





## RESEARCH ARTICLE

# Effect of antioxidant, malondialdehyde, macro-mineral, and trace element serum concentrations in Bangladeshi patients with schizophrenia: A case-control study

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**Abstract**

**Background:** Schizophrenia (SCZ) is an incurable neuropsychiatric disorder generally described by impaired social behavior and altered recognition of reality. For the first time, this study explored serum levels of antioxidants (vitamin A, E, and C), malondialdehyde (MDA), macro-minerals (calcium, potassium, and sodium), and trace elements (zinc, iron, and selenium) in Bangladeshi patients with SCZ and thereby, discovering any pathophysiological correlation.

**Methods:** This case-controlled study evaluated 63 patients with SCZ as cases and 63 healthy individuals as controls. Vitamin A and E levels were defined by RP-HPLC. MDA and vitamin C levels were measured by using UV spectrophotometry, and macro and trace elements by atomic absorption spectroscopy.

**Results:** This study found significantly ( $P \leq 0.05$ ) elevated MDA levels and decreased levels of antioxidants—vitamin A, C, and E and significantly ( $P \leq 0.05$ ) diminished levels of macro and trace elements in cases in contrast to the controls. Serum levels of zinc (Zn), selenium (Se), iron (Fe), potassium (K), calcium (Ca), and sodium (Na) were determined to be  $0.33 \pm 0.008$ ,  $0.0252 \pm 0.00060$ ,  $0.24 \pm 0.01$ ,  $64.18 \pm 2.72$ ,  $36.88 \pm 2.56$ , and  $2657.5 \pm 53.32$  mg/L, respectively, in cases, whereas  $0.79 \pm 0.03$ ,  $0.0650 \pm 0.00355$ ,  $0.78 \pm 0.03$ ,  $168.01 \pm 2.85$ ,  $86.43 \pm 2.55$ , and  $3200.8 \pm 29.96$  mg/L, respectively, were determined in controls. Pearson's correlation analysis revealed a negative correlation between Zn and Na, Zn and K, Zn and Ca, Zn and Fe, Zn and Se, Fe and Na, and Fe and Se in patients.

**Conclusions:** The findings connect that the pathogenesis of SCZ may have a correlation with altered levels of antioxidants, MDA, macro-minerals, and trace elements.

**KEYWORDS**

antioxidant, lipid peroxidation, macro-minerals, schizophrenia, trace element

## 1 | INTRODUCTION

Schizophrenia (SCZ) can be a severely debilitating psychiatric disorder.<sup>1</sup> Symptoms can be classified into three categories, such as positive (eg, hallucinations, delusions), negative (eg, lack of motivation, deficiencies in social function), and cognitive deficiencies.<sup>2</sup> Primary signs and endophenotypic characteristics of cognitive deficits can guide psychotic illness and reveal in general peoples, even though symptoms are typically absent until early childhood.<sup>3</sup> The governing postulation for the cause of SCZ is that differences in several risk genes contributing to a discerning effect in brain advancement.<sup>4,5</sup> Although a diaphanous mechanism responsible for the pathogenesis of SCZ is obscure, oxidative stress as an outcome of abnormal oxidation-reduction rule became an enchanting supposition for describing the pathophysiology of SCZ.<sup>6</sup>

Oxidative stress falls out at what time antioxidant protective mechanism is unable to counterpoise and maintain endogenous reactive oxygen species (ROS) and reactive nitrogen species (RNS) produced from common oxidative reactions or pro-oxidant natural expressions.<sup>7</sup> The physiological experience can describe the relationship between oxidative stress and the disease's pathophysiology, generally called the "oxygen paradox".<sup>8</sup> Extreme ROS may have harmful effects and alter macromolecules like nucleic acids, proteins, and lipids.<sup>9,10</sup> Lipid peroxidation is an effect of ROS resulting in injury to the cell membrane plus cellular organelles.<sup>11-13</sup> Factual evidence says that schizophrenic patients show higher indexes of oxidative stress that may affect the deterioration manifested throughout the disease<sup>11</sup> and may be associated with cognitive deficits in these patients.<sup>14</sup> Modern studies implicated these mechanisms in managing brain pathology, raising the probability that distorted parameters of the basic phenomenon of oxidative stress can lead to the pathogenesis of SCZ and associated abnormalities.<sup>15-17</sup>

