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Evaluation of Some Trace Elements and Vitamins in Major Depressive Disorder Patients: a Case–Control Study

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Abstract

Major depressive disorder (MDD) is a common mental disorder worldwide; however, little is known about its etiology. It is well known that levels of certain trace elements are associated with the pathogenesis of some diseases. Accordingly, this study aims to evaluate the effect of trace elements and vitamins in the etiology of MDD. In this case–control study, sixty men patients with MDD and sixty, age and gender matched, control subjects were examined. Serum levels of Cu, Zn, Ni, Cr, Mn, Mg, and Al were determined by atomic absorption spectrometry as well as serum levels of vitamins E and A were determined using high-performance liquid chromatography. The results revealed that there were significantly higher levels ($p < 0.001$) of Cu, Cr, and Al in patients sera compared with control. While there were significantly lower levels ($p < 0.001$) of Zn, Ni, Mn, Mg, vitamin E, and vitamin A in MDD patients as compared with control. In addition, high Cu/Zn ratio ($p < 0.05$) was observed with the depressive disorder patients. The present study highlights some main indications: a significant relationship between the disturbances of element levels and vitamins (E and A) with MDD. Cu and Zn seemed to have a crucial role in understanding the pathogenesis of depressive disorders, where Cu/Zn ratio could have an important role in the diagnosis and monitoring of MDD. Moreover, the results suggest that the reduction in the antioxidant vitamin E leads to increased risk of MDD. Finally, more studies on using trace element supplementation would be suggested to clarify their effect, in order to improve the therapy of MDD.

Keywords Trace elements · Vitamins · Major depressive disorder · Cu · Zn

Introduction

Mental disorders are a term refers to a range of psychological diseases associated with mental disability that make people unable to think properly [1]. A very large number of mental disorders are classified by psychiatry, and the most common cases include depression, bipolar affective disorder, dementia, intellectual disabilities, and schizophrenia. Globally, depression (also known as major depressive disorder) affects approximately more than 300 million cases of mental disability and therefore is considered as one of the most common psychological diseases [2]. Major depressive disorder (MDD) is a highly complicated disease that affects the entire life of patient, such as mood, behavior, appetite, sleep, and other physical functions. Patients with MDD are almost losing their interest in activities and tend to be alone [3, 4]. So far, the main causes of mental disorders, especially depression, are still unclear and need extensive studies and deep understanding.

Brain is the major organ which consumes about 25% of the human body total oxygen; therefore, it is considered highly susceptible organ to oxidative stress. Oxidative stress occurs when there is an imbalance between the cellular production of reactive oxygen species (ROS) and antioxidant levels. It has been reported that oxidative stress is associated with the majority of mental disorders, including MDD [5, 6].

Antioxidants are substances that may protect cells from the damage caused by unstable molecules known as free radicals [7]. Therefore, antioxidants are molecules capable of slowing or preventing the oxidation of other molecules. Although oxidation reactions are crucial for life, they can also be cell-damaging. The human body has multiple types of antioxidants (e.g., vitamin E) that are essential for maintaining optimal health. It has been found that any decline in the levels of antioxidants can cause oxidative stress and may cause damage or kill cells [8]. Vitamin E is an antioxidant which protects against cellular damage that occurs by molecules containing highly reactive oxygen.

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One of the most important benefits of vitamin E is to diminish the toxic effects of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [9]. Moreover, any deficit in vitamin E can reduce the defense ability against oxidative stress [10].

Trace elements are dietary minerals required in very small amounts for the growth, development, and physiology of the healthy human body. They have crucial catalytic and structural roles, besides they act as cofactor for most of the enzymatic reactions in the body [11]. On the other hand, studies have found that there is a relation between the trace element levels and the body health. It has been found that any changes in the optimum levels of these elements may adversely affect most of the human biological processes, and it has also been reported, to some extent, that excessive levels of trace elements can be toxic for the body health [11, 12]. In fact, brain is one of the most Cu-rich organs among other human organs and any imbalances in the concentration of this metal may lead to many injuries [13]. Cu plays an essential role in the activities of many physiological enzymes including ceruloplasmin, dopamine-beta hydroxylase, and tyrosine hydroxylase. It has been reported that ceruloplasmin can affect the neurotransmitter compounds noradrenaline and 5-hydroxytryptamine, so any imbalances in this enzyme may lead to abnormal mental status [14]. Narang et al. have reported that high levels of Cu may affect the function of dopamine-beta hydroxylase which in turn lead to impaired synthesis of noradrenaline [15].

