Serum Copper and Zinc Levels in Bipolar and Major Depressive Disorders

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Abstract
Background: Micronutrient deficiencies and excesses may indeed contribute to bipolar disorder (BD) and major depressive disorder (MDD).
Objectives: This study aimed to compare the concentrations of copper (Cu) and zinc (Zn) in patients with BD and MDD, as well as to determine the relationship between trace element levels and the profile of affective disorders as biomarkers for the disease.
Patients and Methods: This case-control study was conducted on 135 patients between the ages of 18 and 40, both sexes, who met the DSM-V diagnostic criteria for BD and MDD (regardless of the stage of the illness). Patients were divided into three equal groups. Group A had MDD; group B had BD, while group C was a healthy control individual.
Results: Groups A and B exhibited significantly higher Cu levels compared to group C (P <0.001). Zinc levels were significantly lower in groups A and B compared to group C (P <0.05). The levels of Cu and Zn were similar in both the A and B groups. No correlation was found between serum levels of Cu and Zn and the onset of disease or age. A positive correlation was found between serum Cu levels and (disease severity and YMRS score) ($p < 0.05$), while a negative correlation was identified between serum Zn levels and (illness severity and YMRS score) ($p < 0.05$) and between serum Cu and Zn (P=0.010).
Conclusion: MDD and BD are associated with higher serum Cu levels and lower serum Zn.
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Introduction

Major depressive disorder (MDD) is frequently misdiagnosed as bipolar disorder (BD), with a 33% conversion rate from MDD to BD **(Baryshnikov et al., 2020)**. MDD is a severe mental condition associated with a significant risk of death **(Lin et al., 2018)**. Its defining features are negative feelings, such as anhedonia and atypical behavior. Evidence has demonstrated that MDD is associated with emotional, somatic, and functional impairments, which subsequently impact families and workplaces **(Sheehan et al., 2017)**.

Despite the passage of several years after the onset of depression, the diagnosis was altered. These results suggest that individuals who have received insufficient therapy for an extended period and are labelled as drug-resistant may belong to a subset of undiagnosed bipolar disorder patients **(Nestsiarovich et al., 2021)**.

Decades of research have been devoted to trace elements, including copper (Cu) and zinc (Zn), and their function in humans **(Młyniec et al., 2015)**. They are crucial in several physiological processes essential for survival and expected growth. Severe metabolic disturbances or disorders, such as psychiatric disorders, may result from disrupting the concentration or metabolism of Zn and Cu **(Gromadzka et al., 2020b, Li et al., 2022)**.

Zn is an essential component, vital in numerous fundamental physiological processes **(Hussain et al., 2022)**. Additionally, Zn ions influence the concentration of specific inflammatory cytokines, thereby contributing to the regulation of inflammation processes and the immune system **(Sapkota and Knoell, 2018)**. Even more, Zn has been attributed to neuronal metabolic conditions. It has been established that zinc is necessary for neuromodulation and cellular function regulation **(Kumar et al., 2021)**.

Cu is found in all tissues and is the third most prevalent trace element necessary for vital body processes. It is a necessary cofactor for many enzymes and is implicated in various biochemical processes **(Baj et al., 2023)**. Brain tissue is among the most copper-rich among body organs **(Huang et al., 2018, Gromadzka et al., 2020a)**. Neuronal toxicity resulting from the activation of the extrasynaptic N-methyl-D-aspartate receptor to an excessive degree has been identified **(Zhou et al., 2015)**.

This work aimed to evaluate the correlation between trace element levels and the profile of affective disorders by comparing Zn and Cu concentrations in patients with BD and MDD.

Patients and methods

This case-control study was performed on 135 patients between 18 and 40 years old of both sexes who satisfied diagnostic criteria for BD and MDD as per DSM-V, (regardless of the disease stage).

The study was conducted from January to April 2024, with the appropriate permission from the Ethical Committee of Tanta University Hospitals (approval code: 36264PR519/1/24). The patient provided written informed consent.

Exclusion criteria were severe mental disorders not falling under the category of BD or MDD, such as schizoaffective psychosis or schizophrenia, severe personality disorders, substance abuse-related disorders (except caffeine or nicotine addiction), the simultaneous presence of severe somatic diseases, and breastfeeding or pregnancy.

