The patients were selected from the Psychiatry OPD during their first visit. All patients that attended psychiatry OPD from the date of start of the study were screened once the diagnosis of depression was made, and were included in the study if inclusion and exclusive criteria were met and after obtaining written informed consent. This was continued till 50 patients were included in the study. Age and sex matched control person was selected from attendants, staff, student and colleagues of the researcher.

Sample Size: Sample size calculation was done based on Sample Size Formula for Comparing Means (Equal Group Size). MDA level is the key marker for this study and there are previous levels to refer to from a 2018 study done in Bangladesh [22]. For sample size calculation, power was considered at 95%, confidence interval at 95%, MDA level in patients at 4.49+-1.37, and controls at 2.87+-0.82 from the study mentioned above., the calculated sample size came at 13 in each group. However, as there are 4 parameters being tested, the calculated sample size was multiplied by 4 and rounded to 50 each for patient and control group. Online version of OpenEpi statistical package was used for the calculation.

Inclusion criteria: Patients were selected from individuals diagnosed with MDD at the Psychiatric Outpatient Department. The diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. All patients were assessed using the Hamilton Depression Rating Scale (HAM-D) [17], a widely used tool for determining the severity of depression. Severity was graded according to HAM-D scores as follows: mild (10–13), moderate (14–17), and severe (>17). Healthy controls were selected from volunteers matched with patients for age and gender. All participants provided written informed consent and completed a questionnaire detailing demographic data and medical history.

Exclusion criteria: Exclusion criteria included refusal to participate in the study, the presence of comorbid psychiatric disorders, and any medical illnesses such as endocrine, metabolic, neurological, or autoimmune diseases. Participants with infections, inflammatory reactions, or allergies within two weeks prior to blood sampling, as well as those taking antioxidant medications, were also excluded.

Sample collection and testing

A 5 ml venous blood sample was collected from each participant between 8:00 and 9:00 a.m. in a plain clot-activator vial. Participants were instructed to avoid physical exercise before sample collection. The blood samples were allowed to stand at room temperature for 30 minutes for clot retraction, after which they were centrifuged at 3000 rpm for 10 minutes. The separated serum was stored at −80°C until analysis (almost up to 60 days).

Serum levels of MDA and SOD were measured using the LS Bio ELISA Kit and the Bioligand Technologies SOD Assay ELISA Kit, respectively. Serum Nrf2 levels were determined using an ELISA kit from Invitrogen by Thermo Fisher Scientific. Albumin was measured using the Erba Albumin Kit, and uric acid was estimated using the Erba Uric Acid Kit with a double-beam UV spectrophotometer (Spectrascan UV-2600, Chemito).

Statistical analysis

All data were analyzed using the online statistical tool OpenEpi [18]. The *t*-test, ANOVA, and Chi-square tests were used for comparisons where appropriate. A p-value ≤ 0.05 was considered statistically significant.

Results

Table 1 shows the sociodemographic data of the patient and control groups. No statistically significant differences were observed between the groups in terms of age, gender, or marital status (p > 0.05).

Table 1: The demographic characteristics of patients and controls.

Characteristics	*Patient*	*Control*	*P value*
Age	44.56±4.86 years	42.92±4.88 years	0.98
Gender (Male)	12 (24%)	14 (28%)	0.82
Gender (Female)	38 (76%)	36 (72%)	
Marital status			
Single	3 (6%)	6 (12%)	0.79
Married	35(70%)	29 (58%)	
Divorced	8(16%)	10 (20%)	
Widowed	4 (8%)	5 (10%)	

Note: P value was calculated using students t-test for Age, and for the rest Chi-squared test was done.

Severity of depression according to the Hamilton depression rating scale was found as, with mild depression 24 (48%), moderate depression was 16 (32%) and severe depression was 10 (20%). The mean duration of illness in years was 5.38 and mean number of episodes of disease was 3.38.

Table 2 shows the comparison between the patient group and the control group with respect to MDA, SOD, Nrf2, uric acid, and albumin levels. MDA was significantly increased in the patient group (20.54 ± 1.61 pg/ml) compared to the control group (12.53 ± 0.59 pg/ml), with a p-value of <0.0001. In contrast, SOD, Nrf2, albumin, and uric acid levels were significantly decreased in the patient group compared to the control group (41.4 ± 14.83 µg/ml, 0.44 ± 0.13 pg/ml, 4.20 ± 0.291 g/dl, and 3.42 ± 1.39 mg/dl in the patient group vs. 132.14 ± 10.55 µg/ml, 1.10 ± 0.18 pg/ml, 4.39 ± 0.392 g/dl, and 5.11 ± 1.02 mg/dl in the control group, respectively), with a p-value of <0.05.

Table 2: Comparison of patient and control group regarding MDA (pg/ml), SOD(µg/ml), Nrf2 (pg/ml), albumin(g/dl) and uric acid (mg/dl).

