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Disrupted Oxidative-Antioxidant Balance in Schizophrenia: A Case-Control Study Evaluating Serum Malondialdehyde and Plasma Superoxide Dismutase

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ABSTRACT

Background: Schizophrenia is a chronic neuropsychiatric disorder in which oxidative stress has been implicated as a key pathogenic mechanism. Imbalance between free radical generation and antioxidant defense may contribute to neuronal damage. This study aimed to evaluate oxidative stress and antioxidant status in schizophrenia by estimating serum malondialdehyde (MDA) and plasma superoxide dismutase (SOD) respectively, and to examine their interrelationship.

Methods: This analytical case–control study included 50 participants aged 18–40 years, comprising 25 patients with schizophrenia (diagnosed according to ICD-10 criteria) and 25 age- and sex-matched healthy controls. Serum MDA levels were estimated using the thiobarbituric acid reactive substances method, while plasma SOD activity was measured spectrophotometrically using the PMS–NBT method. Data were analyzed using independent samples Student's t-test and Pearson's correlation. A p-value <0.05 was considered statistically significant.

Results: Mean serum MDA levels were significantly higher in cases compared to controls (5.61 ± 0.36 vs 2.84 ± 0.61 nmol/mL; $p < 0.001$). Plasma SOD activity did not differ significantly between cases and controls (9.40 ± 1.62 vs 9.04 ± 1.87 U/mL; $p = 0.470$). Pearson's correlation analysis revealed no significant association between MDA and SOD in cases ($r = 0.058$, $p = 0.784$), whereas a moderate positive correlation was observed in controls ($r = 0.597$, $p = 0.002$).

Conclusion: The findings indicate increased lipid peroxidation in schizophrenia, reflecting enhanced oxidative stress, without a proportional antioxidant response. The absence of correlation between MDA and SOD in patients suggests disrupted oxidative–antioxidant balance. These results support the role of oxidative stress in the pathophysiology of schizophrenia and

highlight the potential relevance of redox biomarkers in future research.

Keywords: Schizophrenia; Oxidative Stress; Malondialdehyde; Superoxide Dismutase; Lipid Peroxidation; Antioxidants

INTRODUCTION

Schizophrenia is a heterogeneous psychotic disorder characterized by perturbations of thought, language, perception, social activity, affect and volition. The disorder is present in 0.85% of individuals worldwide, with a lifetime prevalence of ~1 to 1.5%. The syndrome commonly begins in late adolescence and persists throughout life, progressing from social withdrawal, perceptual and motor distortions to a state of chronic delusions and hallucinations.[1]

Along with other defects, metabolic defects that affect brain structure and function have been contemplated in Schizophrenia for more than 100 years. Both increased free radical-mediated lipid peroxidation and impaired antioxidant defense system can affect brain cell.[2] There has been abundant evidence that free-radical mediated oxidative-stress are the causes of membrane pathology in the Central Nervous system (CNS) and may play a role in the pathogenesis of neuropsychiatric disorders including Schizophrenia.[3]

Free radicals can be defined as chemical species possessing an unpaired electron in the outermost orbit. Energy created by this unstable configuration is released through reactions with adjacent molecules, such as inorganic or organic chemicals-proteins, nucleic acids, lipids, carbohydrates-particularly with key molecules in membranes and genes/DNA. Moreover, free radicals initiate autocatalytic reactions, whereby molecules with which they react are themselves converted into free radicals to propagate the chain of damage.[4]

Several powerful oxidants are produced during the course of reduction-oxidation reactions that occur during normal metabolic processes. These include Superoxide anion radicals ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), peroxyl radicals (ROO^-) and reactions capable of generating potential Reactive Oxygen Species (ROS) and are referred to as pro-oxidants. On the other hand, compounds and reactions disposing off these species, scavenging them, suppressing their formation, or opposing their actions are termed as antioxidants and include compounds such as NADPH, Glutathione Peroxidase (GSHPx), Superoxide dismutases (SOD), ascorbic acid and vitamin E. [5]