Zinc has an important role in the antioxidant defense systems. It has an inhibitory action for nicotinamide adenine dinucleotide phosphate oxidase (NADPH), which in turn leads to decreased ROS generation. In addition, it plays a role in the metallothionein generation, which is considered a good scavenger of hydroxyl radical [16, 17]. Zn and Cu are a key component of Cu/Zn superoxide dismutase, an enzyme with antioxidant activity [18].

Recently, researchers have focused on investigating the association between trace elements and vitamin levels with some diseases such as toxoplasmosis, asthma, and cancers [19–22]. Here we aim to evaluate the serum content of the elements (Cu, Zn, Ni, Cr, Mn, Mg, and Al) and vitamins (A and E) of MDD patients. Atomic absorption spectrometry and high-performance liquid chromatography (HPLC) techniques were used to determine serum levels of all elements and vitamins, respectively. This study could be useful to understand the potential clinical importance of those elements to be classified as biomarkers of MDD.

Materials and Methods

Patients and Controls

This research was carried out in the Poison Centre at Ghazi Hariri Hospital for Specialized Surgery/Ministry of Health, Nutrition Research Institute (NRI), and Chemistry department/College of Science/Mustansiriyah University, Baghdad, Iraq between December 2016 and October 2017. Sixty men diagnosed with MDD, with age ranging from 40 to 60 years, as well as 60 healthy male volunteers as the control group, with age ranging from 39 to 58 years, were included in this research. All samples of patients were collected from Al-Rashad Psychiatric Hospital/Ministry of Health, Baghdad, Iraq. The symptoms and signs of the patients diagnosed with MDD were evaluated by specialist physicians at the hospital. Exclusion criteria included a history of smoking, drinking alcohol, hypertension, diabetes, acute infection, thyroid disorders, and nutrient supplementation. The healthy volunteers (controls) underwent the same procedures and exclusion criteria as the MDD patients.

Sample Collection, Preparation, and Analytical Methods

Five milliliters of blood, of each individual of patients and healthy control, was withdrawn from vein. Blood sample was placed in a gel tube and allowed to clot on bench for 20 min, then centrifuged at 2000×*g* for 10 min. The obtained serum was stored in a refrigerator at − 20 °C for subsequent analysis.

The standards and chemicals used in this research were purchased from Sigma-Aldrich Company, Germany. Serum levels of Cu, Zn, and Mg for all samples were determined by flame atomic absorption spectrophotometer (FAAS, Model AA646, Shimadzu Corporation, Kyoto, Japan), whereas levels of Ni, Cr, Mn, and Al were determined by flameless atomic absorption spectrophotometer (GFAAS, Model 210VGP, Buck Scientific, USA) [23]. Serum samples were diluted with tenfold deionized distilled water (nanopure water (18.3 Ω)) for Cu and Zn measurements and assayed at wavelengths 324.7 nm and 213.9 nm respectively. The sample was diluted 50-fold by lanthanum chloride heptahydrate for Mg measurement, and the assay was performed at wavelength 285.2 nm. The serum levels of Ni, Mn, Cr, and Al were measured directly by injection to the graphite tube of the GFAAS at wavelengths 232 nm, 379.5 nm, 357.9 nm, and 309.3 nm, respectively.

The calculated detection limits were 0.003, 0.007, 0.001, 0.002, 0.003, 0.002, and 0.001 μg/dl, for Cu, Zn, Ni, Cr, Mn, Mg, and Al respectively. The accuracy of the measurements was confirmed by using a certified reference material, NIST SRM 1640A Trace Elements in Natural Water (National Institute of Standards and Technology (NIST), USA).

Serum levels of vitamins E and A were determined for each sample by HPLC technique, using a slightly modified form of the method previously described by Cetinkaya and Ozcan [24]. All HPLC assays were conducted using a Knauer HPLC system (Berlin, Germany), with an analytical C_{18}, 5 μm (250 × 4.6 mm) reverse phase KNAUER column, under PC control.

