Prognostic factors associating with depression score in male patients; Inflammation, oxidative stress and serum copper and zinc: A cross-sectional study

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Research

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Abstract

Background

The prevalence of depression increased about 18% during a 10-year period between 2005 and 2015. The aim of the present study was to investigate the association between serum zinc and copper, PAB, SOD and hsCRP in men with depression.

Methods

In this study, 3768 men, were recruited as part of MASHAD study. Demographic, anthropometric and metabolic data measured and recorded for all subjects. The Beck Depression Inventory (BDI) was used for assessing depression in all participants. Serum zinc and copper concentration, hs-CRP, PAB (Pro-oxidant- Antioxidant Balance), and SOD (Superoxide dismutase) were measured in all subjects.

Results:

The mean level of copper in males with depression is significantly lower than normal males ($p < 0.05$); despite the lower level of zinc in depressed subjects, this was not significant ($p > 0.05$). The median of hs-CRP and mean of PAB were significantly higher in depressed subjects ($p < 0.001$). Logistic regression analysis was performed to determine the odds ratio (OR) for an association of serum zinc, copper, hs-CRP, SOD and PAB with depression in males. The subjects with a serum copper < 80 µg/dl (Q1) had a 1.337 (1.13–1.582) higher chance of depression and the chance of depression increased 1.021(1.013–1.029) with elevating 1 mg/l of serum hs-CRP. 1.021(1.013–1.029). These data remained the same after adjustment for each other's. Furthermore, our results strongly suggested that hs-CRP and copper were the independent risk factors for depression in male patients.

Conclusion:

Inflammation and copper status, not zinc concentration, are two factors that may play a role in depression in male patients.

Introduction:

According to the World Health Organization, depression affected 350 million people, about 4.4% of the world population in 2015. The prevalence of depression increased about 18% during a 10-year period between 2005 and 2015. Depression accounted for 7.5% of the total Years Lived with Disability (YLDs) globally in 2015. More than 80% of the prevalence of depression globally occurs in low and middle income countries(WHO, 2017). Depression accounted for 8.62% (6.06%-9.2%) of the total YLDs in Iran in 2016 and it is ranked as one of the most important contributors of non- fatal health loss amongst both sexes(IHME, 2018). Zinc is an important trace mineral element and an important cofactor for more than 300 cellular enzymes. It is involved in a variety of biological, structural and catalytic process in the human body(Grønli, Kvamme, Friborg, & Wynn, 2013; Kambe, Tsuji, Hashimoto, & Itsumura, 2015). The

Recommended Dietary Allowance (RDA) is 8 mg/day for women and 11 mg/day for men(CW & CS, 2009). Zn deficiency occurs in all age group and all nationalities. A study conducted in Tehran city showed Zn deficiency in 31.1% of junior high school students(Mahmoodi & Kimiagar, 2001). The prevalence of zinc deficiency in 3–18 years old children in Shiraz, Iran was 7.9%(Dehghani, Katibeh, Haghighat, Moravej, & Asadi, 2011). In another research, the prevalence of zinc deficiency among elementary school children in east of Iran was 28.1% (Fesharakinia, Zarban, & Sharifzadeh, 2009).

Behavioral manifestations of zinc deficiency are known to include: depression, anorexia, impaired cognitive functions, irritability, and lethargy(Maes, De Vos, Demedts, Wauters, & Neels, 1999). Some studies have demonstrated an association between zinc deficiency and depression (Grønli et al., 2013; Młyniec & Nowak, 2012; Siwek et al., 2009; Tassabehji, Corniola, Alshingiti, & Levenson, 2008).

Copper is an essential trace element which is required for growth, bone strength, immune function and brain development. Many enzymes, such as cytochrome c oxidase, ceruloplasmin, Cu/Zn superoxide dismutase, and amine oxidases require copper for catalytic activity(Jaiser & Winston, 2010).

There have been some reports that patients with depression have higher levels of serum copper, even after antidepressant treatment(Russo, 2011; Schlegel-Zawadzka, Zieba, Dudek, Zak-Knapik, & Nowak, 1999). Copper supplement have been reported to reduce anxiety and depression in pregnant women(Kashanian, Hadizadeh, Faghankhani, Nazemi, & Sheikhansari, 2018).