However, this balance can be shifted towards pro-oxidants when production of ROS (e.g. excess lipid peroxidation) is increased greatly or when levels of antioxidants are diminished (e.g. due to inactivation of radical scavenging enzymes).[5] An imbalance between free-radical generating and radical scavenging system result in oxidative stress, resulting in cell injury in many pathological conditions including neurodegenerative diseases like Schizophrenia. [4,6,7]

The brain and nervous system are particularly prone to free-radical damage since it is highly oxygenated and brain in cell membrane contains more than 66% phospholipids, which are rich in polyunsaturated fatty acids (PUFAs).[2] Areas of human brain are very rich in transitional metals and iron, which plays a role in generating free-radical species. [6,8] A growing body of evidence suggests that peripheral activity of antioxidant enzymes and lipid peroxidation are abnormal in schizophrenic subjects. [9]

It is well established that oxidative stress within the CNS is reflected in the peripheral blood (serum, plasma, blood cells). It is possible to infer the nature of pathological changes in the tissues of the body by measuring the activities of certain enzymes and breakdown products in diseases conditions. [8-10]

Lipid peroxidation reflects the interaction between molecular O_2 and PUFA leading to the oxidative deterioration of the later producing lipid breakdown products. An established marker of oxidative stress is

Monodialdehyde (MDA), a major reactive aldehyde. [10]

Superoxide dismutase (SOD) is a family of metalloenzymes protecting against the deleterious effects of superoxides. Superoxide dismutase is an important indicator of antioxidant status of the body. [5,11]

Since neuronal oxidative injury processes and underlying dynamic molecules regulatory mechanism are reflected in peripheral blood, [8] an effort has been made to investigate the serum MDA level, as an indicator of lipid peroxidation and SOD activity in Plasma as an assay of antioxidant enzyme in Schizophrenic patients and compare with age and sex matched healthy control group.

The objectives of this study are as follows:

1. To measure serum malondialdehyde (MDA) levels, a marker of lipid peroxidation, patients with schizophrenia and compare them with age- and sex-matched controls.
2. To determine plasma superoxide dismutase (SOD) activity, an indicator of antioxidant status, in patients with schizophrenia and compare it with that of matched controls.

MATERIALS & METHODS

Study Design: Analytical case–control study.

Study Setting and timeline:

The hospital-based study was conducted in in collaboration with several departments in a tertiary care hospital in Eastern India.

Study Population and size: The study population (total 50) was divided into two groups:

Group I: Cases (n = 25)

Selection of Cases:

The case group comprised 25 patients diagnosed with schizophrenia attending the Psychiatry Outpatient Department.

Inclusion Criteria:

1. Diagnosed with schizophrenia according to the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria.[12]
2. In the phase of acute clinical impairment.
3. Age between 18–40 years.
4. Not receiving antipsychotic medications at the time of sample collection.
5. Free from other psychiatric disorders.
6. Normal nutritional habits.
7. No history of vitamin or antioxidant supplementation during the previous one month.

Exclusion Criteria:

1. Presence of other neuropsychiatric disorders.
2. Current antioxidant or vitamin supplementation.
3. Chronic systemic illness.

Sampling technique:

From the eligible patients, 25 cases were selected by simple random sampling.

Group II: Controls (n = 25): The control group comprised 25 age- and sex-matched apparently healthy individuals.

Selection of Controls:

Controls were selected from individuals attending the Thyroid Clinic in the Department of Biochemistry for Thyroid Function Tests and diagnosed as *euthyroid* based on normal serum T3, T4, and TSH levels.

Inclusion Criteria:

1. No history of schizophrenia or other neuropsychiatric disorders.
2. Euthyroid status confirmed biochemically.
3. Normal nutritional habits.
4. No vitamin or antioxidant supplementation during the previous one month.

