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BIOCHEMICAL MARKERS OF OXIDATIVE STRESS PATHWAYS IN MAJOR DEPRESSION

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Abstract

BACKGROUND: Depression affects 12% of people worldwide throughout the course of their lifetime. Depression is one of the most significant contributors among the 11% of Disability Adjusted Life Years caused by neuro-psychiatric illnesses. Despite so, there are up to 16 suicides per 100,000 people who suffer from depression. When depressed individuals are given the current standard medication therapy, which primarily targets 5-HT receptors, less than two thirds of them experience remission. Despite substantial research in this field, the current theories about major depression do not adequately explain the precise aetiology and character of depression. The pathophysiology of depression now appears to be heavily influenced by inflammation and neurodegeneration. Inflammation, autoimmune tissue damage, and persistent psychological stress all contribute to oxidative stress, which is a significant cause of serious depression.

AIM: The aim of this study was to know the association of free radicals and anti-oxidant status in subjects suffering from major depression.

MATERIAL AND METHOD: The Department of Biochemistry conducted this case-control study. The study comprised 60 major depressive disorder patients that were brand-new and drug-free, as determined by the consultant psychiatrist using the DSM IV. 30 healthy control volunteers who were matched for age and sex and were drawn from the public population made up the control group. None of the patients used or were dependent on alcohol, cigarettes, or any other substance. All of the healthy, non-diabetic, normotensive, tobacco- or alcohol-dependent control subjects included for the study also lacked any signs of acute or chronic infection.

RESULTS: The case population consisted of 50 patients, 20 of whom were male and 30 of whom were female. Among the 50 patients, 35 were from urban backgrounds and 15 from rural ones. Regarding marital status, there were 10 single people and 40 married people, of which 1 was a widow and 1 was divorced. Age and gender between depressed patients, first-degree relatives, and controls did not differ significantly. While the mean plasma levels of nitrite were lower in cases than in controls, this difference was not statistically significant, and the mean plasma levels of MDA were considerably greater in cases as compared to the control group. Despite the fact that patients had lower mean plasma ceruloplasmin levels than controls, these differences were statistically insignificant. Malondialdehyde and ascorbic acid were discovered to be connected on an inverse regression analysis after all parameters had been assessed for the regression analysis.

CONCLUSION: The pathophysiology of depression may involve oxidative stress. This indicates that oxidative stress is a well-recognized result and is evident in samples from a range of demographic groups. It is unknown how far this discovery may be applied to improve clinical outcomes. The current study was cross-sectional; the patient group's biochemical parameter values following treatment could have improved the study's usefulness.

KEYWORDS: Malondialdehyde, Major depression, Nitric oxide, Reactive Oxygen Species, Super oxide dismutase; Nitric oxide and Oxidative stress

Introduction

Depression is a depressed state that affects a person's emotions, thoughts, and behaviours. It is thought to be a high-risk factor for suicide and is the most prevalent psychiatric condition.[1] Investigating this pathway offers a chance to create novel depression therapy approaches.[2] According to the World Health Organization, depression affects millions of people and is the main cause of disability worldwide.[3] Depression's psychopathological mechanisms, however, are not well understood. Many studies have recently suggested that oxidative stress may be important.[4] According to some research, depressed patients had abnormally high levels of oxidative products in their urine, cerebral fluid, postmortem brains, mononuclear cells, peripheral blood red blood cells (RBC), and RBCs.[5,6] Peripheral blood antioxidant system disruption has also been documented.[7] There have been reports of autoimmune reactions against neoepitopes caused by oxidative damage to fatty acid and protein membranes.[8] Magnetic resonance spectroscopy revealed lower glutathione (GSH) levels and a negative correlation between the severity of anhedonia and occipital GSH levels (MRS).[9]

An ongoing imbalance between oxidation and anti-oxidation is referred to as oxidative stress, and it can harm cellular macromolecules.[10] Reactive oxygen species (ROS) and reactive nitrogen species make up the free radicals (RNS). The RNS is made up of nitric oxide (NO), nitrogen dioxide, and peroxynitrite, while the primary ROS include superoxide anion, hydroxy radical, and hydrogen peroxide. Often, nitrite is employed as a measure of NO activity. Curiously, the brain's high concentration of unsaturated fatty acids, high oxygen consumption per unit weight, high concentration of essential components of lipid peroxidation (LP), and dearth of antioxidant defence systems appear to make it more vulnerable to ROS/RNS.[11]