Superoxide dismutase (SOD) catalyzes the dismutation of the superoxide radical into molecular oxygen or hydrogen peroxide. Therefore, superoxide dismutase enzymes are important antioxidant in almost all cells(Perry, Shin, Getzoff, & Tainer, 2010).

Studies have shown a possible pathophysiological role of oxidative and antioxidative molecules in many neuropsychiatric disorders such as depression(Bilici et al., 2001; Selek et al., 2008).

In some studies it was shown that SOD activity is raised in schizophrenia, bipolar mood disorder and major depression (Kodydková et al., 2009; Kunz et al., 2008). In contrast, in another study the activity of SOD was low in the bipolar depressing episode(Selek et al., 2008).

In major depression, the activation of some immune inflammatory markers such as CRP, leukocytes, monocytes, and oxidative stress are increased(Bilici et al., 2001; Wium-Andersen & Nielsen, 2013).

To date, epidemiological studies on zinc and copper status, superoxide dismutase enzymes and their relationship to depression in the Iranian population are limited. The aim of the present study was to investigate association between trace elements, antioxidant defense and inflammation with depression in male patients.

Methods

Study population

In this study, 3768 men were recruited as part of Mashhad Stroke and Heart Association Disorder (MASHAD) study(Ghayour-Mobarhan et al., 2015). They were originally identified using a cluster randomized methodology during 2007–2008, as described previously. (Ghayour-Mobarhan et al., 2015). Informed consent was obtained from all participants using protocols approved by the Ethics Committee of the MUMS(Ghayour-Mobarhan et al., 2015).

The general inclusion and exclusion criteria of MASHAD study and the total characteristics of the sample population such as marriage status, job status, education level, medication use, biochemical and anthropometric measurements have been published before (Ghayour-Mobarhan et al., 2015).

Assessment Of Depression

The Beck Depression Inventory (BDI) was used to assess depression status (Dozois, Dobson, & Ahnberg, 1998). This questionnaire comprises 21 items each assessed on a zero (lack of depressive symptoms) to three (severe depressive symptoms) scale. A score of 0–13 indicates no or minimal depression, 14–19 mild depression, 20–28 moderate depression and 29–63 severe depression(Scogin & Bienias, 1988). Ghassemzadeh et al (Ghassemzadeh, Mojtabai, Karamghadiri, & Ebrahimkhani, 2005) have validated the Persian (Farsi) translation of this questionnaire with an acceptable internal consistency (Cronbach's alpha = 0.87) and test-retest reliability ($r = 0.74$)(Ghassemzadeh et al., 2005). In this study we categorized participants in two groups, without depression (< 13) and with depression (> 14).

Measurement Of Serum Zinc And Copper Concentrations

Serum zinc and copper concentration were measured using Flame atomic absorption (Varian AA240FS) and a standard curve for zinc and copper was prepared using a zinc and copper standard (Merck and Co. Pharmaceutical Company). Serum samples were diluted with distilled water at a ratio of 1:10. The intra-assay and inter-assay coefficient of variation (CV) were 1.5 ± 0.2% and 2.6 ± 0.4% for Zn and 1.3 ± 0.12% and 2.11 ± 0.32% for Cu. The limit of detection was less than 0.1 mg/ L.

Measurement of serum hs-CRP

Serum hs-CRP concentration was determined using a immunoturbidimetry method, with a detection limit of 0.06 mg/L (Pars Azmun, Karaj, Iran)(Kazemi-Bajestani et al., 2007).

PAB Measurement (pro-oxidant- Antioxidant Balance)

A modified PAB assay was used as previously describe (Alamdari et al., 2008), PAB values were measured in serum samples. A standard curve was drawn from the values relative to the standard samples. The PAB values are expressed in arbitrary HK unit, which is the percentage of hydrogen peroxide in the standard solution. The values of the unknown samples were then computed based on the values obtained from the above standard curve(Alamdari et al., 2008).

