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ORIGINAL ARTICLE

Plasma and Tissue Trace Element Levels in Drug Naïve Patients with Schizophrenia in a Tertiary Health Facility in Southwest Nigeria

Niveaux D'oligo-Éléments Plasmatiques et Tissulaires chez des Patients Schizophrènes Naïfs de Médicaments dans un Établissement de Santé Tertiaire du Sud-Ouest du Nigeria

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ABSTRACT

BACKGROUND: Trace elements are involved in oxidation reduction reactions in the body, including the central nervous system. The relationship between trace elements and psychiatric disorders have not been extensively investigated in the local population. We assessed the relationships between selected trace elements and schizophrenia.

METHODS: A cross-sectional study of 70 newly diagnosed participants with schizophrenia, mean age = 33.6 ±10.7 years were recruited by simple random sampling. Sixty age-matched healthy subjects, mean age of 34.2 ± 7.9 years were recruited as control. Plasma Zn, Cu, Mn and Se were measured using atomic absorption spectrophotometer while toe nail Zn, Cu, Mn and Se were measured using inductively coupled plasma optical emission spectroscopy in both participants and controls. Illness severity was assessed using PANSS score.

RESULTS: Mean plasma Zn, Cu and Mn were significantly lower in patients with schizophrenia than in control ($p<0.001$) while mean concentration of plasma Se was significantly higher in patients with schizophrenia than in control ($p<0.001$). Mean concentration of toenail Zn, Cu and

Mn were significantly lower among schizophrenic group than in control group ($p<0.001$), however, mean toe nail Se level was similar in schizophrenic and control groups. In logistic regression, low plasma levels of Zn (Odds Ratio = 2.296, $p<0.001$), Cu ($p<0.001$), Mn ($p<0.001$) and Se ($p<0.001$) were independently associated with schizophrenia. There was no significant relationship between plasma Zn, Cu, Mn and Se and severity of illness using PANSS score.

CONCLUSION: There is a possibility that low levels of Zn, Cu and Mn are involved in the aetiopathogenesis and progression of schizophrenia. **WAJM 2022; 39(12): 1266–1272.**

Keywords: Atomic Absorption Spectroscopy, Inductively Coupled Plasma Optical Emission Spectroscopy, Positive and Negative Syndrome Scale Score, Schizophrenia, Trace elements.

RÉSUMÉ

CONTEXTE: Les oligo-éléments participent aux réactions d'oxydoréduction dans l'organisme, y compris dans le système nerveux central. La relation entre les oligo-éléments et les troubles psychiatriques n'a pas été étudiée de façon approfondie dans la population locale. Nous avons évalué les relations entre certains oligo-éléments et la schizophrénie.

MÉTHODES: Une étude transversale a été menée auprès de 70 participants atteints de schizophrénie, dont l'âge moyen était de 33,6 ± 10,7 ans, recrutés par échantillonnage aléatoire simple. Soixante sujets sains appariés selon l'âge, âgés en moyenne de 34,2 ± 7,9 ans, ont été recrutés comme témoins. Le Zn, le Cu, le Mn et le Se du plasma ont été mesurés à l'aide d'un spectrophotomètre d'absorption atomique, tandis que le Zn, le Cu, le Mn et le Se des ongles des orteils ont été mesurés à l'aide d'une spectroscopie d'émission optique à plasma à couplage inductif chez les participants et les témoins. La gravité de la maladie a été évaluée à l'aide du score PANSS.

RÉSULTATS: La concentration plasmatique moyenne de Zn, Cu et Mn était significativement plus faible chez les patients atteints de schizophrénie que chez les témoins ($p<0,001$), tandis que la concentration moyenne de Se était significativement plus élevée chez les patients atteints de schizophrénie que chez les témoins ($p<0,001$). La concentration moyenne de Zn, Cu et Mn étaient significativement plus faibles dans le groupe schizophrène que dans le groupe témoin ($p<0,001$), cependant, le niveau moyen de Se dans les ongles des orteils était similaire dans les groupes schizophrènes et témoins. Dans la régression logistique, de faibles niveaux plasmatiques de Zn (Odds Ratio = 2,296, $p<0,001$), Cu ($p<0,001$), Mn ($p<0,001$) et Se ($p<0,001$) étaient indépendamment associés à la schizophrénie. Il n'y avait pas de relation significative entre le Zn, Cu, Mn et Se plasmatiques et la gravité de la maladie selon le score PANSS.