Depression is associated with elevated levels of reactive oxygen species (ROS), depleted levels of antioxidants like vitamin E, zinc, coenzyme Q10, and glutathione, and exhausted antioxidant enzyme activity like xanthine oxidase and superoxide dismutase.[12,13] Investigations on post-mortem brain samples have also revealed elevated ROS, such as superoxide and peroxide, as well as altered antioxidant defence levels in depressed patients.[14,15] Clinical experiments have so demonstrated that antioxidant therapy reduces psychiatric symptoms. More than 300 million individuals worldwide experience depression, according to the WHO. The WHO found that depression and other disorders had a close relationship. It raises the danger of diabetes mellitus, heart disease, and substance use disorders. At worst, it causes suicide, which results in 800,000 deaths annually.[16] In general, depression causes impairment. According to projections, major depression will overtake chronic pain as the second greatest cause of disability worldwide.[17]

An elevated amount of malondialdehyde (MDA) and the polyunsaturated fatty acid peroxidation by-product are indicators of oxidative stress damage.[18] The primary regulator of inducible antioxidant responses is nuclear factor erythroid 2-related factor 2 (Nrf2).[19] By reducing ROS production, altering the macrophage M1 phenotype, controlling the expression of the antioxidant response element (ARE) gene The Keap1, and attracting inflammatory cells, Nrf2 activation is essential for the development of inflammation.[20,21] Free Nrf2 moves into the nucleus during oxidative stress and binds to ARE genes such heme oxygenase-1, blocking the NF-KB pathway and causing the downregulation of pro-inflammatory cytokines.[22] In order to assess the degree of differences in oxidative stress markers between depressed patients and control subjects in various sample sources, this study will examine

studies of each oxidative stress marker in depression.

MATERIAL AND METHODS

The Department of Biochemistry conducted this case-control study. The study comprised 60 major depressive disorder patients that were brand-new and drug-free, as determined by the consultant psychiatrist using the DSM IV. Thirty healthy control volunteers who were matched for age and sex and were drawn from the public population made up the control group. None of the patients used or were dependent on alcohol, cigarettes, or any other substance. Individuals over the age of 50 were excluded from the study. All of the healthy, non-diabetic, normotensive, tobacco- or alcohol-dependent control subjects included for the study also lacked any signs of acute or chronic infection. Every study subject gave their written consent in accordance with the institutional ethics committee's rules and regulations. Patients who agreed to participate in the trial with their guardians' permission provided signed informed consent.

Specimen Collection

Blood samples from the patients and controls were obtained after receiving written informed consent. Using the utmost aseptic care, 5 ml of blood were venipuncture from a peripheral vein using a disposable syringe. The 5ml of blood that had been thusly obtained was placed in a clean, dry glass tube and let to stand for 30 minutes at room temperature to allow the clot to retract. The serum was separated by centrifuging this at 3000 rpm for 10 minutes. For analysis, the serum samples were kept in the refrigerator at -800 C. The sample was carefully guarded from hemolysis.

Inclusion criteria

Studies were included in our analyses if they met the following criteria:

- ✓ Cross-sectional studies measuring oxidative stress markers in serum, plasma, or RBC of depressed patients;
- ✓ Studies that assessed oxidative stress markers in patients with an acute exacerbation of depression at baseline and again after antidepressant therapy;
- ✓ Inclusion of a depressed group as diagnosed by standard recognized criteria or screened with a standardized instrument
- ✓ Studies that provided subject numbers, means, and standard deviations. Through our search strategy, we decided to focus on TAC, certain enzymatic antioxidants, non-enzymatic antioxidants, and free radicals.

Exclusion criteria

Studies were excluded from our analyses if they met the following criteria:

- ✓ Reviews, conference abstracts, editorials, and letters
- ✓ Animal studies
- ✓ studies that reported on depressive symptoms in the context of other neuropsychiatric disorders or medical illnesses
- ✓ Dual publications

Estimation of serum analytes

- ➢ **Malondialdehyde:**

Malondialdehyde was estimated by the thiobarbituric acid (TBA) test. MDA reacts with TBA to generate a pink-colored product. In an acid solution, the product absorbs light at 53 nm and is extracted into organic solvents such as butanol.[23]

- ➢ **Nitrite:**

Determination of the nitrite was carried out by the method described by Griess.[24] In this method, a magenta-colored azo product is formed due to the diazotization of NO radical which can be measured at 540 nm.