Exclusion Criteria:

1. Any psychiatric or neurological illness.
2. Thyroid dysfunction.
3. Chronic systemic illness.

Methods of data collection:

All data collected during the study were systematically recorded in a predesigned and pretested case record form. Each person was assigned a unique Identification Number during their enrollment. All information were collected and analyzed against the number, and nothing was attributed by name, to keep their identity secret.

Sample Collection and Processing:

1. Approximately 5–6 mL of venous blood was collected under aseptic precautions.
2. Blood was divided into two vials:
3. One vial containing EDTA (for plasma separation).
4. One plain vial (without anticoagulant) for serum separation.
5. EDTA blood was centrifuged at 3000 × g for 10 minutes. The supernatant plasma was separated and used for the estimation of plasma Superoxide Dismutase (SOD) activity.
6. Blood in the plain vial was allowed to clot. Serum was separated after centrifugation and used for estimation of serum Malondialdehyde (MDA).

Biochemical Parameters Assessed:

1. **Assessment of Lipid Peroxidation** - Estimation of **Serum Malondialdehyde (MDA)**
   Serum MDA, an end product of lipid peroxidation, was estimated spectrophotometrically using the Thiobarbituric Acid (TBA) reaction method. [13]
2. **Assessment of Antioxidant Status:** Estimation of **Superoxide Dismutase (SOD)**
   Plasma SOD activity was estimated spectrophotometrically by the method based on chromogen production using phenazine methosulphate (PMS), nitroblue tetrazolium (NBT) and NADH in presence of SOD enzyme. [14]

Ethical considerations:

Participation in the study was voluntary and confidential. Participants had the option to decline to answer specific questions, undergo physical examination, give blood samples or withdraw from the study at any time if they do not wish to participate. Confidentiality was maintained in the processes of collection, management and analysis of data.

Clearance from the 'Institutional Ethics Committee' was taken prior to the study. All necessary ethics protocols were maintained during the conduction of the study.

Informed and written consent was obtained from the participants or guardians after explaining the objectives and procedures of the study before they were enrolled in the study.

Statistical Analysis

The data quality and validity of the measurements was ensured. After cleaning the data, appropriate statistical tests were used. Analysis was done using Statistical Program for Social Sciences (SPSS) software. Continuous variables (Serum MDA, Plasma SOD) were expressed as Mean ± Standard Deviation (SD). Categorical variables (sex distribution) were expressed as frequency and percentage.

Prior to analysis, the distribution of continuous variables was assessed for normality using the Shapiro–Wilk test. As the data were found to be normally distributed ($p > 0.05$), parametric tests were applied. Comparison between cases and controls was performed using the independent samples Student's t-test. Equality of variances was assessed using Levene's test. All results were considered as statistically significant at $p < 0.05$ and highly significant at $P < 0.01$ (both two-tailed).

RESULT

A total of 50 subjects belonging to age group 18 to 40 years were included in the present study. Among them were 25 cases (15 males and 10 females) and 25 age and sex matched controls.

Normality testing using the Shapiro–Wilk test demonstrated normal distribution of serum MDA concentration and plasma SOD activity in both groups ($p > 0.05$). Therefore, parametric tests were applied for intergroup comparison.

The mean serum MDA concentration in cases (5.61 ± 0.36 nmol/mL) was significantly higher than in controls (2.84 ± 0.61 nmol/mL). Independent samples t-test (equal variances not assumed) showed a very highly significant difference ($t = 19.73$, $df = 38.75$, $p < 0.001$).

The mean plasma SOD activity in cases was 9.40 ± 1.62 units compared to 9.04 ± 1.87 units in controls. Independent samples t-test revealed that the difference was not statistically significant ($t = 0.728$, $df = 48$, $p = 0.470$) as shown in Table 1.