An intricate balance of trace elements is essential for maintaining physical and mental health, as they are required for various physiological and metabolic mechanisms in the human body. Their scarcity would cause numerous metabolic disorders, while elevated levels are toxic.<sup>18</sup> Elements such as Pb, Cd, and Al are incredibly harmful in hint quantities and have been suggested to be coupled with neurological abnormalities. In the peripheral and central nervous systems, they play influential roles and components in nervous tissue.<sup>19,20</sup> In-coordination in the optimum levels of these elements may badly affect biological processes and are coupled with many psychiatric diseases, including SCZ.<sup>21,22</sup> Se, Mn, Cu, Zn, Fe, and Na, K are known as essential trace elements and macro-minerals, which have been suggested in several abnormalities like neurological, psychiatric, and autoimmune disorders.<sup>23-25</sup> The observed alterations in the level of these elements seen in SCZ are attributed to brain elemental homeostasis oxidative stress caused by an increase in the brain's neurotransmitter activities, most especially dopamine and serotonin.<sup>26</sup> Zn plays a role like a neurotransmitter.<sup>27-30</sup> Besides, Fe overload has been suggested to be an unrecognized cause of psychiatric morbidity.<sup>27</sup> Se influences compounds with hormonal activity (and neurotransmitters) in the brain, and this is presumed to be the cause it affects moods in humans and behavior in animals.<sup>31</sup>

No research with serum samples with Bangladeshi schizophrenic patients is found to explore the serum lipid peroxidation, antioxidant, trace elements (Zn, Fe, and Se), and macro-minerals (Na, K, and Ca) level. Therefore, we aimed to find out if there is any correlation between the serum levels of malondialdehyde (MDA), antioxidant vitamins (A, E, C), Zn, Fe, Se, and Na, K, Ca, and the degree of the mental disorder like SCZ to postulate on the pathogenesis and prognosis of the disease.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

This study was conducted in the National Institute of Mental Health (NIMH), Sher-e-Bangla Nagar, Dhaka, from January to June 2018. Ethical permission (following the Declaration of Helsinki) has been received from the ethical committee of NIMH. It was recruited 63 patients (39 male and 24 female) as cases, and 63 healthy volunteers (35 male and 28 female) were selected as control subjects.

### 2.2 | Sample collection

The patients were chosen with a primary clinical diagnosis of SCZ by following the DSM-IV-TR classification criteria. A detailed history from patients and controls was taken with a predesigned questionnaire by regularly attending to the hospital. Both the sample and control groups were diagnosed by a physician who is specialized in psychiatry. All subjects and their guardians were informed deliberately about the purpose of the research work, and written consent was collected from every respondent before inclusion in this study. If the patient was unable to give consent, written consent was obtained from the relevant primary caregiver. The study was directed according to the Helsinki Principles Declaration. Healthy volunteers, who are about to match their age with SCZ patients, had no history of alcohol or smoking habits, and any other psychotic abnormalities were considered as a control group. The dismissal criterion incorporated with patients with other abnormalities excluding SCZ like any other chronic and systemic diseases, a viral infection that might intervene to the research, and non-cooperative patients and children, individuals taking antioxidant and nutrition supplementation were also put out of the study. Therefore, samples were to go through a scheduled check-up for physical fitness, including weight, nutritional condition, blood pressure, complete blood count (CBC), and electrocardiogram (ECG). Besides, serum creatinine, urea, liver enzyme, and glucose examinations were conducted for each sample to reveal the genuine pathological conditions.

A 5 mL blood sample was drawn from each subject in a metal-free sterile tube. Serum extraction from the blood sample was carried out using the centrifugation method and then collected and stored in Eppendorf tubes at  $-80^{\circ}\text{C}$  until the experiment day. These samples were then used for exploring the malondialdehyde—MDA (lipid peroxidation), antioxidant vitamins (vitamin A, E, C), trace elements (Zn, Fe, Se), and macro-minerals (Na, K, Ca) level in serum.

## 2.3 | Assessment of vitamin A, E, and C

In this study, levels of vitamin A and E in serum were quantified at 291 nm by a slightly modified RP-HPLC method reported by Bieri et al with UV detection.<sup>32</sup> Vitamin A and E were explored by the liquid-liquid extraction method using Sample Concentrator (DB-3, Techne, UK) at 40°C under a nitrogen stream. 20 µL was injected delicately into the chromatography from the reassembled sample on a C18 column flowing at 1 mL/min with (75:25) acetonitrile: methyl alcohol mobile phase.