- ➢ **Ascorbic acid:**

Ascorbic acid was measured by a method described by Roe JH et al., Ascorbic acid is oxidized by the copper to form dehydroascorbic acid and diketogulonic acid. These products form the derivative bis-2, 4-dinitrophenylhydrazine when treated with 2, 4-dinitrophenylhydrazine. This compound undergoes a rearrangement to form a product that can be measured at 520 nm.[25]

- ➢ **Superoxide dismutase (SOD):**

Superoxide Dismutase (SOD) was estimated by the pyrogallol auto-oxidation method described by Marklund and Marklund in 1974.[26]

➢ **Ceruloplasmin:**

Ceruloplasmin was measured by its oxidase activity. Ceruloplasmin catalyzes the oxidation of a dye p-phenylene diamine to a violet product, the absorbance of which is measured at 546nm.[27]

STATISTICAL ANALYSIS

Statistical analysis between group 1 (controls) and group 2 (patients) was performed by the Independent 't-test using the statistical packages (SPSS Software Windows Version 16.0). The data were expressed as mean ± SD. $p < 0.05$ was considered significant.

RESULT: -

The case population consisted of 50 patients, 20 of whom were male and 30 of whom were female. Among the 50 patients, 35 were from urban backgrounds and 15 from rural ones. Regarding marital status, there were 10 single people and 40 married people, of which 1 was a widow and 1 was divorced.

Table 1: Demographic profile of depressive patients, their first-degree relatives, and healthy controls.

	Control Patient	Case Patient	P Value
Number of patients	30	50	
Age, Years	24.21 ± 0.80	28.22 ± 1.73	P < 0.0001
FBS, mg/dL	75.23 ± 1.1	79.05 ± 1.66	P < 0.0001
Cholesterol, mg/dL	105.3 ± 1.2	114.6 ± 2.0	P < 0.0001
Total Bilirubin, mg/dL	0.56 ± 0.02	0.52 ± 0.02	P < 0.0001
ALP, U/L	102.5 ± 6.5	127 ± 8.1	P < 0.0001
SGPT, U/L	28.19 ± 1.45	26.21 ± 1.86	P < 0.0001
TLC	6449 ± 190.4	6694 ± 196.3	P < 0.0001

There were significant differences in FBS, Cholesterol, ALP and TLC in Depressed patient as compare to the control group. We also observed Total Bilirubin and SGPT were Significantly decreased in Depressed patients.

Table 2: Status of oxidants and antioxidants in cases and controls

Parameters	Cases (n=50)	Control (n=30)	P Value
Ceruloplasmin (mg/dL)	5.17 ± 2.3	6.02 ± 4.5	P = 0.2673
Ascorbic acid (mg/mL)	0.34 ± 0.12	0.63 ± 0.38	P < 0.0001
SOD (µg/mL)	0.12 ± 0.06	0.17 ± 0.03	P = 0.0001
MDA (mmol/L)	1.89 ± 1.02	0.36 ± 0.17	P < 0.0001
Nitrite (mmol/L)	19.11 ± 10.06	23.16 ± 5.62	P = 0.0467

While the mean plasma levels of nitrite were lower in cases than in controls, this difference was not statistically significant, and the mean plasma levels of MDA were significantly higher in cases as compared to the control group. SOD and ascorbic acid mean plasma concentrations were significantly lower in patients compared to controls. Despite the fact that patients had lower mean plasma ceruloplasmin levels than controls, these differences were statistically insignificant. Malondialdehyde and ascorbic acid were discovered to be connected on an inverse regression analysis after all parameters had been assessed for the regression analysis.

DISCUSSION

In addition to determining the antioxidant level in these people, our study sought to identify oxidative stress in subjects with significant depression. Normal controls that were age and sex matched were used for the comparison. There were 50 participants in the experimental group and 30 in the control group. The majority of the participants were adults in their 20s and 30s. The bulk of the individuals were married and from rural areas, and the groups were evenly split by gender.