CONCLUSION: Il est possible que de faibles niveaux de Zn, Cu et Mn soient impliqués dans l'étiopathogénie et la progression de la schizophrénie. **WAJM 2022; 39(12): 1266–1272.**

Mots clés: Spectroscopie d'absorption atomique, spectroscopie d'émission optique du plasma à couplage inductif, score PANSS (Positive and Negative Syndrome Scale), schizophrénie, oligo-éléments.

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Abbreviations: AAS, Atomic Absorption Spectrophotometer; **APA,** American Psychiatric Association; **CNS,** Central Nervous System; **Cu,** Copper; **DSM,** Diagnostic and Statistical Manual of Mental Disorders; **DNA,** Deoxyribonucleic Acid; **FDA,** Food and Drug Administration; **HF,** Hydrofluoric Acid; **ICD,** International Classification of Diseases; **ICP-OES,** Inductively-Coupled Plasma Optical Emission Spectroscopy; **Mn,** Manganese; **NE,** Norepinephrine; **NO,** Nitric Oxide; **PANSS,** Positive and Negative Syndrome Scale; **ROS,** Reactive Oxygen Species; **Se,** Selenium; **SELENBP 1,** Selenium Binding Protein 1 Gene; **SOD,** Superoxide Dismutase; **SPSS,** Statistical Package for the Social Sciences; **ZNF804A,** Zinc finger protein 804A.

INTRODUCTION

Schizophrenia is a devitalizing mental disorder that usually commence in early adult life and is oftentimes recurrent and vitiates the bodily activities and mental qualities of patients.[1] Predominant symptoms commonly exhibited at diagnosis include hallucinations and delusions. Other commonly associated symptoms include persistent negative symptoms such as distorted thoughts, social disconnection, aloneness, and distressed resourceful oriented behavior.[1] Schizophrenia affects about 0.7% of the entire population with a peak age of onset being early 3rd decade and late 3rd decade in males and females respectively.[2]

The role of revised dopamine theory in the pathogenesis of schizophrenia cannot be overemphasized.[1] This is due to the exaggerated activity of dopamine transmission which has been linked to the symptoms of schizophrenia exhibited at diagnosis.[1] In spite of numerous studies over the years, the aetio-pathogenesis of schizophrenia remains ill-defined and vague, albeit schizophrenia is considered a multifarious disorder with genetic and environmental factors being partly responsible for the overall menace.[3]

Trace elements are obligatory substances that are required in immeasurable amounts for the proper growth, development, and various biochemical processes in the body.[4] The role of trace elements in the human body cannot be overstated. They perform antioxidant and pro-oxidant functions, influence metabolic reactions, and they have considerable impacts on psychological functions.[4] They are important components of proteins, enzymes and complex carbohydrates and they get involved in various biochemical reactions in conjunction with enzymes.

For instance, Cu is an essential constituent of many metalloenzymes, in addition to tyrosinase and dopamine hydroxylase,[5] both of which play a fundamental role the metabolism of dopamine and other monoamines. This has been linked to the pathogenesis of schizophrenia.[6]

Considerable number of studies have suggested that variations in the level of trace elements may not be unconnected to the development of schizophrenia and other psychiatric disorders.[7–10] Normal homeostasis is usually disrupted when there is alteration in the concentration of several essential trace elements which may further precipitate a contagious effect leading to changes in the levels of other trace elements simultaneously.[11]

More importantly, alteration in the concentration of these trace elements may exaggerate or alleviate the symptoms of these psychiatric disorders, including schizophrenia. Although, there are different school of thoughts as to whether the alterations in the levels of these trace elements could be the precipitating factor to developing schizophrenia. Many of these trace elements such as Zn, Cu, Se, and Mn are very critical in maintaining homeostasis in the functionality of the central nervous system.[12–16]

Multiple studies have reportedly linked changes in the concentrations of essential trace elements, for example, Zn and Cu to the development of schizophrenia [12,17] while others reported no significant relationship.[18,19]