The samples were prepared for injection to the HPLC system, by adding 100 μl ethanol to 200 μl of serum, the solution incubated at room temperature for 10 min followed by the addition of 400 μl methanol (MeOH) and vortexes for 15 s. To this mixture, 1000 μl of hexane was added and vortexed for another 60 s. The mixture was centrifuged for 5 min at 3000×*g*. The supernatant was transferred to a fresh tube (the hexane extraction step was repeated three times). Hexane was evaporated, and the sediment was reconstituted in 100 μl mobile phase (MeOH/H_2O) and then filtrated by passing through a Millipore 0.22 μm Millex-GS sterilizing filter unit.

The serum pre-treatment samples then chromatographically analyzed using MeOH/H_2O (90–10%) as mobile phase with 1.2 ml/min flow rate and UV detection at wavelength 286 nm.

Statistical Analysis

All data were analyzed using descriptive statistics and Independent-Samples Student *t* test of the Statistical Package for Social Sciences (SPSS) program version 22.0. The resulting values were expressed as mean ± standard deviation (SD). Pearson's correlation analysis was also carried out to determine the relationships between all study variables. The statistical tests were considered to be significant at the $p < 0.05$ and highly significant at the $p < 0.01$ with 95% confidence interval.

Results

The detailed statistical treatment of the obtained data containing mean ± standard deviation, lower and upper limits, and *p* values has been presented in Tables 1 and 2. A significant difference in the serum levels of all studied parameters was reported between the MDD patients and the healthy controls. The serum levels of Cu, Cr, and Al in the patient group were found raised when compared to those of the control group, Table 1 and Figs. 1 and 2. This increase in Cu, Cr, and Al concentrations of MDD was found to be statistically highly significant ($p < 0.001$). In contrast, the serum levels of Zn, Ni, Mn, and Mg of the MDD group showed a clear reduction in the concentration as compared to the control group, see Table 1 and Figs. 1 and 2. The difference between the two groups was found to be statistically highly significant ($p < 0.001$). Additionally, the Cu/Zn ratio calculated for the patients with MDD and control groups was 2.16 and 1.17 respectively, and this difference was statistically significant.

Data analysis revealed that there was a marked depletion of serum vitamin (E and A) levels in the MDD patients when compared to the control group, Table 2 and Fig. 3. Although the reduction in the vitamin E level was more noteworthy than vitamin A, they both showed statistically significant values, Table 2.

Pearson's correlation analysis revealed a tendency for a positive correlation to appear between the age of patients and the levels of Ni as shown in Table 3. The analysis also revealed a tendency toward a positive correlation between the body mass index (BMI) of patients and the levels of Mg and Mn, Table 3. Furthermore, Cu was found positively correlated with Ni and vitamin A. In addition, Zn was also found positively correlated with Cr and vitamin A. Also there was a tendency toward a positive correlation between Ni and vitamin E, and between Mg and vitamin E, Table 3.

Discussion

Trace elements play essential roles in many human metabolic and physiological processes. These processes can be affected by imbalances in the optimum levels of trace elements, which in turn have been found to be associated with several diseases such as cancer, psychiatric disorders, and schizophrenia [11, 25–27]. In the present case–control study, the levels of some elements were decreased, but some were increased as compared to controls. This disturbance could be associated with

Table 1 Comparison of trace elements Cu, Zn, Cr, Mg, Ni, Mn, and Al between the MDD patients and control groups

Element	Control group				Patient group				*p* value
	Mean	SD	Lower limit	Upper limit	Mean	SD	Lower limit	Upper limit	
Cu (μg/dl)	112.22	13.06	108.84	115.59	155.23	11.58	152.22	158.21	< 0.001
Zn (μg/dl)	96.02	10.82	93.22	98.81	71.75	8.33	69.59	73.91	< 0.001
Ni (μg/dl)	0.051	0.012	0.048	0.055	0.023	0.006	0.022	0.025	< 0.001
Cr (μg/dl)	0.134	0.021	0.129	0.139	0.211	0.041	0.201	0.221	< 0.001
Mn (μg/dl)	0.169	0.029	0.161	0.176	0.063	0.018	0.059	0.068	< 0.001
Mg (μg/dl)	164.2	14.6	160.4	167.9	109.5	10.9	106.7	112.4	< 0.001
Al (μg/dl)	0.006	0.001	0.0059	0.0063	0.021	0.003	0.019	0.022	< 0.001

Table 2 Comparison of vitamins (E and A) between the MDD patients and control groups

Element	Control group				Patient group				*p* value
	Mean	SD	Lower limit	Upper limit	Mean	SD	Lower limit	Upper limit	
Vitamin E (μg/dl)	1231	406	1126	1336	351	90	328	375	< 0.001
Vitamin A (μg/dl)	56	16	51	60	48	15	44	52	< 0.05

MDD or with other reasons, which encourages further specific studies.