To analyze serum vitamin C (ascorbic acid), 5% trichloroacetic acids (TCA) treated serum was centrifuged at 3000 rpm for 10 minutes. The supernatant was stored at -80°C for future study. The serum status of vitamin C was evaluated using a UV spectrophotometer (Model: UV-1201, Shimadzu) by using an indicator as phenylhydrazine based on the method mentioned by Islam et al.<sup>33</sup>

## 2.4 | Determination of serum MDA level

MDA level was quantified following the technique mentioned by Nahar et al.<sup>34</sup> First, 100 µL of serum was properly mixed with 900 µL of 0.9% saline solution. Then 2 mL of thiobarbituric acid (TBA) reagent and 30 µL of 50 mM butylated hydroxyl toluene (BHT) were incorporated. The incubation temperature was 60°C for the mixture for 15 minutes and then put in frost water for 5 minutes more. After that, the centrifugation of the samples was done for 10 minutes at 5000 rpm. Lastly, spectrophotometrically the supernatant absorbance was explored at 535 nm, where 1,1,3,3-tetra ethoxy-propane was used as standard.

## 2.5 | Measurement of trace elements and macro-minerals

Quantification of the mineral level was designed by using flammable atomic absorption spectrometry-FAAS, Model: Varian Spectra AA 220, and furnace graphite according to the technique found by Sarwar et al.<sup>35</sup> By a dilution factor of 10, the samples of all subjects were diluted with deionized water. Distinct levels (0.5, 1.0, 2.0, 5.0 and 10.0 mg/ L) of different minerals were examined for standard graphs calibration. Absorbance for Na, K, Ca, Zn, Fe, and Se was taken at 589.0, 766.5, 422.7, 213.9, 248.3, and 196.0 nm, respectively, in the FAAS. The standard solutions were employed to verify the analysis veracity for every 10 samples. A software, known as Spectra AA, was used to explore the status of Na, K, Ca, Zn, Fe, and Se.

## 2.6 | Statistical analysis

All the values were expressed as mean ± SEM. Between schizophrenic and control groups, an independent sample *t*-test was performed. Pearson's correlation test was performed to find the correlation between trace elements and macro-minerals levels. The significance

level was considered at  $P < 0.05$ . All analyses carried out using the SPSS software package, version 20.0 (SPSS, Inc. Chicago, IL).

## 3 | RESULTS

This study made up of schizophrenic patients as cases and healthy individuals as controls. The characteristics of the study subjects are presented in Table 1.

### 3.1 | Characteristics of the study population

From the characteristics of the study population, it is reported that the mean age of the patient group and control group was  $29.28 \pm 1.19$  and  $27.74 \pm 0.93$  years, respectively. The mean values of duration of illness of the patient group were  $63.54 \pm 3.19$  months (Table 1).

### 3.2 | Serum MDA and vitamins status

Serum MDA and antioxidant vitamin levels in patient and control groups are shown in Table 2. The table shows a statistically significant ( $P \leq 0.05$ ) difference for antioxidants (vitamin C and MDA) between the two groups. The study found that SCZ patients had an elevated MDA level and decreased level of antioxidant vitamins A, E, and C than those of the healthy subjects.

### 3.3 | Serum macro-minerals and trace elements status

Serum levels of trace elements and macro-minerals in the subjects are shown in Table 3. There is a notable variation for all the 95% confidence interval ( $P \leq 0.05$ ).

### 3.4 | Correlation among trace elements and macro-minerals

To reveal the inter-element correlations of the trace elements and macro-minerals, either they had positive (direct) or negative (inverse

**TABLE 1** Characteristics of the study population

Parameters	Values (Mean ± SEM)	
	Patient group	Control group
No. of subjects	63	63
Male/Female	39/24	35/28
Age (Years)	$29.28 \pm 1.19$	$27.74 \pm 0.93$
Duration of illness (Months)	$63.54 \pm 3.19$	—

**TABLE 2** Serum antioxidants and MDA levels in schizophrenia patients and control subjects

Parameters	Values (Mean ± SEM)		p value
	Patient group	Control group	
Vitamin A (µmol/L)	0.38 ± 0.04	0.61 ± 0.10	$P > 0.05^{NS}$
Vitamin E (µmol/L)	3.52 ± 0.25	5.84 ± 0.01	$P \leq 0.001^{***}$
Vitamin C (µmol/L)	7.55 ± 0.43	11.08 ± 0.31	$P \leq 0.001^{***}$
MDA (µmol/L)	1.99 ± 0.06	1.58 ± 0.05	$P \leq 0.001^{***}$

Note: \*\*\*indicates  $P \leq 0.001$  when compared to control, NS = Not significant.