Biomarker	*Patient group(n=50) (Mean±SD)*	*Control group (n=50) (Mean±SD)*	*P value*
MDA (pg/ml)	20.54±1.61	12.53±0.59	<0.0001
SOD (µg/ml)	41.4±14.83	132.14±10.55	0.02 (<0.05)
Nrf2 (pg/ml)	0.44±0.13	1.10±0.18	0.02 (<0.05)
Albumin (g/dl)	4.20±0.291	4.39±0.392	0.04 (<0.05)
Uric acid (mg/dl)	3.42±1.39	5.11±1.02	0.03 (<0.05)

Note: Students' t test is done for inferential statistics.

Table 3 shows the comparison among mild, moderate, and severe depression groups with respect to MDA, SOD, Nrf2, uric acid, and albumin levels. ANOVA was used to compare the groups. The MDA level was significantly increased across the severity grades of depression, with an F-value of 26.79 and a p-value of <0.0001. The SOD level decreased progressively with increasing severity of depression, and this difference was statistically significant (F = 87.35, d.f. = 49, p < 0.0001). Similarly, Nrf2 and uric acid levels also decreased significantly with increasing depression severity (F = 60.02, d.f. = 49, p < 0.0001; and F = 26.73, d.f. = 49, p < 0.0001, respectively). Although albumin levels decreased across the severity grades of depression, the difference was not statistically significant (p > 0.05).

Table 4 shows the correlation between MDA, SOD, Nrf2, uric acid, albumin, and selected variables (age, duration of illness, and number of episodes) in the patient group. There was a significant positive correlation between the duration of illness and MDA (r = 0.72), as well as between the number of episodes and MDA (r = 0.71). Additionally, there was a significant negative correlation between the duration of illness and SOD (r = −0.72), and between the number of episodes and SOD (r = −0.66). Nrf2 also showed a significant negative correlation with both the duration of illness (r = −0.71) and the number of episodes (r = −0.62). Uric acid and albumin showed no significant correlation with the duration of illness, number of episodes, or age. Table 4 shows correlation coefficient (r-value) in crosstab manner, with significance (p-value) inside bracket.

Table 3: Comparison between mild, moderate and severe depression regarding MDA(pg/ml), SOD(µg/ml), Nrf2(pg/ml), uric acid (mg/dl) and albumin (g/dl).

Biomarkers	*Mild MDD*	*Moderate MDD*	*Severe MDD*	*ANOVA statistics*
MDA (pg/ml)	19.43±1.23	21.13±1.09	22.29±0.75	F= 26.79 d.f = 49 P value <0.0001
SOD (µg/ml)	53.7±7.48	35.68±7.89	21±1.32	F= 87.35 d.f = 49 P value <0.0001
Nrf2 (pg/ml)	0.54±0.08	0.40±0.05	0.27±0.06	F= 60.02 d.f = 49 P value <0.0001
Uric acid (mg/dl)	4.43±1.22	2.79±0.73	2.04±0.20	F= 26.73 d.f = 49 P value <0.0001
Albumin (g/dl)	4.26±0.30	4.10±1.41	3.42±1.02	F= 3.06 d.f = 49 P value =0.06

Table 4: Correlation between MDA, SOD, Nrf2, uric acid, albumin and some variables (Age, duration of illness, and number of episodes) in patient group.

	Duration of illness	*No of episodes*	*Age*
MDA	0.72 (0.0001)	0.71(0.0001)	-0.31 (0.13)
Nrf2	-0.71(0.0001)	-0.62(0.0001)	-0.11(0.45)
SOD	-0.72(0.0001)	-0.66(0.0001)	-0.19 (0.19)
Uric acid	-0.18(0.21)	-0.01(0.94)	0.35(0.11)
Albumin	-0.04(0.78)	-0.12(0.41)	0.11(0.45)

Discussion

In recent years, inflammation and neurodegeneration have been recognized as crucial contributors to the pathogenesis of depression. Various types of biomarkers—such as those related to neurodegeneration, cytokines, and markers of oxidative stress—have been identified in depression, with their significance supported by findings from animal models [19]. The brain is particularly vulnerable to the harmful effects of reactive oxygen species (ROS) due to its high metabolic rate and limited antioxidant capacity. This underscores the role of free radicals in several neuropsychiatric disorders.

Free radicals contribute significantly to the pathophysiology of depression through multiple mechanisms, including tissue damage, inflammation, neurodegeneration, autoimmune responses triggered by cellular injury, and apoptosis [20]. In this study, we aimed to assess oxidative stress in patients with Major Depressive Disorder (MDD), along with evaluating the levels of key antioxidants. Malondialdehyde (MDA) was used as a biomarker of oxidative stress. Increased MDA levels have been observed in various depressive disorders and are associated with impairments in auditory-verbal working memory, visuospatial function, and both short-term and delayed declarative memory [7].