In a study conducted in India, serum Zn and Cu were reported to be significantly elevated in patients with schizophrenia than in healthy control.[20] Although, all the patients in either group had values within the reference intervals for Zn and Cu. Conversely, a study reported unaltered concentration of zinc in subjects with schizophrenia when compared to healthy control.[21]

Zinc plays an important role in a wide variety of cellular processes in the body which include signal transduction and gene expression. In a study, it was reported that the gene, ZNF804A is well known to play an essential role in the development of schizophrenia. It has been postulated that therapeutic intervention aimed at this gene may be a novel treatment for patients with schizophrenia.[22]

In another study, it was reported that reduced levels of Cu, Fe, Se, and Al as well as elevated levels of Mn and Cr were associated with an increased risk of schizophrenia.[23] Mn is a very essential trace element in the human body and the role in the brain physiology cannot be overemphasized.[24] It is incorporated in numerous enzymes and many proteins. It acts as a cofactor of many enzymatic processes.[24–26]

Elevated concentration of Mn has a predilection for the brain tissue, it accumulates in the mitochondria area of the brain which predisposes to the development of neurodegenerative disorders such as schizophrenia and learning difficulties.[10] Research has shown that low plasma levels of Mn play an important role in the progression to schizophrenia possibly by distorting the homeostatic mechanisms involved in the stability of membranes and affectation of arginine-nitric oxide pathway.[10]

Selenium is a crucial antioxidant trace element that safeguards against ROS and it also promotes the activities of many selenoproteins involved in antioxidant defenses in the CNS.[27]

A previous study conducted in Han Chinese population reported a low concentration of selenium in patients with schizophrenia.[28]

The present study is an attempt to examine plasma and toe nail levels of Zn, Cu, Mn, and Se in drug naive patients with schizophrenia and to determine their relationship with severity of this psychiatric illness.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Departments of Chemical Pathology and Mental Health of the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Osun-State, a tertiary health facility in Southwest, Nigeria. Informed consent was sought and obtained from the respondents and or guardians, and relatives and from healthy controls after objectives of the study was explained to them. Only those who satisfied the inclusion criteria were involved in the study. A total of 70 newly diagnosed drug-naive patients within the ages of 18–65 years, and confirmed to have schizophrenia by a consultant psychiatrist using ICD-10 clinical diagnostic criteria were recruited for the study from the psychiatric outpatient clinics. Sixty (60) apparently healthy participants were used as controls. Their

current mental status and personal or family history of any mental disorder was assessed by unstructured interviews. The exclusion criteria considered for the two groups were the same and included patients with medical conditions that can alter or interfere with plasma trace element levels such as hypertension, liver diseases, diabetes mellitus, seizure disorders, dependence on alcohol and other substances were all excluded from the study using clinical history and physical examination. Ethical approval was obtained from Research and Ethics committee of the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife with registration number – NHREC/ 27/02/2009a before commencement of the study. Five (5) milliliters of venous blood was collected into a lithium heparin tube and centrifuged at 3000rpm for 15 minutes at room temperature to separate plasma and each sample was divided into aliquots in acid washed, plain, screw capped specimen tubes. Plasma separation was carried out in a dust free environment. All aliquots were stored frozen at –20C and protected from light until analyzed.

Toenail clippings were also obtained from the patients using sterile, rust free disposable surgical blades and stored in clean, sterile, polythene bags with zip-lock at room temperature. Analyses of plasma trace elements was carried out using Buck 210/211 AAS by Buck Scientific Inc. 58 Fort Point St, East Norwalk, USA.

Determination of Plasma and Toenail Trace Element Concentrations

A concentrated acid mixture consisting of perchloric acid ($HClO_4$), nitric acid (HNO_3) and hydrochloric acid (HCl) (1:2:3) was prepared. Ten (10ml) of the acid mixture was added into each digestion tube containing 250µl of plasma sample and mounted on digestion block that was thermostatically regulated to 120°C for 2 hours in a fume hood. The digestion tubes were secured tightly using heat resistant paraffin paper. Each digestion tube was made up to 50ml using ultra-pure water. They were subsequently transferred into centrifuge tubes, secured tightly and properly labeled. They were thoroughly swirled and centrifuged for 5 minutes at 500rpm. The supernatant for each sample was extracted into a plastic vial and assayed for Zn, Cu, Mn and Se in an acetylene-air flame using Buck 210/211 AAS.