The patients were classified into three similar groups. Patients with MDD comprised Group A, patients with BD comprised Group B, and healthy individuals (the control group) comprised Group C matched in age and sex with the study groups.

The assessment of patients' depressive symptoms' severity was conducted utilizing the Hamilton

Depression Rating Scale (HDRS) **(Obeid et al., 2018)**. To assess the intensity of manic symptoms, the Young Mania Rating Scale (YMRS) was implemented **(Samara et al., 2023)**.

Using the Monovette closed blood collection system, each enrolled patient's venous blood was drawn to a maximum of 9.8 ml following the study protocol. Following thrombus formation, the samples underwent a 30-minute centrifugation at 1,800 RPM. The sample was preserved at–80°C until the analysis commenced as planned. The samples were quantitatively analyzed using flame-atomic absorption spectrometry to ascertain Zn amount and electrothermal atomic absorption spectrometry to determine the amount of Cu, respectively, after a thorough thawing and mixing procedure. The pre-treatment temperature was maintained at 950°C, whereas the temperature during the atomization process was 2,300°C.

Cu was determined at 324.8 nanometers, Zn at 213.9 nanometers, and 0.7 nm slit. A triplicate estimation was conducted on the samples. Recovery analysis was utilized to evaluate the precision; for Zn, this ranged from 94% to 99%, and for Cu, 96% to 103%.

The primary outcome was the serum Cu concentration in MDD and BD. The secondary outcomes were correlations between the serum zinc concentration and HDRS score, and YMRS scores.

Sample Size Calculation: The G*Power 3.1.9.2 software package was utilized to compute the sample size (Universitat Kiel, Germany). Based on a prior investigation **(Styczeń et al., 2016)**, the serum Cu concentration (the primary outcome) in group A was 0.81 ± 0.27 µg/ml; in group B, it was 0.84 ± 0.04 µg/ml; and in group C, it was 1.05 ± 0.32 µg/ml as per a prior investigation **(Świądro et al., 2021a)**. The sample size was determined based on the following considerations: 0.273 effect size, 95% confidence limit, 80% power of the study, group ratio 1:1, and three cases added to each group to overcome dropout. As a result, 45 patients were recruited for each group.

Statistical analysis

The SPSS v27 software, developed by IBM®, Chicago, IL, USA, was used for statistical analysis. Histograms and the Shapiro-Wilks test were used to analyze data distribution normality. The ANOVA (F) test with the Tukey post-hoc test was used to analyze the quantitative parametric data, and the results were provided as the mean and standard deviation (SD). The Chi-square test was used to analyze the qualitative variables examined using the Chi-square test, and the results were as follows: frequency and percentage (%). The Pearson moment correlation equation was used to determine how different variables were related. Statistical significance was determined by a two-tailed P value less than 0.05.

Results

There were no significant variations in the demographic characteristics or usage of electroconvulsive therapy across the groups. However, there was a significant disparity in the family history of psychiatric illness, with a significantly higher prevalence in Groups A and B than in Group C ($p = 0.002$). Furthermore, the disease onset was significantly quicker in Group A than in Group B ($p < 0.001$). On the other hand, the severity of the disease was comparable between Groups A and B, (**Table.1**).

Table 1. Demographic data of the studied groups

Variables		Group A (n=45)	Group B (n=45)	Group C (n=45)	P-value
Age (years)		31.1 ± 5.5	29.2 ± 5.25	28.3 ± 6.35	0.066 ##
Sex	**Male**	32 (71.11%)	29 (64.44%)	30 (66.67%)	0.790 #

	Female	13 (28.89%)	16 (35.56%)	15 (33.33%)	
Weight (kg)		72.9 ± 14.26	74.7 ± 9.35	70.6 ± 8.86	0.216 ##
Height (m)		1.7 ± 0.08	1.67 ± 0.07	1.66 ± 0.08	0.090 ##
BMI (kg/m^2)		25.4 ± 5.32	26.9 ± 4.32	25.8 ± 4.58	0.331 ##
Family history of the psychiatric disease		11 (24.44%)	17 (37.78%)	1 (2.22%)	0.002 #
Electro convulsive therapy		15 (33.33%)	19 (42.22%)	---	0.384 #
Onset (years)		3.98 ± 2.06	9.09 ± 5.73	---	<0.001 ###
Severity of the disease	**Mild**	3 (6.67%)	4 (8.89%)	---	0.922#
	Moderate	16 (35.56%)	16 (35.56%)	---	
	Severe	26 (57.78%)	25 (55.56%)	---	

BMI: Body mass index. # Chi-square test, ## One way ANOVA test, ### Unpaired student T test

There were no significant variations in serum Cu levels between groups A and B, although both groups A and B had significantly higher levels than group C ($p < 0.001$). Serum Zn levels were comparable between groups A and B but were significantly lower in both groups A and B than in group C ($p < 0.05$). Group A had significantly higher scores on the HDRS, and YMRS scales compared to group B while both group A and B had higher scores than group C ($p < 0.05$), (**Table.2**).