Herein, serum copper levels of MDD patients have significantly differed from those obtained in healthy volunteer samples. Results reveal a remarkable increase in serum level of Cu in patient as compared to control. Likewise, previous studies have indicated elevated levels of Cu in sera of patients diagnosed with mental retardation and depressive disorder [15, 25, 28]. Whereas, another study has not recognized a difference between Cu values in MDD patients and control [29]. According to our results, it could be suggested that high Cu levels may presumably interfere with the pathogenesis of MDD.

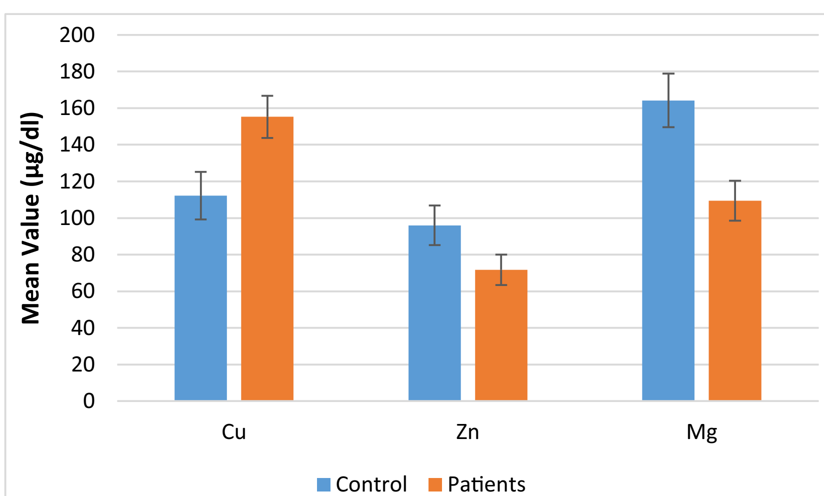
It has previously been reported that there is a relation between low Zn levels and mental disorders [5]. In addition, it has found that Zn levels in hair and nails were associated with chronic depression [30]. The present study demonstrates that the serum Zn levels in MDD patients were significantly lower than those obtained in healthy volunteers. These findings give further evidence for the association of low Zn level with the risk of MDD, which are consistent with the results reported by previous studies [28, 31]. On the contrary, our findings disagree with another previous study, which has demonstrated high Zn concentration in the serum of patient with MDD [25]. However, it has been found that Zn deficiency is quite common among depression and psychogeriatric patients [32].

A previous study suggested that an imbalance of the Cu/Zn ratio could be a useful indicator of the prognosis of diseases than Zn or Cu levels separately [33]. Moreover, the present study indicates a significant increase of the Cu/Zn ratio in MDD patients (2.16) compared with the control group (1.17), ($p < 0.05$). In fact, it has been found that there is a strong relationship between oxidative stress and Cu/Zn ratio [34]. Therefore, we could suggest that the imbalance in the Cu/Zn ratio here is probably a useful indicator of diagnosis and prognosis of MDD, and an indicator of the weakening of the antioxidant defense system of patients.

Previous studies around the Mg levels have not shown any statistically significant differences in patients with MDD when compared to control [25, 35]. Conversely, the current study shows that Mg concentrations were lower in MDD patients than in controls. These results are consistent with those obtained by other studies which have reported low levels of Mg among MDD patients [28, 36, 37]. In fact, Mg deficiency has been shown to influence numerous biological processes of the human body, and it is accompanied by increased levels of oxidative stress [38]. Thus, from the results of the present work, it can be concluded that increased risk of MDD may be related, to some extent, to the decline of Mg concentration.