Zalar et al2018[28] have shown that the genetic makeup of MDD patients with a positive family

history of depression is different from sporadic cases. The current study showed elevated ROS/RNS levels in the PMNs of MDD patients using a robust and reliable flow cytometry technology. Notably, a study by Frank et al. demonstrated increased ROS production by depressive patients' monocytes and connected their function with inflammation.[29] A favourable link between oxidative stress and the severity of depression has been documented, but most studies to date have only examined oxidative stress in depression patients.

Using 30 depressive patients and 30 healthy controls, **Billici et al.**[30] discovered that plasma MDA was considerably greater in depressed patients than in healthy controls. The frequency of episodes and length of the disease were both positively correlated with its plasma level, they also discovered. **Bajpai et al.2014**[31] examined the MDA level in 60 depressed patients and 40 controls and found that its level was significantly higher in patients than in controls.

Similarly, **Camkurt et al.2016**[32] found that the MDA level was significantly higher in patients with major depression than in controls with medians at 4.04 nmol/mg and 1.64 nmol/mg, respectively. They also looked at SOD, which was shown to be considerably lower in depressive patients than controls (means of 143 /mg and 298.12/mg, respectively, p 0.001); this is consistent with our study, in which the patient group's SOD level was lower than the control group. **Bajpai et al.2014**[31] found that MDA was higher in patients than the controls and SOD were lower in patients. **Rangaswamy and Swath2014** [33] found that there was a moderate positive correlation between MDA levels and clinical severity of depression as measured by a 21-item Hamilton rating scale for depression score which was found to be statistically significant, and the study of **Kotan et al.2011**[34] who found that there was a positive correlation between the severity of depressive symptoms and SOD activity. This was contrary to **Bal et al. 2012**[35] who studied 42 patients (37 women, and 5 men) diagnosed with MDD and no correlation was found between HAMD scores and MDA in the patient group. Furthermore, our study revealed significantly lower levels of SOD and Nrf2 in patients with moderate depression and mild depression, respectively, compared to the control group. This was consistent with the study of **Rawdin et al.2013**[36] who found that Nrf2 did differ along the continuum of depressive symptom severity across groups.

Nitritide levels and serious depression have also been researched.[37] In this study, it was predicted that lower nitrite levels may indicate that depressed patients' central nervous systems produce less nitric oxide, which may further contribute to the cardiovascular dysfunction that is frequently associated with severe depressive illness. A study by **Srivastava et al.2002**[38], revealed that nitrite content in the depressive subject decreases more than in normal one. Ceruloplasmin is an oxidase that contains copper. In the face of oxidative stress, it serves as a protective agent. Its status changes as a result of the sick state.[39] Although the function of ceruloplasmin in depression has not yet been determined, depression is not a common presentation in disorders when ceruloplasmin levels are low. Ceruloplasmin also functions as an antioxidant. Ceruloplasmin was shown to be lowered in our study, however it was not significantly so. This may be a result of using this antioxidant as oxidative stress has increased.[40]

Increased oxidative stress results from oxidative damage. The many antioxidant systems (ascorbic acid, vitamin E, SOD, and others) keep the increasing oxidative stress in check, and varied uncontrolled disease situations change the antioxidant status.[41] It is generally known that the antioxidant ascorbic acid negatively correlates with serious depression.[42] Ascorbic acid has been demonstrated to be beneficial in the mouse model of depression even in the current situation.[43] The use of ascorbic acid as a therapy adjuvant to fluoxetine has been proven to be successful in a study conducted in the pediatric age range.[44]

SOD is a strong indicator of oxidative stress. It serves as a scavenger for reactive oxygen species, removing them while preserving oxidative valence.[45] Its activity altered the number of diseases.[46] SOD activity was found to be decreased in different depressive animal

model.[47] **Rybka et al.2013**[48] reported low levels of SOD in the cases of major depression as compared to healthy controls but this was not significant.

CONCLUSION:

The pathophysiology of depression may involve oxidative stress. This indicates that oxidative stress is a well-recognized result and is evident in samples from a range of demographic groups. It is unknown how far this discovery may be applied to improve clinical outcomes. The current study was cross-sectional; the patient group's biochemical parameter values following treatment could have improved the study's usefulness. Our findings show that oxidative stress can affect MDD because free radicals are produced when there is a lack in antioxidants. This helps us understand the pathophysiology of depression and allows us to create novel therapeutic approaches.

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