Table 2. Serum copper and zinc, HDRS, and YMRS scores of the studied groups

Variables	Group A (n=45)	Group B (n=45)	Group C (n=45)	P-value	Post hoc
Serum copper (mg/L)	1.25 ± 0.39	1.17 ± 0.15	0.97 ± 0.14	<0.001 ##	P1=0.601 P2<0.001 P3<0.001
Serum zinc (mg/ml)	2.83 ± 1.54	2.55 ± 1.35	3.79 ± 2.05	0.001 ##	P1=0.708 P2=0.019 P3=0.002
HDRS score	25.64 ± 7.83	21.31 ± 5.13	6.36 ± 3.23	<0.001 ##	P1=0.001 P2<0.001 P3=0.049
YMRS score	38.69 ± 9.47	34.71 ± 7.28	7.13 ± 3.91	<0.001 ##	P1=0.028 P2<0.001 P3=0.007

One way ANOVA test. P1: P value between group A and group B; P2: P value between group A and group C; P3: P value between group B and group C; MADRS: Montgomery–Åsberg depression rating scale; HDRS: Hamilton depression rating scale; YMRS: Young Mania rating scale.

No correlation was detected between serum levels of Cu and Zn and the onset of disease or age. A positive correlation was found between serum Cu levels and (illness severity and YMRS score) ($p < 0.05$), while a negative correlation was identified between serum Zn levels and (disease severity and YMRS score) ($p < 0.05$) (**Table.3**).

A negative correlation was identified between serum Cu and Zn ($r = -0.220$, $P = 0.010$) , (**Fig.1**).

Table 3. Correlation between serum copper and zinc and (onset of disease, age, severity of the disease and YMRS score) of the studied groups

Variables		Serum copper (mg/L)	Serum zinc (mg/ml)
Onset (years)	**r**	-0.140	-0.090
	P-value #	0.187	0.396
Age (years)	**r**	0.058	-0.156
	P-value #	0.498	0.07
Severity of the disease according to HDRS score	**r**	0.279	-0.281
	P-value #	0.034	0.002
YMRS score	**r**	0.354	-0.272
	P-value #	<0.001	0.001

r: Pearson coefficient. # Pearson correlation.