The biological function of Ni in the human body is still unclear [11]. Up to date, no information is available about the influence of Ni on mental disorders. Hence, this study

Fig. 1 Serum Cu, Zn, and Mg levels in MDD patients and controls



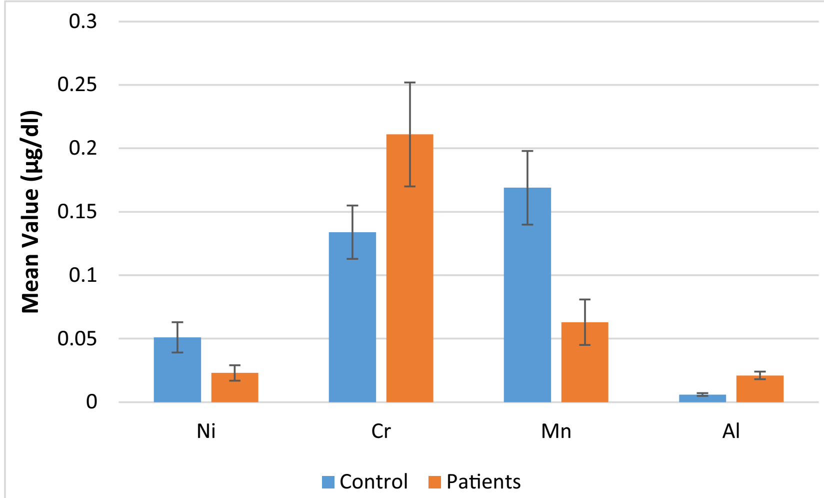


Fig. 2 Serum Ni, Cr, Mn, and Al levels in MDD patients and controls

can be regarded as one of the first attempts to evaluate the association between Ni and MDD. In which, Ni levels were found to be statistically lower in MDD patients when compared to healthy controls, so these results may be particularly important and reliable source of knowledge about the potential role of Ni in mental disorders, especially depression. More studies are still needed to clarify the implication of nickel in the pathogenesis of mental disorders.

We have found that the Cr contents in the serum of MDD patients were significantly higher than those of healthy persons. These results give a strong suspicion of an association between Cr exposure and increased risk of MDD. As a toxic agent, Cr is able to induce oxidative stress in the human body and ultimately leads to cell disruption [39]. Therefore, the high levels of Cr estimated in the present work might be suggested to be associated with the pathogenesis and etiology of mental disorders.

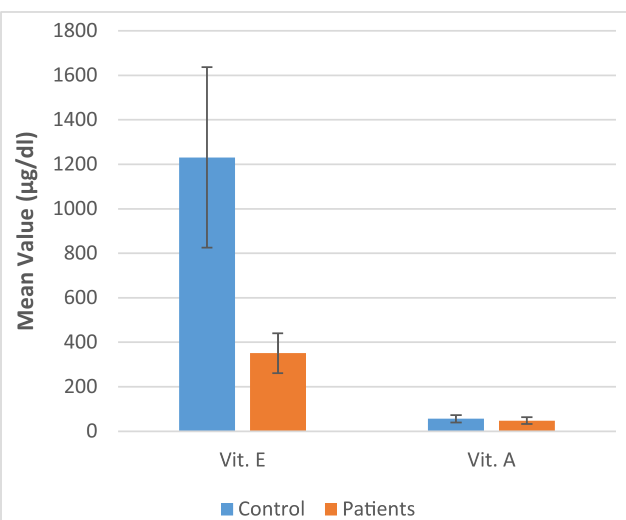


Fig. 3 Serum levels of vitamins (E and A) in MDD patients and controls

Manganese is a cofactor with many cellular enzymes, especially those with antioxidant activity [40]. Several studies have attempted to examine the expected role of Mn in pathogeneses of a variety of mental disorders such as Wilson's disease, Pick's disease, and schizophrenia, whereas, it has been found that this element plays an important role in mental function [41, 42]. It has also been found that Mn content in hair and nails was strongly associated with chronic depression [30]. The mean value of serum Mn has been found lower in depressed patients than healthy controls [28]. Similarly, in this work, the results recorded a significant decrease in serum Mn levels of MDD patients in comparison with controls, which may reflect the valuable participation of this element in antioxidant processes to reduce the oxidative stress induced in patients with mental disorders.