In our study, MDA levels were higher in patients with major depression compared to healthy controls ($p < 0.0001$). Moreover, there was a strong positive correlation between MDA levels and both the number of depressive episodes and the duration of illness ($r = 0.71$ and $r = 0.72$, respectively). These findings align with those of Bilici et al. [21], who reported significantly higher plasma MDA levels in depressed patients compared to controls (4.82 ± 1.3 µmol/L vs. 2.89 ± 1.1 µmol/L), along with positive correlations with the number of episodes and the duration of illness ($r = 0.28$, $p < 0.05$). Similarly, Bajpai et al. found significantly elevated MDA levels in 60 depressed patients compared to 40 controls (1.95 ± 1.04 mmol/L vs. 0.366 ± 0.175 mmol/L). Camkurt et al. also observed significantly higher MDA levels in patients with major depression than in controls.

Regarding superoxide dismutase (SOD), we found lower levels in patients with major depression compared to healthy controls ($p < 0.05$). SOD is a potent antioxidant enzyme that scavenges reactive oxygen species, thereby maintaining oxidative balance. Decreased SOD activity has been demonstrated in various animal models of depression [22]. Similarly, other studies have reported significantly reduced SOD levels in depressed patients compared to healthy individuals [23]. Camkurt et al. also reported significantly decreased SOD levels in depressed patients (143 µ/mg vs. 298.12 µ/mg, $p < 0.001$), which is consistent with our findings. Bajpai et al. found lower SOD levels in patients (0.123 ± 0.068 µg/ml) than in controls (0.177 ± 0.042 µg/ml).

With regard to nuclear factor erythroid 2–related factor 2 (Nrf2), our study found reduced levels in depressed patients compared to controls ($p < 0.05$). A recent study reported that Nrf2 expression in the dorsolateral prefrontal cortex of MDD patients was reduced by approximately 21% [24]. Gabriele Sani et al. also reported that Nrf2 levels are lower in depression and that antidepressant therapies—pharmacological or otherwise—can increase Nrf2 expression. Several studies support the role of Nrf2 in the treatment of depression, with the therapeutic effects of various antidepressants strongly linked to Nrf2 activation [25]. Collectively, these findings suggest that impaired Keap1–Nrf2 signaling plays a crucial role in the pathophysiology of mood disorders such as MDD and bipolar disorder [26].

Uric acid is a major contributor to the total radical-trapping antioxidant parameter (TRAP), accounting for 38–47% of the total capacity, compared to vitamin C (13–17%) and vitamin E (2–8%) [27]. In our study, uric acid and albumin levels were significantly lower in the patient group compared to the control group ($p = 0.03$ and $p = 0.04$, respectively). These findings are consistent with those reported by Choudhary et al., Maes et al [19]. The decreased levels may be attributed to the increased scavenging of free radicals by uric acid and albumin in the brain.

Oxidative stress across different severity levels of depression has been evaluated in only a limited number of studies. In our study, patients with severe depression had significantly higher MDA levels compared to those with mild depression ($F = 26.79$, d.f. = 49, $p < 0.0001$). This is consistent with the study by Rangaswamy and Swath. Similarly, SOD activity decreased significantly with increasing severity of depression ($F = 87.35$, d.f. = 49, $p < 0.0001$), aligning with findings by Kotan et al. [28], who reported a positive correlation between depression severity and reduced SOD activity. However, this contrasts with the findings of Bal et al. (2012) who studied 42 patients (37 women and 5 men) diagnosed with MDD and found no correlation between HAMD scores and SOD activity.

Our study also revealed lower Nrf2 levels across increasing severity grades of depression ($F = 60.02$, d.f. = 49, $p < 0.0001$), consistent with the study by Rawdin et al. [29], who reported changes in Nrf2 levels along the continuum of depressive symptom severity. Sarandol et al. also reported a positive correlation between symptom severity and reduced SOD activity.

Serum uric acid levels also decreased with increasing severity of depression ($F = 26.73$, d.f. = 49, $p < 0.0001$). Although albumin levels declined across severity grades, the change was not statistically significant ($F = 3.06$, d.f. = 49, $p = 0.06$).

Additionally, we observed a significant positive correlation between the duration of illness and the number of depressive episodes with elevated MDA levels ($r = 0.72$ and $r = 0.71$, respectively), and a strong negative correlation with reduced levels of SOD and Nrf2. These findings are in agreement with studies by Bilici et al. and Stefanescu and Ciobica (2012) .

Limitations of the study: This study was conducted at a tertiary care hospital in Assam and included a relatively small number of patients. As such, the findings may not fully represent the disease profile of the broader population and are insufficient to draw definitive conclusions. Larger, multicentric studies are needed to further elucidate the role of oxidative stress and endogenous antioxidants in major depressive disorder.

Conclusion

Based on our study, we conclude that oxidative stress may play a significant role in the pathophysiology of major depressive disorder (MDD), as evidenced by increased free radical production and concurrent antioxidant deficiency. Biomarkers such as MDA, SOD, Nrf2, albumin, and uric acid may serve as useful indicators of MDD. Their evaluation could contribute to a better understanding of the disease and potentially aid in the development of novel therapeutic strategies.

Conflicts of interest

Authors declare no conflicts of interest.

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