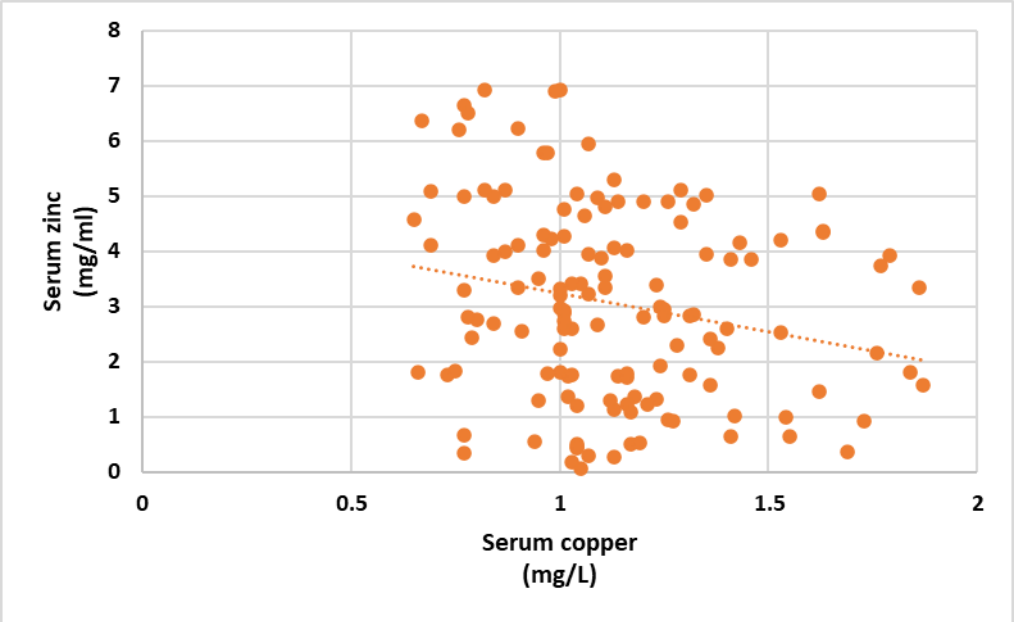

Fig.1. Correlation between serum copper and zinc and of the studied groups

Discussion

The human body necessitates trace elements such as Zn or Cu in optimal concentrations for optimal physiological functioning. Deficiencies in these elements can lead to a range of metabolic disorders, whereas excessive amounts can be toxic **(Taheri et al., 2021)**.

Cu is a crucial trace element that is situated in the brain. Significantly contributing to an extensive range of biochemical processes, including mitochondrial, neurobehavioral, respiration, and antioxidant activities. Cu operates as a cofactor for numerous enzymes **(Chen et al., 2023)**.

Zn, a vital trace element, is integral to maintaining human health across all stages of life. Zn imbalances in the brain have been linked to a range of negative consequences, including anorexia, dysphoria, learning, and cognitive impairments, and certain neurological disorders. Their involvement may extend to the pathophysiology and therapeutic aspects of depression **(Gower-Winter and Levenson, 2012)**.

In this study, neither the MDD nor the BD groups revealed a statistically significant difference in serum Cu levels; nevertheless, both groups showed significantly elevated Cu levels compared to the control group. Although serum Zn

levels were comparable between the MDD and BD groups, both groups exhibited significantly reduced Zn levels compared to the control group. No significant correlation was observed between age, disease onset, and serum Cu and Zn levels. Serum Cu and Zn were found to be negatively correlated with disease severity, while serum Cu was positively correlated with disease severity.

Our findings were in accordance with **(Sampath et al., 2022)** reported that age was not correlated with serum Cu or Zn levels. Comparable to our findings, **(González-Estecha et al., 2011)** stated that serum Cu levels were significantly higher in BD compared to healthy controls. While there was a statistically significant rise in serum Zn concentration in BD compared to the control group, This difference may be related to serum levels of Zn being significantly affected by diet **(Gibson, 2007)**.

Also, **(Islam et al., 2018)** demonstrated that the MDD group exhibited significantly greater serum Cu and lower Zn levels than the control group.

As demonstrated by our findings, **(Styczeń et al., 2017)** stated that in MDD patients, the mean serum Zn concentration was lower than in the healthy control group.

Additionally, **(Styczeń et al., 2017)** showed that serum samples from patients with MDD contained a significantly lower concentration of Zn than those from healthy volunteers.

Moreover, **(Siwek et al., 2016)** determined whether reduced serum Zn levels during the depressive phase of bipolar disorder are associated with this disorder. They demonstrated that depressive episodes were associated with a lower serum Zn concentration than the healthy control group.

Contrary to the findings we obtained, Sampath et al. **(Sampath et al., 2022)** reported that Cu levels were considerably lower in the BD group than in the control group, whereas Zn concentrations were comparable between both groups. The observed variation could potentially be attributable to the determination of elemental concentrations in brain samples.

Also, Swiadro et al. **(Świądro et al., 2021b)** stated that the mean serum Cu level was 0.84 ± 0.04 in patients with BD, 0.89 ± 0.15 in patients with MDD, and 1.02 ± 0.24 in the control group. In patients with BD and MDD, the mean serum Zn concentrations were 4.91 ± 2.42 and 4.99 ± 1.65, respectively, compared to 3.75 ± 0.69 in the control group.

Further studies comparing Cu and Zn concentrations in different tissues are recommended. Further studies are needed to assess the concentration of other trace elements. Further investigation is warranted to examine the trace elements present in additional psychiatric disorders, as such research could potentially contribute to the early detection and treatment of such conditions. Further investigation is also needed to assess the effect of supplemental Zn on Cu levels in MDD and BD.

Conclusion

MDD and BD are associated with higher serum Cu levels and lower serum Zn.

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