Unknown concentration of samples were determined using a built-in software computer program which interprets the signal intensity from each sample by comparing with the signals of the standards using a calibration curve. The outcome of the relationship brings the final concentrations after taking into consideration the sample preparation volume and sample dilution factors. Absorbances were read at 213.9, 327.4, 279.8 and 196.0 for Zn, Cu, Mn and Se respectively.

Blanks and duplicates of samples were digested under the same conditions as the samples. Working standard concentrations of 0.0, 2.0, 4.0, 6.0, 8.0 parts per million (ppm) concentrations were used for the element of interest. The reference combined standards used were obtained from Katchey Fisher's Scientific Incorporation, Merck 64271 Darmstadt, Germany (1000ppm for each element).

Toenails were analyzed using inductively coupled plasma optical emission spectrophotometer (Perkin Elmer Corporation Product, Uberlingen, Germany).

The nail samples were washed and cleaned thoroughly using ultra-pure water and the nails were allowed to air dry. The nails were subsequently crushed to a reducible sized particles with a miller. 0.25g of each crushed nail sample was weighed into digestion tubes and 2.5ml of hydrofluoric acid (HF) was added into each digestion tube and heated to dry at 150°C. Acid mixture of HCL: HNO_3: $HClO_4$ (2:2:1) was prepared, 20ml of the acid mixture was pipetted into all the acid digestion tubes, the temperature was subsequently increased from 150°C to 250°C and heated for 3hours until clear digest was obtained and it was allowed to cool at room temperature. They were all made up to 25ml volume. They were all transferred into a set of centrifuge tubes and mixed thoroughly for 10 minutes using a mechanical shaker, they were subsequently centrifuged for 5minutes at 500rpm. The supernatant was transferred into a set of plastic vials. A set of working reference standard (0.0, 2.0, 4.0. 6.0, 8.0 parts per million (ppm) concentration were prepared from 1000ppm purchased from Katchy incorporate, Darmstadt, Germany. Unknown concentrations were determined using a built in software computer program which interprets the signal intensity from each sample by comparing with the signal of the standards using a linear calibration curve. The outcome of the relationship brings the final concentration after taking into consideration the weight of the sample, the sample preparation volume and sample dilution factor.

Analytical accuracy and precision were ensured by simultaneous analyses of commercially prepared control sera (at levels in low, normal and elevated ranges) for monitoring assay performance in each batch of samples that were analyzed. All plasma and nail specimens were analyzed in batches. Intra-assay, inter-assay and day-to-day coefficients of variation were estimated for each batch and were within allowable limits of acceptance for each analyte.

Psychopathological Assessment

Plasma and toe nail trace element levels were related to the severity of schizophrenia in the subjects using the overall positive and negative syndrome scale (PANSS). The assessment was carried out by a Consultant Psychiatrist. The higher the score on each of the subscale and the overall total score, the more the severity of the patient's condition.

Statistical Analysis

Statistical analyses of data was done using SPSS (Statistical Package for Social Sciences) version 20.0. Results were presented as means ± standard deviation. Student's t-test was used to compare mean values of measured variables between test subjects and controls. Pearson's correlation test was used to test for the relationship between some selected trace elements and the degree of severity of schizophrenia. P-values of ≤ 0.05 were considered statistically significant.

RESULTS

The mean age for all the study groups were; (34.2 ± 7.9) years for control and (33.6 ± 10.7) years for schizophrenia. There was no significant difference when mean age were compared between the study groups ($p>0.05$). Their mean weight, height and BMI are shown in Table 1. Seventy (70) newly diagnosed subjects with schizophrenia recruited, consist of 32 males (45.7%) and 38 females (54.3%) and 60 apparently mentally healthy controls (18 – 62 years) made up of 36 males (60%) and 24 females (40%). Subjects with schizophrenia significantly weighed less (59.6 ± 8.7 Kg) compared to control group (66.6 ± 9.5Kg) ($p < 0.001$). The mean BMI of subjects with schizophrenia (22.3 ± 2.5Kg M^{-2}) was significantly lower as compared to that of control (23.6 ± 2.3KgM^{-2}) ($p < 0.05$).