Assay Of SOD

For measuring serum SOD activity, Tris–cacodylic acid buffer (0.05 M, pH 8.2) and pyrogallol solution as previously describe (Ahmed, Schott, Gauthier, & Vasta, 2003). The reactions were read in a plate reader at 405 nm in 5-min intervals during of 1 h. The blocking of pyrogallol oxidation was graphically characterized for every dilution of SOD. A level of SOD that inhibited the oxidation of pyrogallol by 50% (relative to the control) was defined as a unit of SOD activity under the conditions described

Statistical analysis

SPSS version 18(SPSS Inc. Chicago, IL, USA) was used for all statistical analyses. The normality of distribution was evaluated using Kolmogorov–Smirnov test. Descriptive statistics including mean, frequency, and standard deviation (SD) were defined for all variables and expressed as Mean ± standard deviation (SD) for variables with normally distribution or median ± IQR for not normally distributed variables. ANOVA and t-test were used for comparing variables with normally distribution and Mann-Whitney U test and Kruskal-Wallis H for not normally distributed variables. For categorical parameters, a chi-square, or Fisher exact tests were used. Logistic regression analysis was used to evaluate the association of zinc and copper quartiles and hs-CRP, PAB and SOD with depression in males. All the analyses were two-sided and p- value < 0.05 was considered as significant.

Results:

Table 1 shows the demographic and biochemical parameters according to zinc quartiles for the participants. 22.8% of all participants and 23.3% of those that had a high depression score had a serum zinc < 70 µg/dl (Q1). There were no significant differences between depression, smoking status, hs-CRP and PAB with zinc quartiles ($p > 0.05$). Serum SOD activity was significantly lower in quartile 1 and 4 than quartile 2 and 3 ($p < 0.05$) (Table 1).

Table 1
demographic and biochemical parameters according to serum zinc quartiles in men

		Q2,3 (70–95)	Q1 < 70	Q4 > 95	p-value
Prevalence,%		1905 (50.6%)	860 (22.8%)	1003 (26.6%)	
Age, y		48.69 ± 7.86	48.16 ± 7.6	48.42 ± 7.85	0.39
Depression	No, 2630	1309(49.8%)	595(22.6%)	726(27.6%)	0.1
	Yes, 1131	593(52.4%)	263(23.3%)	275(24.3%)	
Smoking	Never,2170	1100(50.7%)	484(22.3%)	586(27%)	0.63
	Former,569	295(51.8%)	124(21.8%)	150(26.1%)	
	Current,1027	508(49.5%)	252(24.5%)	267(26%)	
Serum hs-CRP, mg/l		2.37(1.3–4.87)	2.65(1.33–6.06)	2.75(1.5–5.69)[b]	0.46
Serum PAB,		53.14 ± 58.84	54.19 ± 59.87	52.45 ± 55.19[a]	0.6
Serum SOD, U/ ml		2.38 ± 2.28	2.01 ± 2.27[a]	2.12 ± 2.39[a]	0.016
Depression Score		10.75 ± 8.99	10.45 ± 8.52	10.48 ± 9.07	0.61

Data presented as Mean ± SD or inter quartile range. One-Way ANOVA or Kruskal-Wallis H has done for comparing 3 groups.

a: Q2,3 vs Q1 and Q4; b: Q1 vs Q4

There were significant differences between smoking status and depression with serum copper quartiles. Serum SOD activity was significantly lower in quartile 1 of serum copper and as expected PAB level was significantly higher in this group ($p < 0.05$). Interestingly, depression score was also significantly higher in this group ($p < 0.01$). However, the level of hs-CRP was higher in quartile 4 for serum copper ($0 < 0.001$) (Table 2)

Table 2
demographic and biochemical parameters according to serum copper quartiles in male

		Q2,3 (80–130)	Q1 (< 80)	Q4 (> 130)	p-value
Prevalence,%		1956 (51.7%)	914 (24.2)	913 (24.1%)	
Age, y		48.23 ± 7.45	48.67 ± 7.89	48.58 ± 7.23	0.41
Depression	No, 2647	1401(52.9%)	596(22.5%)	650(24.6%)	0.002
	Yes, 1130	554(49%)	315(27.9%)	261(23.1%)	
Smoking	Never,2178	1137(52%)	554(25.3%)	496(22.7%)	0.036
	Former,571	277(48.5%)	133(23.3%)	161(28.2%)	
	Current,1024	541(52.8%)	227(22.2%)	256(25%)	
Serum hs-CRP, mg/l		2.7(1.4–5.92)	2.37(1.34–4.94)	2.59(1.33–6.03)[b]	< 0.001
Serum PAB, HK		53.19 ± 59.87	56.14 ± 58.84	49.45 ± 55.19[b]	0.008
Serum SOD,U/ml		2.22 ± 2.27	2.01 ± 0.028[a]	2.52 ± 0.039[ab]	< 0.001
Depression score		10.2 ± 8.54	11.58 ± 9.65[a]	10.39 ± 8.66[b]	< 0.001

