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Research Article

The relationship between serum level of copper and zinc and depression in older people of Amirkola City

Sakhi Gezel[1], Sedigheh Variani[1], Seyed Reza Hosseini[2]*, Foruzan Kheirkhah[1], Sanaz Azadforuz[1], Hadi Parsian[1], Mostafa Taherkhani[1] and Masoumeh Dadghar[1]

[1]Medical Sciences of Bobol University
[2]Research Center of Factors Influencing Health,
Medical Sciences of Tehran University

ABSTRACT

Background: copper and zinc are essential trace elements in the body. Previous studies have shown that these elements play a vital role in neurological disorders. This study was conducted to investigate the relationship between copper and zinc and depression in older people of Amirkola City.

Methods: This study was conducted as a part of the plan examining the health status of the older people of Amirkola City on 1616 people aged 60 years and older. Demographic data were collected by questionnaire and serum level of copper and zinc was determined by specific kit. Geriatric Depression Scale (GDS) was used to assess depression symptoms, and depression status was interpreted natural (0-4), mild (5-8), moderate (9-11) and severe (12-15). Results were analyzed using SPSS-18 software.

Results: In this study, 500 subjects (52%) were male and 462 subjects (48%) were female. The mean of serum level of copper and zinc in older people was 130.98 ± 55.44 and 36.95 ± 62.47 mcg / dl, respectively. The mean of serum level of zinc in depressed older people was significantly more than that in non-depressed older people (respectively, 49.08 ± 97.65, 93.55 ± 46.36, p=0.05), but the mean of serum level of copper in two groups was similar (respectively, 134.75 ± 56.04, 128.00 ± 54.83 and p=0.06) .The mean of serum level of copper and zinc was significantly different in older people separately based on depression status (p_{cu}=0.01 and p_{zn}=0.05) and serum level of copper in the older people with severe depression was more than that in other older people (respectively, 153.06 ± 53.29, 129.77 ± 53.33 and p=0.004). However, this result was not significant in the case of zinc (p=0.06). The relationship between serum level of copper and depression score was low and negligible (r=0.006).

Conclusions: the results showed that serum level of zinc in the older people with higher depression symptoms was more than that in non-depressed older people, while the serum level of copper in older people with severe depression symptoms was more than that in other older people. Additionally, in people with mild and moderate depression symptoms, no significant difference was found among them in terms of serum level of copper.

Keywords: depression, older people, serum level of copper and zinc, depression symptoms, Amirkola

INTRODUCTION

One of the most common mental health problems of older people is depression that represents different obvious symptoms of prevalence in different parts of the world [1]. Older people

depression is often called subthreshold depression or minor depression. Older depressed people are less complaining of feelings of sadness and longing and even they deny it sometimes. These groups of depressions have mostly physical symptoms, such as fatigue and loss of appetite. Mental preoccupation with health and extreme and obsessively attention to physical symptoms, such as defecation frequency etc., are other features of depression in the older people. Complaints of cognitive symptoms such as forgetfulness and distraction are other common symptoms of depression in older people [2]. Depression leads to increased drug consumption and increased patients' costs for prescriptive and non-prescriptive drugs [3]. The cause of depression in the older people, as younger people is bio-social. Diseases and physical disorders and taking certain medications are important factors in depression [4]. In addition, various risk factors have been proposed for depression in older people, including female gender, positive family history, smoking, sleeplessness, chronic diseases, low level of education, and low economic status [5]. Some studies have shown the correlation between depression and serum level of copper and zinc [6 and 7].

Copper is an essential trace mineral that acts as cofactor in many body processes and plays role in enzymes involved in neurotransmitters' function of brain [6]. Previous studies have shown that copper plays a vital role in neurologic disorders [8, 9]. The conversion of dopamine to norepinephrine in the brain depends on copper. Copper deficiency leads to decreased dopamine and norepinephrine in the brain of rats[10] . Some studies in rats have shown that copper deficiency leads to reduced body growth, reduction in brain development, and significant reduction in mielinizacion [11]. It has been reported that copper may have an impact on the concentration of the serotonin in the brain areas that are neurotransmitter [11].