Four elements were analyzed in the study, including Zn, Cu, Mn, and Se. The bivariate analysis by *t* test showed that the concentrations of plasma Zn, Cu, Mn, and Se were different between subjects with schizophrenia and the normal control group. Zn, Cu, and Mn in schizophrenic group were lower than those of normal control group, and plasma levels of Se in schizophrenic group was higher than those of control group.

The *t* test results showed that plasma Zn, Cu, Mn, and Se content differences were statistically significant ($p < 0.001$).

In view of the significant difference in BMI between the study and control groups, BMI was controlled for during further analyses. Multivariate logistic regression analyses was done to determine the independent predictor of schizophrenia. Result showed that Zn, Cu, Mn and Se were independently related to schizophrenia. The odd ratios (ORs) of plasma Zn, Cu and Mn were 2.296, 1.421 and 2.372 respectively. The OR of plasma Se was below 1 (Table 3).

In subjects with schizophrenia, there was no significant relationship between plasma and toe nail concentrations of Zn, Cu, Mn and Se (Table 5).

In control group, there was a significant positive correlation between plasma Cu and nail Cu. There was no significant correlation between plasma Zn and nail Zn, plasma Mn and nail Mn, plasma Se and nail Se (Table 6).

Table 1: General Characteristics of Study Population

Characteristics	Schizophrenia Mean ±SD (n =70)	Control Mean ±SD (n= 60)	P-value
Age (Years)	33.6 ± 10.7	34.2 ± 7.9	p = 0.904
Weight (Kg)	59.6 ± 8.7	66.6 ± 9.5	p < 0.001**
Height (M)	1.63 ± 0.05	1.67 ± 0.06	p < 0.001**
BMI (Kg/m^2)	22.3 ±2.5	23.6 ± 2.3	P = 0.008**

P-value defines the Level of Significance, SD, Standard Deviation.

Table 2: Mean Plasma Trace Element Levels in Study Groups

Measured Variables	Schizophrenia Mean ± SD	Control Mean ± SD	P-value
Zinc (µmol/L)	11.8 ± 3.4	16.7 ± 1.1	P< 0.001**
Copper (µmol/L)	19.3 ± 2.9	22.2 ± 2.5	P < 0.001**
Manganese(nmol/L)	7.1 ± 1.9	12.3 ± 2.1	p < 0.001**
Selenium (µmol/L)	1.3 ± 0.3	0.8 ± 0.3	P < 0.001**

P-value defines the Level of Significance among Antioxidants; SD, Standard Deviation.

Table 3: Result of Multivariate Logistic Regression

Measured Variables	OR	95% C I	P – value
Zinc	2.296	1.633 – 3.210	p < 0.001**
Copper	1.421	1.221 – 1.653	P < 0.001**
Manganese	2.372	1.796 – 3.134	P < 0.001**
Selenium	0.028	0.007 – 0.112	P < 0.001**

P-value defines Level of Significance among Trace Elements; OR, Odds ratio, CI, Confidence Interval.

Table 4: Mean Nail Trace Element Levels in Study Groups

MeasuredVariable	Schizophrenia	Control	p – value
Zinc (mmol/L)	1.61 ± 0.2	1.83 ± 0.2	p <0.001**
Copper (µmol/L)	566.5 ± 64.5	637.3 ± 89.7	p < 0.001**
Manganese (nmol/L)	38.2 ± 3.6	43.7 ± 5.5	p < 0.001**
Selenium (µmol/L)	5.1 ± 0.6	5.1 ± 1.5	p > 0.05

P-value defines the level of significance among trace elements; SD, Standard Deviation.

Table 5: The Relationship between Plasma And Toe Nail Zinc, Copper, Manganese and Selenium Concentrations in Schizophrenic Subjects

	P Znr-value	P Cur-value	P Mnr-value	P Ser-value
N Zn	–0.022 (p=0.856)	0.059 (p=0.628)	–0.09 (p=0.431)	–0.06 (p=0.574)
N Cu	–0.003 (p=0.978)	0.046 (p=0.705)	–0.072 (p=0.05)	–0.07 (p=0.560)
N Mn	0.011 (p=0.927)	0.018 (p=0.884)	–0.093 (p=0.444)	–0.05 (p=0.674)
N Se	0.091 (p=0.453)	–0.012 (p=0.923)	–0.054 (p=0.655)	–0.09 (p=0.424)