Data presented as Mean ± SD or inter quartile range. One-Way ANOVA or Kruskal-Wallis H has done for comparing 3 groups.

a: Q2,3 vs Q1 and Q4; b: Q1 vs Q4

In depressed participants CRP and PAB were significantly higher in comparison to the non-depressed, despite the reduced serum SOD activity in depressed subjects it was not statistically significant ($p > 0.05$) (Table 3). Also, the level of zinc and copper were lower in depressed subjects and zinc/ copper ratio was higher in this subjects, but this reduction was only significant in the case of serum copper.

Table 3
Trace elements, antioxidant defense and hs-CRP status according to depression in male

	No Depression	Depression	p-value
Serum Zinc	85.8 ± 19.71	84.55 ± 18.38	0.063
Serum Copper	105.94 ± 37.48	102.63 ± 38.88	0.014
Serum Zinc Copper Ratio	0.994 ± 0.77	1.043 ± 0.85	0.094
Serum hs-CRP	1.33(0.88–2.61)	1.66(0.93–3.84)	< 0.001
Serum PAB	51.36 ± 42.73	58.52 ± 45.47	< 0.001
Serum SOD	2.22 ± 2.28	2.24 ± 2.02	0.87
Data presented as Mean ± SD or inter quartile range. T-test or Mann Whitney U has done for comparing 2 groups			

Table 4 shows the associations between zinc and copper quartiles, hs-CRP, PAB and SOD in individuals with different depression scores. The crude odds ratios (ORs) with 95% confidence intervals (CIs) of depression indicated lowest copper quartile versus quartile 2, 3, hs-CRP, PAB were positively associated with depression. After multivariate analysis, the results showed that the subjects with serum copper level < 79 (μg/dl), had a 1.35-fold higher risk of a high depression score and a one unit increase, mg/l, of hs-CRP can elevate the odds of getting depressed 1.016.

Table 4
Unadjusted and Multivariate-Adjusted Odds Ratios of Depression according to zinc and copper quartiles, hs-CRP, PAB and SOD in Male

Serum Zinc	Unadjusted	p-value	Multivariate-Adjusted by each	p-value
Quartile 2,3 (70–95)	Reference			
Quartile 1 (< 70)	0.976(0.819–1.162)	0.78	0.878(0.684–1.125)	0.3
Quartile 4 (> 95)	0.836(0.706–0.99)	0.036	0.874(0.696–1.099)	0.24
Serum Copper				
Quartile 2,3 (80–131)	Reference			
Quartile 1 (< 80)	1.337(1.13–1.582)	0.001	1.35(1.077–1.692)	0.009
Quartile 4 (> 131)	1.015(0.835–1.209)	0.85	0.852(0.664–1.092)	0.2
Serum hs-CRP	1.021(1.013–1.029)	< 0.001	1.016(1.005–1.027)	0.004
Serum PAB	1.004(1.002–1.005)	< 0.001	1.002(1-1.004)	0.082
Serum SOD	0.985(0.741–1.309)	0.86	1.082(0.759–1.543)	0.66

Discussion:

Our study demonstrated that there was no significant difference in serum zinc between depressed and non-depressed subjects, but ORs (95% CI) of depression were 1.35(1.077–1.692) and 1.016(1.005–1.027) in lowest serum copper quartile versus quartiles 2, 3 combined and for serum hs-CRP respectively. The association between zinc to copper ratio, PAB, SOD and depression was not statistically significant.

Similar to our study, in a case control study of 88 depressive patients and 88 volunteers, median serum zinc concentration in depressive patients did not differ from control group(Irmisch, Schlaefke, & Richter, 2010). Our findings were in a good agreement with other studies. Gronli et al. showed that in different psychiatric diagnoses, patients who were not depressed had a higher prevalence of zinc deficiency (Grønli et al., 2013).

Narang et al. illustrated that the mean plasma zinc levels in controls and depressed patients were not significantly different(Narang, Gupta, Narang, & Singh, 1991).