Table 1: Comparison of Serum MDA Concentration and Plasma SOD Activity between Cases and Controls

Parameter	Group	N	Mean ± SD	t-value	p-value
Serum MDA Concentration (mmol/L)	Cases	25	5.61 ± 0.36	19.73	<0.001
	Controls	25	2.84 ± 0.61		
Plasma SOD Activity (U/ml)	Cases	25	9.40 ± 1.62	0.728	0.47
	Controls	25	9.04 ± 1.87		

Pearson's correlation analysis showed a very weak positive correlation between serum MDA concentration and plasma SOD activity in cases ($r = 0.058$, $p = 0.784$), which was not statistically significant. The coefficient of determination ($R^2 = 0.003$) indicates that only 0.3% of the variability in SOD activity could be explained by MDA concentration (Figure 1).

There is evidence of moderate positive correlation between serum MDA concentration and plasma SOD activity among controls ($r = 0.597$, $p = 0.002$), which was statistically highly significant. The coefficient of determination ($R^2 = 0.356$) indicates that 35.6% of the variability in SOD activity could be explained by MDA concentration (Figure 1).

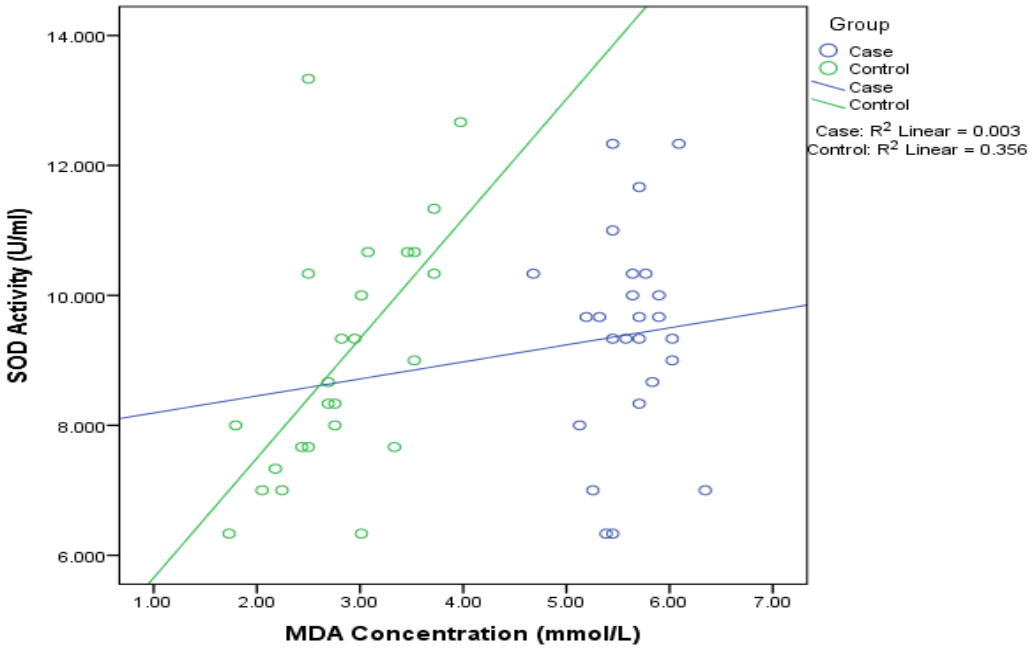

Figure 1: Combined scatter plot showing the correlation between serum MDA concentration and plasma SOD activity among cases and controls.

A statistically significant moderate positive correlation was observed in controls ($R^2 = 0.356$), whereas no significant correlation was observed in cases ($R^2 = 0.003$).

DISCUSSION

The present case–control study evaluated oxidative stress status in patients with schizophrenia by estimating serum malondialdehyde (MDA) concentration and plasma superoxide dismutase (SOD) activity. The findings demonstrated significantly elevated MDA levels in cases compared to controls, while SOD activity did not differ significantly. Importantly, a statistically significant moderate positive correlation between MDA and SOD was observed in controls but not in cases.