Since Zinc was discovered, it was found that it plays an important role in many biological processes, including enzymatic function, nucleic acid and apoptosis metabolism. It also plays a vital role in the brain and the immune system development and function (6). It has been reported that intracellular zinc deficiency is associated with damage to the DNA and it plays role in resistant depression treatment. It is proposed that zinc acts as a powerful antioxidant (6). Russo et al (2011) reported that serum level of copper in patients with depression has been increased compared to healthy control group, but it requires more studies to examine its relationship with GABA levels. Moreover, the serum level of zinc in patients with depression was reduced compared to that in control group in this study. Mlyniec et al (2014) reported that copper level was increased during long-term treatment with antidepressants drugs, but zinc level was decreased [13]. Due to the contradictory results in the studies mentioned above, this study was conducted to investigate the relationship between serum level of copper and zinc and depression in older people of Amirkola city.

MATERIALS AND METHODS

This cross-sectional study was a part of the Cohort plan titled as "investigating the health status of the older people in Amirkola" conducted on all people aged 60 years and older in Amirkola City [project number 892 917]. Inclusion criterion of study was consent to participate in the study and exclusion criteria included mineral supplements, taking antidepressants, chronic diseases such as hepatitis B, diabetes mellitus, rheumatoid arthritis, cirrhosis of the liver, kidney disease, and taking iron tablets.

Among the population of study, 962 people met the criteria to be included in the study. Data collection tools were a questionnaire consisted of demographic characteristics and a questionnaire to examine depression status in older people. 15-item Iranian version of Geriatric Depression Scale was used to measure the depression symptoms that its validity and reliability were approved by Malakouti (15). In this scale, score between 0 and

4 is interpreted as natural, score between 5 and 8 is interpreted as presence of mild depression symptoms, score between 9 and 11 is interpreted as moderate depression, and a score between 12 and 15 is interpreted as severe depression symptoms.

Fasting blood sample was taken of all older people, and samples were transferred to the Cellular and Molecular Research Center Laboratory of University. After centrifugation and separation of serum and diluting it with glycerol, serum level of copper and zinc was determined by specific kit. Data were entered into the computer and they were analyzed by SPSS-18 software using descriptive statistics (mean and standard deviation) and analytical tests (T-Test, Chi square and Pearson correlation and Logistic Regression). Significance level for all tests was less than or equal to 0.05.

Findings

Out of 1616 older people studied, 500 (52%) of them were male and 462 (48%) of them were female. The mean of serum level of copper in studied older people was 130.98 ± 55.44 (within the range of 0.60-534.80 mcg / dl). Depression frequency in women, older people living alone, and the illiterate older people was respectively higher than that in male older people, older people who are not living alone, and literate older people (Table 1) .The highest serum level of copper and zinc was observed in patients who had severe depression (Table 2). The mean of serum level of copper in older people with severe depression was significantly higher compared to that in older people without severe depression (p=0.004), but the serum level of zinc was similar in both groups (p=0.06) (Table 3).

The relationship between serum level of copper and depression score was low and negligible. Depression frequency was 21 (7.7%) in older people whose serum level of copper was more than 155, while it was 4.2% in older people whose serum level was below 140.

Based on the serum level of zinc, subjects were divided into three groups of ≤80, 80-120, 120 ≤, and the mean score of GDS was compared in them that it was 4.58 ± 3.42, 4.37 ± 3.45 and 5.11 ± 3.62. Based on Tukey HSD test, significant relationship was found between the groups of 80-120 and more than 120 (p=0.03).

Table 1. Mean and standard deviation of studied variables based on depression status in older people of Amirkola (2011-2012).