In a placebo-controlled, double blind study, sixty patients, 18-55-year old, received antidepressant and either placebo or zinc supplementation. This study obtained no significant difference in the BDI scores between case and control groups(Siwek et al., 2009).

Several studies have shown an association between zinc deficiency and depression (Maes et al., 1997; Marcellini et al., 2006; Siwek et al., 2010).

In contrast to our study, such inconsistencies may be due to the fact that we studied people with depressive symptoms, rather than a clinical diagnosis of depressive disorder.

Therefore, there is still some ambiguity in the role of serum zinc in depression (Styczeń et al., 2017).

Our study also showed that the mean depression score for those with lowest quartile of copper was significantly higher than highest quartile. In a population based study of 14834 American adults, the daily intake of copper in participants with depression were significantly lower than those without depression. The roles of copper in depression are not well established and future researches are needed to explore the underlying mechanisms(Li, Wang, Xin, Song, & Zhang, 2018).

A case-control study in Korean adolescent girls illustrated an inverse relationship between copper intake and depression(Kim, Choi, Lee, & Park, 2015). It is also shown that Copper supplement may reduce anxiety and depression during pregnancy(Kashanian et al., 2018).

In contrast to our study, some researches showed that patients with depression have higher levels of blood copper, even after antidepressant treatment(Russo, 2011; Schlegel-Zawadzka et al., 1999).

However the roles of copper in depression are not well established and further research is needed to explore the underlying mechanisms(Li et al., 2018). The association between SOD and depression was not statistically significant in the present study. Some studies showed raising of SOD activity in schizophrenia, bipolar mood disorder and major depression(Kodydková et al., 2009; Kunz et al., 2008), while in one study the activity of SOD was low in bipolar depressive episode(Selek et al., 2008).

Studies have showed a possible pathophysiological role of oxidative and antioxidative molecules in many neuropsychiatric disorders(Bilici et al., 2001; Selek et al., 2008). In some studies serum SOD activity were reported to be raised in schizophrenia, bipolar mood disorder and major depression; in contrast in another study the activity of SOD was low in bipolar depressing episode(Selek et al., 2008).

CRP levels were associated with symptoms of depression in our participants which is consistent with previous findings (Elovainio et al., 2009; Liukkonen et al., 2006; Wium-Andersen & Nielsen, 2013). Studies have suggested link between oxidative stress and serval mental disorders such as depression, anxiety disorders, schizophrenia and bipolar disorder(Ng, Berk, Dean, & Bush, 2008; Salim, 2014). In our depressed participants, serum PAB was higher in comparison to the non-depressed, but after multivariate-adjusted analysis this value was no longer significant.

A major strength of this study was a large sample size. Since, our study has a cross-sectional design, it is difficult to make causal inference, and our sample was limited to male subjects only.

In conclusion, our results indicated that there was no significant difference in serum zinc content between depressed and non-depressed subjects. Lowest copper quartile versus highest quartile and hs-CRP, were positively associated with depression. The association between zinc to copper ratio, PAB, SOD and depression was not statistically significant. However due to cross-sectional design, we could not prove causality relationship. Future studies are needed to confirm these findings.

Abbreviations

Zn
Zinc
Cu
Copper
Zn/Cu
Zinc to copper ratio
SOD
superoxide dismutase
PAB
Pro-oxidant anti-oxidant balance
Q
quartile

Declarations

Ethics approval and consent to participate: Not applicable Consent for publication: yes Availability of data and material: Not applicable Competing interests: None Funding: Mashhad University of Medical Sciences Authors' contributions: Susan Darroudi: Write a paper, statistical analysis, Zn & Cu analysis; Habibollah Esmaily: Study design; Batool Tayefi: Write a paper; Narjes Khalili: Write a paper; Haniyeh Darroudi: statistical analysis; Samaneh Abolbashari: Zn & Cu analysis; Gordon A. Ferns: Study design; Amir Hooshang Mohammadpour: Study design; Majid Ghayour-Mobarhan: Study design Acknowledgments: We thank Prof. Gordon A. Ferns and Prof. Gholam Hossein Haghnia for their critical review of this manuscript. Declaration of interest: None Conflict of interest: None Ethical approval: The study's protocol was approved by Mashhad University of Medical Sciences Ethics committee Informed consent: all participants provided informed written consents

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