**Correlation is significant at the 0.05 level (2-tailed) **Correlation is significant at the 0.01 level (2 tailed), r- Pearson's product correlation coefficient, p-value defines the level of significance among the antioxidants, N se – Nail selenium, N Mn – Nail manganese, N Cu – Nail copper, N Zn Nail zinc, P Zn – Plasma zinc, P Cu – Plasma copper, P Mn – Plasma manganese, P Se – Plasma selenium.*

Table 6: The Relationship between Plasma and Toe Nail Zinc, Copper, Manganese and Selenium Concentrations in Control Group

	P Znr-value	P Cur-value	P Mnr-value	P Ser-value
N Zn	0.096 (p=0.467)	0.48** (P<0.001)	0.063 (p=0.632)	0.37** (p<0.05)
N Cu	0.075 (p=0.569)	0.44** (P<0.001)	0.087 (p=0.508)	0.31* (p<0.05)
N Mn	0.049 (p=0.713)	0.46** (p<0.001)	0.084 (p=0.524)	0.27* (p<0.05)
N Se	0.035 (p=0.788)	0.188 (p = 0.149)	0.123 (p=0.348)	0.151 (p=0.257)

**Correlation is significant at the 0.05 level (2-tailed), ** Correlation is significant at the 0.01 level (2-tailed), r – Pearson's product correlation coefficient, p – value defines the level of significance among the antioxidant trace elements, N Zn – Nail zinc, N Cu – Nail Cu, N Mn – Nail manganese, N Se – Nail selenium, P Zn – Plasma zinc, P Cu – Plasma copper, P Mn – Plasma manganese, P Se – Plasma selenium.*

Table 7: The Relationship between Plasma Concentrations of Zinc, Copper, Manganese and Selenium and Severity of Illness in Subjects with Schizophrenia, using PANSS Score

	Zinc r-value	Copper r-value	Manganese r-value	Selenium r-value
PANSS	0.164 (p = 0.174)	0.234 (p = 0.051)	0.136 (p =0.262)	0.133 (p = 0.272)

PANSS –Positive And Negative Syndrome Scale, p –Defines the level of significance, r – Pearson's product correlation coefficient.

Table 8: The Relationship between Toe Nail Concentrations of Zinc, Copper, Manganese and Selenium and Severity of Illness in Schizophrenic Subjects using PANSS Score

	Zinc r-value	Copper r-value	Manganese r-value	Selenium r-value
PANSS	0.065 (p = 0.594)	0.078 (p = 0.521)	0.027 (p = 0.828)	0.0.063 (p = 0.604)

PANSS – Positive And Negative Syndrome Scale, p –Defines the level of significance, r – Pearson's product correlation coefficient.

There was no significant relationship between plasma Zn, Cu, Mn and Se concentrations and severity of illness in subjects with schizophrenia based on overall total PANSS score.

There was no significant relationship between toe nail Zn, Cu, Mn and Se concentrations and severity of illness in subjects with schizophrenia based on PANSS score.

DISCUSSION

Earlier studies on the role of trace elements in patients with schizophrenia have been equivocal.[28–30]

In this study, we found that the patients with schizophrenia had significantly low plasma and toenail Zn than the corresponding levels in healthy control group; this finding is similar to the results reported by a study in Ghana.[29] Zn plays a very elaborate role in the CNS. Zn deficiency is culpably involved in the pathogenesis of schizophrenia.[31] Our finding is supported by the work of other researchers who also reported significantly lower plasma Zn levels in patients with schizophrenia compared to controls.[30,32] However, the finding in this study is contrary to the report of other studies that reported higher concentration of Zn in plasma,[17, 28] and in hair[12] of patients with schizophrenia when compared to healthy controls. The conflicting report may be due to cultural diversity, their way of life and different psychopathology. These inconsistent findings might also be due to the use of medicated patients with schizophrenia and a relatively small sample size in some of the studies as opposed to drug naïve subjects used in this study. Furthermore, Zn is very important in the generation of nitric oxide (NO) due to the effective regulation of the activities of the enzyme NO synthase which converts L-arginine to L-citrulline. NO, which is a second messenger is capable of diffusing freely through membranes of target cells thereby regulating diverse range of cellular functions and activities in the body. Remarkable disruptions and alterations in the levels of NO and L-arginine in the body has been implicated as a major mechanism in the development of schizophrenia.[32] The implication of this is that low level of Zn can influence the metabolism of L-arginine and subsequently NO synthesis thereby predisposing to the development of schizophrenia.[32]