Variable	Depression	mean±SD	p-value
Age (year)	Yes	69/91 ±7/38	0/11
	No	69/15 ±7/46	
Body mass index (Kg / m²)	Yes	27/43 ±4/92	0/28
	No	27/10 ±4/50	
Physical activity score	Yes	103/75 ±58/71	0/14
	No	109/44 ±61/42	
Thyroid stimulating hormone (TSH)	Yes	3/47 ±4/18	0/38
	No	3/74 ±5/31	
Copper (mg / dL)	Yes	134/75 ±56/04	0/06
	No	128/00 ±54/83	
Zinc (mg / dL)	Yes	97/65±49/08	0/18
	No	93/55 ±46/39	
Copper/zinc	Yes	1/85 ±1/51	0/33
	No	1/76 ±1/39	

Table 2: Frequency distribution and percentage of some variables in terms of depressive symptoms in older people of Amirkola (2011-2012)

Variable	Depression	Yes		No		p-value
		Frequency	percentage	Frequency	percentage	
Gender	Males	149	29/8	351	70/2	0/001
	Females	276	59/7	186	40/3	
Living alone	No	375	42/5	507	57/5	0/001
	Yes	30	62/5	50	37/5	
Education level	Illiterate	301	48/2	324	51/8	0/001
	Elementary and guidance	113	42	156	58	
	High school and academic	11	16/2	57	83/8	
Smoking	Yes	361	45/6	431	54/4	0/06
	No	64	37/6	106	62/4	

Table 3: Comparison of serum level of copper and zinc in terms of depression symptoms status in older people of Amirkola (2011-2012)

Depression status	n	mean±SD Copper	p-value	mean±SD zinc	p-value
Healthy	537	128/00 ±54/88	0/01	93.55±46.39	0/05
Mild	262	133/34 ±57/98		99.43±50.20	
Moderate	113	129/91 ±51/34		89.23±43.33	
Severe	50	153/06 ±53/29		107.39±53.41	
Total	962	130/98 ±55/44		95.36±47.62	

Table 4: Comparison of copper and zinc level and the copper / zinc ratio in older people with severe depression symptoms in Amirkola city (2011-2012)

Variable	Severe depression	mean±SD	p-value
copper(mg/dl)	Yes	153/06 ±53/29	0/004
	No	129/77 ±53/33	
zinc(mg/dl)	Yes	107/39 ±53/41	0/06
	No	94/70 ±47/22	
Copper/zinc	Yes	1/91 ±1/43	0/56
	No	1/79 ±1/44	

Table 5-4- comparison of frequency and percentage of severe depression in the older people with copper serum level of less than 140 and more than 155

Severe depression Copper level (mg / dL)	Yes		No		OR 95% CI	p-value
	Frequency	Percentage	Frequency	Percentage		
Less than 140	29	%4/2	662	%95/8	(1/07-3/42) 1/91	0/02
More than 150	21	%7/7	250	%92/3		

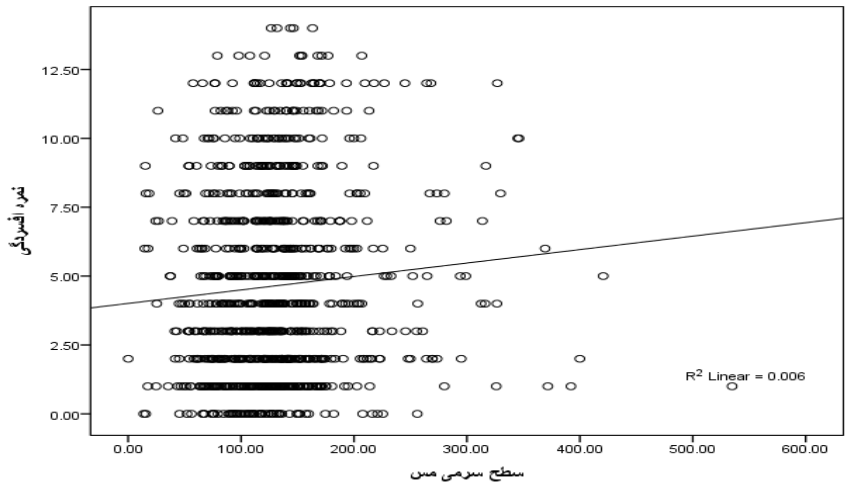

Chart 1: The relationship between serum level of copper and depression score in older people participated in the study