**TABLE 3** Serum level of Zn, Fe, Se, Na, K, and Ca in the study population

Parameters	Values (Mean ± SEM)		P value
	Patient group	Control group	
Zn (mg/L)	0.33 ± 0.008	0.79 ± 0.03	$P \leq 0.001^{***}$
Fe (mg/L)	0.24 ± 0.01	0.78 ± 0.03	$P \leq 0.001^{***}$
Se (mg/L)	0.0252 ± 0.001	0.0650 ± 0.004	$P \leq 0.001^{***}$
Na (mg/L)	2657.5 ± 53.32	3200.8 ± 29.96	$P \leq 0.001^{***}$
K (mg/L)	64.18 ± 2.72	168.01 ± 2.85	$P \leq 0.001^{***}$
Ca (mg/L)	36.88 ± 2.56	86.43 ± 2.55	$P \leq 0.001^{***}$

Note: \*\*\* indicates  $P \leq 0.001$  when compared to control group.

correlation) values Pearson's correlation test was performed. In Table 4, the correlation coefficient, along with the significant levels, has been presented.

## 4 | DISCUSSION

SCZ is a severe neurodevelopmental disorder that is becoming more prevalent around the world. This is the first research of its kind on Bangladeshi schizophrenic patients, and it shows that schizophrenic patients have higher serum MDA levels and lower vitamin A, C, and E levels than the control groups. It also found that lower level of macro and micronutrients in schizophrenic patients than the control groups.

Oxidative stress occurs due to abnormal reduction-oxidation (redox) control over ROS's overproduction and deficiency of the antioxidant defense mechanisms.<sup>7,10</sup> Superfluous ROS, however, may have exaggerated effects by targeting cellular components in living systems, including essential macromolecules such as DNA, proteins, and lipids.<sup>10</sup> The idea of oxidative stress is closely related to the concept that, in many psychological disorders, mitochondrial energy production is theatrical.<sup>36</sup> Molecular and genetic studies suggest that inconvenience in redox reactions is part of the pathophysiology of SCZ, including the testimony of variations in elements of gene transcript, protein and metabolite levels that are engaged in mitochondrial function, and oxidative stress responses.<sup>37</sup>

Vitamin C and E are essential for normal brain activities, whereas vitamin A elevates the antioxidant latent of brain tissues.<sup>21,38</sup> It means alterations in antioxidants' levels are related to the oxidative trauma

**TABLE 4** Correlation study between various research parameters in patients and control groups

Correlation parameters	Patient group		Control group	
	r	P	r	P
Ca and Na	0.150	0.241	-0.034	0.790
Ca and K	0.198	0.120	-0.079	0.540
Ca and Fe	0.034	0.789	-0.022	0.864
Ca and Se	0.070	0.585	-0.142	0.267
K and Na	0.152	0.236	-0.048	0.707
K and Se	0.110	0.391	-0.165	0.197
Zn and Na	-0.189	0.137	-0.086	0.504
Zn and K	-0.021	0.869	-0.029	0.820
Zn and Ca	-0.087	0.499	-0.039	0.763
Zn and Fe	-0.143	0.263	0.115	0.370
Zn and Se	-0.097	0.448	0.071	0.579
Fe and Na	-0.070	0.586	-0.102	0.428
Fe and K	0.047	0.712	-0.022	0.865
Fe and Se	-0.119	0.353	0.050	0.698

Note: r = Correlation co-efficient; P = Significance; Values with negative sign indicate an inverse correlation.

resulting in neuropsychiatric oddities that afford the idea that elevated oxidative injury and decreased antioxidants may act to increase the number of psychiatric abnormalities.<sup>21,39</sup> Our study revealed significantly ( $P \leq 0.05$ ) lower levels of antioxidant vitamins (E, C) (Table 1) in people with SCZ, which concord with others that narrate elevated levels of oxidative stress were exhibited in SCZ.<sup>40-43</sup> Although vitamin A level was not significantly changed, a substantially higher level of MDA was evident in this study. The inconvenience of oxidant-antioxidant equality becomes a perfect record in SCZ.<sup>44</sup> Therefore, this study would be competent evidence expressing antioxidant vitamins and MDA imbalance as the possible causative factor for the pathophysiology and progression of SCZ.