Oxidative Stress in Schizophrenia

In the present study, significantly elevated serum MDA levels in cases indicate enhanced lipid peroxidation. MDA, a stable end product of polyunsaturated fatty acid oxidation, reflects membrane damage and oxidative injury. [15] These findings are consistent with prior studies reporting increased lipid peroxidation in schizophrenia patients. [2,3,7,8,9-11] Elevated oxidative stress may disrupt neuronal membrane integrity, receptor function, and intracellular signaling pathways central to dopaminergic and glutamatergic transmission.

Contemporary knowledge in neurobiochemistry increasingly emphasizes the role of free radicals in the genesis of structural and functional changes of neuronal membrane that could be responsible for the beginning of aggravation of the basic disease. [3,8] The brain possesses high potential for initiation of free radical reactions, which, relative to other tissues, can cause more damage in brain due to high levels of PUFA, low glutathione, high free iron and existing intensive aerobic metabolism accompanied with oxygen radical production. [6,8]

ROS, by their activation of immune inflammatory reactions, increase monoamine catabolism (e.g., dopamine and nor-epinephrine), and abnormalities in lipid metabolism, cause an overproduction of ROS and lipid peroxidation products, reflected by increased serum MDA. [3] As indicated earlier, phospholipid, by their unique contents of EPUFA play a crucial role in brain and behavioral development. Actual metabolism in Schizophrenia may have implications for neurodevelopmental and behavioral deficits, related to abnormal neuronal circuitry and membrane receptor signal transduction by several neurotransmitters and neurotrophic factors. [16]

Antioxidant Defense and SOD Activity

Superoxide dismutase constitutes a primary enzymatic antioxidant defense against superoxide radicals.[10] Although MDA levels were elevated in cases, SOD activity did not differ significantly between groups. Previous literature demonstrates inconsistent findings regarding SOD levels in schizophrenia, with reports of increased, decreased, or unchanged activity. [11,14] Such variability may reflect differences in disease chronicity, treatment status, nutritional factors, and methodological heterogeneity.

The absence of a significant difference in SOD activity in our study may represent a compensatory but inadequate antioxidant response. Alternatively, enzymatic antioxidant levels alone may not fully capture systemic oxidative imbalance. A third possibility may be that the increased SOD enzymes due to compensatory mechanisms were consumed in the destruction of increased peroxidation products produced to keep the balance, so the increased SOD activity is not reflected in plasma. [17,18]

Disrupted Oxidative–Antioxidant Coupling

A key finding of this study is the differential correlation pattern between MDA and SOD across groups. In controls, a moderate positive and statistically significant correlation was observed ($R^2 = 0.356$), suggesting a coordinated physiological response whereby antioxidant activity increases in proportion to oxidative stress. Approximately 35.6% of the variability in

SOD activity was explained by MDA levels in healthy individuals.

In contrast, no significant correlation was observed in cases. The loss of this association suggests impaired regulatory coupling between oxidative stress and antioxidant defense in schizophrenia. This dysregulation may reflect defective adaptive responses to oxidative burden, potentially contributing to neuronal vulnerability and disease progression.[19]

These findings align with the hypothesis that schizophrenia involves not only increased oxidative stress but also impaired redox homeostasis that led to increased neuronal membrane damage.

CONCLUSION

The present study demonstrates significantly increased lipid peroxidation in patients with schizophrenia, indicating enhanced oxidative stress. Although plasma superoxide dismutase (SOD) activity did not differ significantly, the absence of correlation between serum malondialdehyde (MDA) and SOD in cases suggests disruption of normal oxidative–antioxidant homeostasis, unlike the coordinated response observed in controls.

These findings support the role of oxidative imbalance in the pathophysiology of schizophrenia, possibly contributing to neuronal membrane damage and altered cellular signaling. The results also emphasize that evaluating the interaction between oxidative and antioxidant systems may be more informative than assessing individual markers alone.

Overall, oxidative stress biomarkers may serve as valuable tools in schizophrenia research, while antioxidant-based adjunctive therapies may offer potential clinical benefits, warranting further study.

Declaration by Authors

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