DISCUSSION AND CONCLUSION

The results of the present study conducted to investigate the relationship between the serum level of copper and zinc and depression in the older people in Amirkola city showed significant and direct relationship between zinc serum level and depression. Serum level of copper in older people with severe depression symptoms was significantly higher than that in non-depressed older people, and significant relationship was found between serum level of copper and depression score in the severe depression. However, serum level of copper had no significant relationship with depression score, that it was consistent with results of similar studies [16 and 17].

Results of Russo et al in America showed that serum level of copper and zinc is higher in patients with severe depression than that in healthy patients [7], that it was similar to current study. The highest copper level was observed in older people who suffered from severe depression. After treatment with zinc, zinc level became normal. However, symptoms of depression in people with initial depression remained. Therefore, result of this study show that there is significant difference between lower level of zinc and depression, but depression symptoms were not improved by prescribing zinc and normalization of its level. Therefore, firm conclusion cannot be achieved and there is contraversy in this regard.

Results of studies conducted by Salustri et al in Italy showed that copper is a component of oxidative stress. Depression may be related to autoimmune disorders of body that these reactions may lead to abnormal copper homeostasis. In other words, depression may lead to an increase in copper [17]. In our study, in older people with mild to moderate depression, copper levels were not significantly different from non-depressed older people, that this result was consistent with Salustri results. Salustri stated that the loss of balance between copper and ceruloplasmin is important, while he did not emphasize on copper increases or decreases .In this study, severe depression was significantly correlated with increased copper level, that it can be justified by the fact that copper is symptomatic of depression. In terms of lack of significant relationship in mild and moderate depression in this study, our results are similar to results of Cryton et al who stated that copper level in depressed and non-depressed older people was similar.

In terms of lack of a significant relationship in mild and moderate depression in our study, our

results were similar to results of a study conducted by Cryton who reported that copper in depressed women with a history of postpartum depression was significantly higher than that in other groups. However, in the mentioned study, there was no significant difference among three groups in terms of serum level of zinc. It was not in line with result of this study [6]. In his study, no significant difference was found between family history of postpartum depression group and healthy group in terms of copper level. It may be stated that the history of postpartum depression is indicative of severe depression that it is similar to result of our study. According to results of study conducted by Cryton, the high level of copper may not be the cause of depression, but an association is reported in this regard. It can be justified by autoimmune mechanisms causing depression and an increase in the serum level of copper.

A significant relationship between severe depression and high copper in this study is similar to results of the study conducted by Mezzetti et al [18] who reported a significant correlation between increased levels of copper and major (severe) depression. The level of copper was significantly high in women compared to men, that this result is in line with result of a study conducted by Mezzetti. Mezzetti reported that normal level of copper has no correlation with depression, even in the presence of zinc, but it should be necessarily higher than normal level. In addition, his study showed that zinc level in people with chronic disease is significantly less than that in healthy older people.

In terms of lack of a significant linear relationship between depression score and copper level, this study is not in line with results of Maha [19]. Some of the reasons for this inconsistency include low sample size in Maha study, the lower average age in the samples of Maha study (50 years old), and the use of different questionnaires in two studies. Findings of Maha study were also different from results of current study in the case of zinc. Two another reasons that can be important in this regard include: First, all studied people suffered from Kidney failure that it can justify the incorrect diet and lower intake of zinc. Second, depression in these people may be associated with chronic Kidney disease without lower level of zinc impact. Additionally, Maha A.Hassan has referred to other reasons such as reduced protein absorption, reduced zinc absorption, and reduced levels of albumin.