In this study, we found significantly low levels of plasma and toe nail Cu when compared to healthy controls. Similarly in another study, significantly lower serum Cu level was reported in treatment naïve patients with schizophrenia than controls [33]. It is possible that alteration in the level of Cu in the body affect CNS. Cu is very important in regulating normal brain and monoamine metabolism.[33] Cu is incorporated in the enzyme dopamine β-hydroxylase which is responsible for the conversion of dopamine to NE by acting as a cofactor. In deficiency states, there is a corresponding remarkable decline in the activities of the enzyme dopamine β-hydroxylase and tyrosine hydroxylase with a consequent increase in dopamine levels accompanied by a reduction in NE levels. The alteration in the metabolism of catecholamine occurring as a result of impaired hemostasis of Cu may precipitate the development of early abnormal symptoms seen in schizophrenia.[33] Our result was in agreement with previous studies.[23,34] However, the finding of elevated Cu levels in the plasma of patients with schizophrenia have also been reported when compared to healthy controls,[18,35] surprisingly, a study in

Romania did not find significant alteration in Cu levels in patients with schizophrenia when compared to controls.[17] This contradictory finding may be due factors relating to variations in the genetic make-up of affected individuals and a relatively small sample size used in other studies.

In our study, plasma Se level was found to be significantly higher in patients with schizophrenia when compared to those of healthy controls. However, there was no significant difference in nail Se when compared to controls. Similarly, a higher plasma Se level was reported in patients with schizophrenia by some earlier workers but the difference between the groups were not significant.[18,36] Another study also reported elevated Se in the hair of male but not female patients with schizophrenia.[37] In a study conducted in California, USA, selenium binding protein 1gene (SELENBP 1) was identified using genetic based techniques and was discovered to be culpably involved in the development of schizophrenia and other psychiatric illnesses such as bipolar affective disorders. It is one of the paramount biomarkers implicated in brain disorders and was found to be significantly elevated in the blood and brain of patients with schizophrenia. However, the exact role of SELENBP 1 has not been properly elucidated particularly in the CNS, although, it is known to be involved in the modification of neurites.[38] On the contrary, earlier workers reported lower serum levels of selenium in patients with schizophrenia when compared to controls.[23,39] These contradictory findings have been attributed to varying topographical disparities with different soil micro-nutrient levels, which plays a significant role in determining optimum Se uptake from food produced in that geographical location. Some authors have insinuated that the geographical distribution of schizophrenia may not be unconnected to some specific trace element and micronutrient deficiencies.[40] However, it is difficult to say if patients with schizophrenia actually have Se insufficiency preceding diagnosis.

In this study, plasma and toenail Mn levels were found to be significantly lower in patients with schizophrenia when compared to controls. This is similar to previously reported findings of lower plasma Mn in newly diagnosed patients with schizophrenia compared to controls.[18,41] The role of Mn in the body metabolism cannot be overstated. It is required for enzymes activation such as hydrolase, kinase, decarboxylase and transferase which are necessary for many biochemical processes in the body such as lipid metabolism, energy production and bone mineralization.[28] It stimulates adenylate cyclase in the brain and other tissues including free radicals that cause lipid peroxidation and protein oxidation which impairs the activity of DNA and RNA, and potentiates Mn deprivation.[28] Additionally, Mn was reported to play a key role in the arginine-nitric oxide pathway in a related study. This study suggested that the arginine-nitric oxide pathway was implicated in schizophrenia as demonstrated by reduced Mn level, reduced arginase activity and high NO level.[42] NO is a well-recognized brain neurotransmitter.[43] The ability of neuroleptic drugs to lower NO levels in schizophrenic patients is an indication for possible treatment success.[28] Reduced levels of Mn may be due to decreased antioxidant capacity of Mn SOD that eventually leads to increased oxidative stress.[28]

On the contrary, a related study documented no significant difference in serum Mn level in drug naïve schizophrenic patients when compared to controls.[44]

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