This study aimed to determine serum Ca, Na, K, Fe, Zn, and Se levels in schizophrenic patients. These minerals are essential for being adequate in human food to live a hale and hearty life.<sup>45</sup> Na governs acid-base equilibrium and fosters membrane-potential. A previous study found hyponatremia in people with SCZ, similar to our findings.<sup>46</sup> It is well-known that SCZ derives from complex interactions

between multiple genes and natural factors. Polymorphisms in a primate-specific isoform of  $K^+$  channel *KCNH2* are connected to SCZ. This isoform produces a frequently deactivating  $K^+$  current and high-frequency neuronal firing model.<sup>47</sup> The study exposed a significantly depleted level of K (Table 2) in the patients; therefore, it can be claimed that a reduced level of K may be a trigger of SCZ pathophysiology. On the other hand, Ca is the second messenger necessary for neurons to exert neurotransmitters in the brain. Ca plays a vital role in the areas of the brain accountable for storing and recuperating memory. Although in the patient group, Ca showed a positive correlation with all the elements tested excluding Zn (Table 3), according to the result, our conjecture is the diminished level of Ca in the body may be accountable for the disease evolution.

Zn also plays a vital role in axonal and synaptic dispatch and is necessary for nucleic acid metabolism and brain tubulin development and phosphorylation.<sup>48</sup> Although some studies showed a higher level of Zn the people with SCZ,<sup>49,50</sup> our research found a significantly decreased level of Zn than the corresponding levels in the healthy control group. Meanwhile, Rahman and his fellows found a lower Zn level in the hair samples of people with SCZ,<sup>25</sup> which supports our finding. Studies manifest that Zn is an important element for the general functioning of superoxide dismutase and thymidylate synthase enzymes; diminished Zn levels in patients with SCZ lead to depleted antioxidative capacity and elevated oxidative stress.<sup>48</sup> Moreover, Zn showed a negative correlation with all other elements tested in the patient group (Table 3). Therefore, it can be suggested that the Zn level's alteration has an undeniable effect on the disease prognosis.

Fe is the most significant metal in the human body, and the brain contains a higher level of iron than any other metals.<sup>51</sup> Fe is indispensable for hemoglobin synthesis, which is liable for the oxygenation of blood. For dopamine synthesis, Fe acts as a coenzyme; therefore, iron scarcity may control the level and function of dopamine receptors, which in turn has been implicated in the pathogenesis of SCZ.<sup>52</sup> Besides, the research explored that CAT (catalytic activity of catalase) activity is inevitable for the antioxidant system,<sup>53</sup> was significantly lower in SCZ patients, suggesting a relation between iron deficiency and SCZ.<sup>42</sup> There are many other reports which reveal that iron deficiency may hamper the brain development of the infants and may also cause adulthood SCZ<sup>54-56</sup> that support our finding. However, another research reported the increased level of Fe in people with SCZ.<sup>57</sup>

Se is an essential trace mineral that is taken into the body in water and food. It plays a special responsibility in the activity of the GPx (glutathione peroxidase) antioxidant system, which can alter peroxides and hydroxyl radicals into nontoxic forms.<sup>58,59</sup> Thus decreased function of GPx, induced by Se insufficiency, may lead to oxidative stress related to SCZ, which may support our findings on the level of antioxidants and Se. This phenomenon was also reported by Vural et al, who asserted that erythrocyte GPx function and plasma Se status were significantly lower in patients with psychotic abnormalities.<sup>53</sup> Again, various research found that increased Se levels in the secondary blood were oppositely linked with different mental abnormalities and SCZ.<sup>49,52</sup> Likewise, the Se level was significantly ( $P < 0.05$ ) lower in people with SCZ corresponding to the study's controls.

Despite the significance of the analysis, some limitations should be mentioned. We did not include the effect of dietary supplementation and social classes in our study criteria. Therefore, further research is required to see whether a nutritional intervention can improve the quality of schizophrenic patients or not. Again, the research only included a small number of participants. A large-scale study with a larger number of samples from different parts of Bangladesh could better represent the condition of this population. Despite the limitations, we believe that our research would contribute significantly to the development of new pathological tools for SCZ patients.

## 5 | CONCLUSION

Our findings showed an elevated level of MDA level. Lower levels of vitamins (A, E, and C) and the minerals Ca, Na, K, Fe, Zn, and Se in the SCZ patients compared with controls, which upholds the hypothesis that alteration of antioxidant and mineral level are causative factors in the pathogenesis of SCZ. However, several factors might be affected, such as daily intake, the use of antipsychotics, and socioeconomic condition. Therefore, dietary supplementation may be recommended to reduce the risk of the disease. To manage the potential mystifying trends, additional research may catch the stated issues into account.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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## TRANSPARENCY STATEMENT

Mohammad Safiqul Islam, the corresponding author, confirms that this manuscript is an authentic, reliable, and transparent account of the

study being reported; that no important aspects of the study have been omitted.

#### DATA AVAILABILITY STATEMENT

All data and materials are contained and described in the manuscript. The data set was deposited in the Department of Pharmacy, Noakhali Science and Technology University, Noakhali-3814, Bangladesh.

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