ORIGINAL ARTICLE

Trace metal profiling in patients with depression in Pakistani population

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Abstract

Objective: To determine level of trace metals in patients with depression in order to explore any association between the two.

Method: The case-control study was conducted at the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology and Armed Forces Institute of Mental Health, Rawalpindi, Pakistan, from January to December 2017, and comprised diagnosed cases of depression with equal number of age- and gender-matched controls. Depression was diagnosed by a consultant psychiatrist as per the International Classification of Diseases version 10 / Diagnostic and Statistical Manual of Mental Disorders -IV criteria and a self-reported depression screening through Siddiqui-Shah Depression Scale. Blood samples were collected from each subject for the measurement of metals like zinc, chromium and copper. Data was analysed using SPSS 24.

Result: Of the 370 subjects, there were 185(50%) in each of the two groups. There were 82(44.3%) males and 103(55.7%) females among the cases with an overall mean age of 37.75±11.49 years, and 65(35.1%) males and 120(64.9%) females with an overall mean age of 39.38±12.56 years among the controls. Mean levels of zinc and copper were significantly different between the groups ($p<0.05$), while the difference was non-significant for chromium ($p>0.05$). Equivocal prevalence of depression was present between males and females ($p=0.04$) without any significant age group association ($p=1.92$).

Conclusion: Blood level of serum zinc and copper were found to be associated with depression.

Keywords: Chromium, Copper, Depression, Pakistan, Zinc.

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Introduction

[1]Depression refers to a condition manifested by feelings of sorrow, desperation, apprehensiveness, distress or hopelessness that incapacitates a person to face challenges, and ups and downs of life with a positive attitude. A depressed person loses his sense of realisation and fails to maintain peace within him as well as in society. Depression reduces people's functioning in terms of years lived with disability and at its worst leads to suicidal attempts, causing about 100,000 deaths per annum globally.[1] These facts were taken as a wake-up call and the Mental Health Action Plan 2013-2020 was formulated. It emphasised upon depression awareness, treatment and preventive measures at national and international levels along with other mental illnesses.[2] But this under-rated mental disorder continued gaining high potential due to modernisation, machines replacing human labour, and insecurities originating from collapsing economies worldwide.[3]

According to Global and Regional Estimates 2005-2015, depression-affected global populace increased by 18% during this period. Out of these 322 million people, almost half lived in South East Asia and Western Pacific regions. Depression can affect anyone but was found more prevalent in females. It has also been declared as the "sole" greatest contributor to world's non-fatal health loss.[4]

Factual figures show that the disease burden of depression in Pakistan is 7.1%.[5] It has affected urban as well as rural populace, students and professionals and even children. Shockingly, its prevalence ranges up to 60%,[6] so the situation is quite worrisome for such a country whose mental health expenditure is only 0.4% of the total healthcare budget.[7]

Underlying mechanisms of depression are complex. A plethora of research indicated disproportion of blood trace metal ions, like zinc (Zn), chromium (Cr), copper (Cu), manganese (Mn) etc., as one of its aetiologies.[8] Zn, the most prolific trace metal in nature, whose deficiency threatens glutamatergic transmissions, ligand and voltage gated ion channels and serotonin receptor dysfunction, which leads to depressive disorders.[9] The role of Zn in central nervous system (CNS) was studied in detail for the first time in 1989. In 2013, Swardfager et al.[9] did meta-analysis and concluded that decreased serum Zn levels were found in depression.

In 1969, Walter Mertz worked on Cr.[10] Brownley et al.[11] in 2015 proved that Cr supplementation improved depression by enhancing insulin receptor activity, indirectly affecting serotonin receptor dysfunction.

Maes et al. studied effects of Cu in depression in 1997. Cu, the 3rd most abundant trace element, is necessary for

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catecholamine transmission and Cu/Zn superoxide dismutase (SOD) that eliminates reactive oxygen species (ROS). Defect in ROS elimination or over-stimulation of N-methyl-D-aspartate (NMDA) receptors lead to depression.[12] Cu levels in depression have been quite controversial. Some studies show raised serum Cu levels in depression[13] whereas others suggest insignificant change in serum Cu levels this mental disorder.[14]

Research regarding this issue is sparse in Pakistani population. Manser et al.[15] in 1989 worked on trace metals, including Zn and Cu, in patients with depression, mental retardation and seizures in Karachi. Being a multi-factorial disorder, blood levels of these trace metals might be different in various regions of Pakistan.

The current study was planned to determine levels of Zn, Cr and Cu in patients with depression, and to explore any association between the two.

Patients and Methods

The case-control study was conducted at the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology (AFIP) and Armed Forces Institute of Mental Health (AFIMH), Rawalpindi, Pakistan, from January to December 2017, and comprised diagnosed cases of depression with equal number of age- and gender-matched controls. After approval from the institutional review board, the sample size was calculated using formula $n=Z_{\alpha/22}pq/(MOE)^2$.[6] The sample was raised using non-probability consecutive sampling technique from among patients of depression at the AFIMH, and healthy controls. Informed written consent and demographic information was obtained from the subjects. The cases were patients of depression diagnosed by consultant psychiatrist as per the International Classification of Diseases (ICD) version 10 / Diagnostic and Statistical Manual of Mental Disorders-IV (DSMIV)[16] criteria and a self-reported screening through the Siddiqui Shah Depression Scale (SSDS).[17] Subjects who had any major illness, like diabetes mellitus (DM), hypertension (HTN) or thyroid disorder, and those who were taking any dietary supplement containing Zn, Cr or Cu were excluded. Later, the cases were further divided into four sub-groups depending on the severity of depression assessed using SSDS. Subjects having score <26 were placed in the normal group, 27-36 in mild, 37-50 moderate and >50 severe sub-groups. Zn, Cr and Cu levels were analysed in blood samples of all the subjects. Blood specimens were run on Agilent 200 Atomic Absorption Spectrophotometer®.[18] Quality control was maintained by ClinChek®-Control for trace metals.