It has previously been found that Al is implicated in the etiology of mental disorders, e.g., Alzheimer's disease and schizophrenia [43, 44]. It has been also reported that workers in the Al industries are suffering from mental problems, such as cognitive decline, memory affection, depression, and anxiety [45]. In addition, it has been found that high level of Al can inhibit the activity of dopamine-beta-hydroxylase which leads to the impaired synthesis of the noradrenaline. Noradrenaline deficiency has found to be associated with depression [46]. Therefore, the findings of the present work suggest that higher levels of Al might be associated with an increased risk of MDD. However, more clinical experiments should be carried out to explore the role of Al in the pathophysiology of mental disorders.

The present work has also indicated that the level of vitamin E was significantly decreased in MDD patients as compared to controls. The results have also indicated, for the first time, moderately low levels of vitamin A in MDD patients. Many previous studies have reported similar results with regard to vitamin E [47, 48]. It has been proved that oxidative stress plays a vital role in the pathophysiology of depression

Table 3 Correlations between all variables in MDD patients (*R*-value)

Parameter	Age	BMI	Cu	Zn	Ni	Cr	Mn	Mg	Al	Vitamin E	Vitamin A
Age	1	−0.029	0.035	−0.109	0.434**	0.231	−0.063	0.246	−0.134	0.007	−0.023
BMI	−0.029	1	0.053	0.123	0.081	0.075	−0.353**	−0.267*	−0.106	0.162	0.002
Cu	0.035	0.053	1	−0.016	0.293*	0.169	−0.144	−0.250	−0.195	−0.117	−0.275*
Zn	−0.109	0.123	−0.016	1	−0.155	−0.266*	−0.174	−0.051	0.077	0.198	−0.297*
Ni	0.434**	0.081	0.293*	−0.155	1	0.044	−0.056	0.032	−0.042	−0.296*	−0.194
Cr	0.231	0.075	0.169	−0.266*	0.044	1	−0.134	0.116	0.157	−0.107	0.171
Mn	−0.063	−0.353**	−0.144	−0.174	−0.056	−0.134	1	−0.017	−0.149	−0.108	0.191
Mg	0.246	−0.267*	−0.250	−0.051	0.032	0.116	−0.017	1	−0.142	0.334**	0.071
Al	−0.134	−0.106	−0.195	0.077	−0.042	0.157	−0.149	−0.142	1	−0.152	0.049
Vitamin E	0.007	0.162	−0.117	0.198	−0.296*	−0.107	−0.108	0.334**	−0.152	1	−0.202
Vitamin A	−0.023	0.002	−0.275*	−0.297*	−0.194	0.171	0.191	0.071	0.049	−0.202	1

**Correlation is significant at the 0.01 level (2-tailed)

*Correlation is significant at the 0.05 level (2-tailed)

[49]. Thus, decreased antioxidant vitamin concentrations, especially vitamin E, might be linked to increase risk of MDD.

Conclusion

Despite valuable information about the influence of trace elements and vitamins on the human health, their negative impact on mental disorders, especially MDD, is still unclear. The present work confirms that Cu excess and Zn deficiency may have a crucial role in the pathogenesis of depressive disorders. Likewise, the alteration of Cu/Zn ratio could be one of the useful indicators to recognize MDD patients, as long as no other disorders. Therefore, it is recommended to evaluate both Cu and Zn levels in MDD patients for their prognostic value. Moreover, this study has shown some significant disturbances in the serum levels of Ni, Cr, Mn, Mg, and Al of MDD patients, which might be used to follow up on the progression of the disease. The deficiency of some elements (Cr and Al) and elevation of others (Ni, Mn, and Mg) are perhaps highlighting their partial involvement in the disorder process.

Equally important, the present study confirms that vitamins can also be used to follow up on the health status of patients suffering from mental disorders and predict other complications. Where, the study concludes a potential relation of vitamins E and A with MDD.

It has previously been revealed that Zn supplementation can improve the treatment of MDD patients along with antidepressant therapy [50]. Therefore, further investigations on the effect of trace element supplements on the MDD are recommended, especially those which have decreased here such as Zn, Ni, Mn, and Mg. The uptake of such supplements may improve the response of MDD patients toward the treatment.

Finally, the present study raises the hypothesis that mental disorders, especially MDD, are related to a dramatic effect of trace elements and vitamins. So, further expanded studies and more details are required to clarify the actual role and involvement of trace elements in the pathogenesis of MDD, and the possibility to document them as biomarkers for mental disorders.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the research committee of Mustansiriyah University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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