In terms of a significant relationship between severe depression and high levels of copper, our study results were consistent with results of Huang [21] and Toneli [22]. Lack of significant relationship between depression and age, marital status, and personality was significant with studies conducted by Maha et al, Roozbeh et al [20] and Cunha et al [21] .Lack of relationship between mild and moderate depression in this study was in contrast with a study conducted by Chang who reported that there is a significant relationship between them [22]. The possible cause was small sample and low average age (32-38 years). In addition, total copper level was measured in both studies .Total copper level was measured in our study, but free level of copper was measured in other studies. Some studies, including Panichi stated that a significant positive relationship between the level of copper and depression could be related to ceruloplasmin, while in his investigation, he found that high ceruloplasmin has no correlation with depression[23].

Salustri et al (20100 reported the relationship between depression and high free copper. Russo conducted a study on two groups of anxious and depressed patients and he found that increased level of copper and reduced level of zinc after treatment led to increased level of zinc and copper, but copper level was reduced and zinc level was increased in the anxious group. In the depressed group, there was a significant relationship between the high level of copper and severe depression, similar to our study.Mitani et al reported that serum level of glutamate in patients with depression is significantly higher than that in normal people. In addition, serum glutamate level showed positive correlation with the severity of

depression [24]. In a laboratory study conducted in Tehran, Rafiei et al reported that copper oxide, even at high doses, has no effect on glutamate releasing, but it may lead to reduced glutamate uptake [25]. This result may justify results of our study in which older people with severe depression have higher level of serum and copper. In addition, Yeiser et al reported high level of free zinc and accumulation of melatoniinin in damaged parts of brain tissue in rats.

Fukushima et al (2013) reported that serum level of copper and zinc in the non-depressed patients with Parkinson disease is higher than that in depressed patients with Parkinson disease. Additionally, copper serum level in the control group was higher than that in depressed people with Parkinson. These results are in contrast with results of our study. Its possible justification can be related to use of criteria for diagnosis of depression instead of questionnaire. The nature of Parkinson's disease can also affect the results. Fontana et al (2006) reported that serum level of copper in depressed patients is significantly more than that in control group. Additionally, significant positive correlation was found between serum level of copper and severity of depression. The results of this study are somewhat inconsistent with our study. Reasons for this inconsistency can be small sample size, different questionnaires and different measurement methods used in their study.

Very few studies have selected older depressed people to examine serum level of copper, and this is considered one of the strengths of this study. Another strength of the study is sufficient sample size. One limitation of this study was the lack of investigating and removing the confounding dietary factors to determine serum level of copper accurately. Additionally, as this study was cross-sectional one, we cannot explain cause and effect relationship thoroughly. Results of our study are somewhat similar to results of a study conducted by whittle N. He reported that if diet of rats reduces to 40%, depression symptoms might be improved or created in a way that during the first two weeks, antidepressant behaviors may be observed usually, but in the long-term dietary deficiency, pre- depression behaviors are created. This difference may be due to lack of relationship between zinc level of blood and its brain level.

Takeda and Tamano H have stated that the most important part of zinc related to mood disorders is vesicular and extracellular zinc that they are not changed necessarily in rats with serum deficiency. Observing the antidepressant effects during first few weeks of zinc deprivation can be described as a compensatory mechanism .In the first days, metallothioneins may increase the zinc releasing more than usual. Metallothioneins can bind to zinc atom simultaneously and temporarily. Therefore, when the zinc of cytoplasm is high, they can bind to it and release it, while its level is low (26).

CONCLUSION

The results of this study conducted to examine the relationship between the serum level of copper and zinc and depression in the older people of Amirkola city indicated that mood disorders such as depression are significantly correlated with changes in serum level of zinc and copper. Considering the relationship between serum level of zinc and depression, direct and positive relationship was observed, but considering other studies, it is better that this study to be conducted in a prospective method. The relationship between serum level of copper and severe depression was also direct and significant in this study. It seems that copper has an impact on absorption and release of some neurotransmitters involved in the process of depression. Therefore, further studies are needed for better understanding of severe depression mechanism.

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