Data was analysed using SPSS 24. Frequencies and percentages were determined for qualitative variables whereas mean ± standard deviation (SD) were calculated for quantitative data. Mean values of trace metal levels were compared in the groups by one-way analysis of variance (ANOVA). Appropriate tests of significance were applied, like 1–sample t test. Odds ratio (OR) with 95 % confidence interval (CI) using chi–square test were also calculated.

Results

Of the 370 subjects, there were 185(50%) in each of the two groups. There were 82(44.3%) males and 103(55.7%) females among the cases with an overall mean age of 37.75±11.49 years, and 65(35.1%) males and 120(64.9%) females with an overall mean age of 39.38±12.56 years among the controls.

Serum level of Zn and Cu were significantly different in the groups when compared against cut-off values (Table 1).

Mean serum Zn level of the cases was significantly low than the controls (p=0.001), while mean Cu level of the cases was significantly higher (p=0.001) compared to the controls. Mean Cr level in both the groups was not significantly different (Table 2). According to SSDS score, 8(4.30%) patients had normal sadness, 41(22.20%) mild

Table-1: Trace metals level in cases and controls (n=185).

Trace Metal levels	Cut-off (µmol/L)	Cases n (%)	Controls n (%)	Chi-square test	*p*-value
Zinc	<12	89(69.5)	39(30.5)	29.862	0.000
	≥12	96(39.7)	146(60.3)		
Copper	>24	51(87.9)	07(12.1)	39.584	0.000
	≥ 24	134(42.9)	178(57.1)		
Chromium	<0.01	99(50.8)	96(49.2)	0.098	0.755
	≥ 0.01	86(49.1)	89(50.9)		

Table-2: Comparison of means between cases and controls (n=185).

Trace metal	Cases Depressed Mean±SD (µmol/L)	Controls Non depressed Mean±SD (µmol/L)	t- test	*p*- value
Zinc	11.83±4.17	13.32±3.63	3.679	0.00
Chromium	0.009±0.01	0.008±0.01	0.628	0.530
Copper	19.14± 6.17	15.73±4.20	6.204	0.00

SD: Standard deviation

Table-3: Association between SSDS and trace metals level in Cases (n=185).

Trace Metals	Siddiqui Shah Depression Scale (SSDS)				*p*-value
	I Normal sadness Mean±SD (µmol/L)	II Mild Depression Mean±SD (µmol/L)	III Moderate Depression Mean ±SD (µmol/L)	IV Severe Depression Mean ±SD (µmol/L)	
Zinc	13.45±3.61	11.87 ±3.94	11.97 ±4.37	11.31 ±3.71	0.003
Copper	15.4 ±4.11	18.9 ±5.74	19.0 ±5.86	19.9 ±7.09	0.000
Chromium	0.009±0.01	0.013 ±0.02	0.008 ±0.01	0.002 ±0.01	0.001

SD: Standard deviation

depression, 101(54.60%) moderate depression, and 35(18.90%) patients had severe depression.

There was an inverse association between SSDS and blood Cr and Zn levels in depressed patients, indicating that the severity of depression correlated with lower Cr (p=0.001) and zinc (p=0.003) levels. There was a significant positive correlation between serum Cu level and SDSS score (p=0.001) (Table 3).

Discussion

In the current study, depression was found to be equivocal in males and females (p<0.05). Sarah et al.[19] conducted a study in 23 countries and found prevalence of depression much more in females than in males. Although we did not observe marked contrast between age groups in both genders, we noticed that negative manifestations, like lack of emotional sensitivity, provocation, interaction and inability to succeed, predisposed depression.

There is expanding evidence proposing that transition metal ions are vital for various metabolic mechanisms and their balance is crucial for life. As disproportion of trace metal ions is one of the aetiologies of depression, we observed blood levels of Zn, Cr and Cu to get better understanding of this association. Most of the available studies have dealt with single metal in depression, and, thus, the current study has an edge over such studies.

We found a significant fall in the blood levels of Zn in depressed patients in contrast to controls. Our results correlate with the findings of a previous meta-analysis[20] which reported that Zn deficiency is associated with depression and Zn has promising future in pharmacological antidepressant therapy. Another study[21] found Zn as a potential biomarker in major depressive disorder when 50 depressed patients were compared with healthy volunteers. In contrast, Gronli et al.[22] found Zn deficiency even in the absence of depression when 100 people aged >64 years were studied.

We found raised Cu levels in depressed population. Mustak et al.[23] showed higher Cu levels in 50 depressed patients compared to their controls, coinciding with our work.

There was non-significant decrease in the levels of Cr in our study which is in accordance with the findings of a study[24] done in 2011 on 178 individuals working in iron and steel industry in Spain. On the other hand, a randomised controlled trial (RCT)[25] in 2005 on 113 depressed adults observed low levels of Cr before trial that improved after Cr supplementation.

Dissimilarities between studies may arise from the difference in time of metal ions measurement, depressive phase of the participants, resistance to medication, duration of illness or lifestyle of the participants.

Larger longitudinal multi-centre follow-up studies with larger sample size are required to confirm the potential application of blood levels of Zn and Cu in the early detection of depression and their role in the monitoring of disease progression. Lifestyle, socioeconomic status and dietary habits also affect blood trace metals level and that also need to be accounted for in further studies.

Conclusion

Cu toxicity and Zn deficiency were found to be associated with depression, whereas no association was found for Cr.

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