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Relationship of Dietary and Serum Zinc with Depression Score in Iranian Adolescent Girls

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Abstract

Zinc deficiency, which is common among Iranian populations, is believed to play a crucial role in the onset and progression of mood disorders such as depression in different stages of life. We have therefore investigated the relationship between serum/dietary zinc status and depression scores among adolescent girls living in northeastern Iran. Serum zinc was measured by flame atomic absorption (Varian AA240FS) and the mean zinc intake was assessed using 3-day food record. A validated Persian version of the Beck Depression Inventory (BDI) was used to determine the severity of depressive symptoms for all subjects. Data were analyzed using SPSS 18 software. There was a statistically significant correlation between dietary zinc intake and serum zinc concentration ($r = 0.117$, $p = 0.018$). Dietary intake of zinc (7.04 ± 4.28 mg/day) was significantly lower among subjects with mild to severe depression symptoms than those with no or minimal depression symptoms (8.06 ± 3.03 mg/day). Dietary zinc intake was inversely correlated with depression score ($r = 0.133$, $p = 0.008$). However, there was no significant difference in serum zinc concentrations among individuals with no or minimal and mild to severe depression symptoms ($p = 0.5$). Dietary zinc intake, but not serum zinc concentration, was inversely associated with depression symptoms. Therefore, controlled clinical trials are needed to determine the efficacy of zinc supplementation in the treatment of depression disorders.

Keywords Serum zinc · Zinc intake · Depression · Adolescence

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Introduction

Zinc deficiency, which is defined as a serum zinc concentration below 70 μg/dl, is associated with neuro-sensory disorders [1, 2]. It is also reported to be strongly associated with the presence of mood disorders such as depression [3, 4]. Moreover, zinc is involved in the regulation of inflammation, neurogenesis, neuroplasticity, and overactivity of the glutamate system in the central nervous system (CNS) [5]. Since derangement of zinc homeostasis may accompany mood disturbances, zinc therapy has been suggested as a potential candidate in the treatment of depression [6]. Several mechanisms have been suggested for the antidepressant properties of zinc including the antagonism of *N*-Methyl-D-Apart receptor (NMDA receptor) which is known to be a zinc channel protein, found on nerve cells, involved in controlling synaptic plasticity [7, 8]. It has been shown that zinc reduces NMDA receptor reactivity and enhances expression of the 5-HT1A serotonergic receptor [9, 10]. Moreover, zinc producing antidepressant-like effects seems to be mediated through its interaction with NMDA receptors and the l-arginine- nitric oxide (NO) pathway [11]. There is a high prevalence of zinc deficiency in some Iranian populations [12], which is partially related to the low soil zinc content in some regions of Iran. Therefore, this study was conducted to determine the relationship between serum/dietary zinc status and depression symptoms in a sample of adolescent girls from northeastern Iran.

Material and Methods

Subjects and Blood Samples

A total of 408 girls aged 12–18 years old were recruited, using a randomized clustering method and computer-generated random number among different areas in Mashhad, northeastern Iran [13]. Subjects who were receiving supplements or antidepressants or had any chronic disease, or hospitalization history in the past 3 month were excluded. Approval was given by the Ethics Committee of Mashhad University of Medical Sciences, and written consent was obtained from their parents. Subjects each completed a 3-day food record with the help of trained staff. This food record included two weekdays and 1 day of the weekend. Data on type, amount, preparation, and time of food or beverage consumed by each subject was obtained. Five milliliters of venous blood was collected by an experienced laboratory technician from each participant, to determine serum zinc concentrations.

Demographic, Anthropometric, and Metabolic Data

For all participants, height (cm), weight (kg), and BMI (kg/m^2) were measured based on standard protocols. Height was measured to the nearest millimeter with a tape measure and body weight was measured to the nearest 0.1 kg with electronic scales. In terms of family characteristics, data regarding parental education, parental marital status, and parental death as well as passive smoking were gathered by questionnaires.

Fasting blood samples were collected after a 12-h overnight fast to determine fasting blood glucose (FBG) and a full fasted lipid profile, consisting of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglyceride (TG), as previously described [13]. The serum high-sensitivity C-reactive protein (hs-CRP) concentration was estimated using an immunoturbidimetric method, with a detection limit of 0.06 mg/L (Pars Azmun, Karaj, Iran).

Measurement of Serum Zinc Concentration

Serum samples were diluted with nitric acid at a ratio of 1:10. Flame atomic absorption (Varian AA240FS) was used to measure serum zinc concentrations. A zinc standard curve was constructed using a zinc standard (Merc and Co. Pharmaceutical Company). The accuracy of the method was 93.0 ± 4.8% which was estimated by measuring a certified reference material (Merc KGaA 64271 Darmstadt, Germany) containing a known amount (1000 ± 2 mg/l) of zinc. The intra-assay and inter-assay coefficient of variation (CV) were 1.5 ± 0.2% and 2.6 ± 0.4%, respectively. The limit of detection was less than 0.1 μM.

Assessment of Dietary Zinc Intake

A 3-day food record was obtained from each participant to assess dietary zinc intake. Each record was analyzed for micro- and macronutrient content using the Nutritionist IV software (version 7.0; N-Squared Computing, Salem, OR, USA) which was modified for Iranian food items. The Estimated Average Requirement (EAR) of 7.3 mg/day has been reported for girls aged 14–18 years [14].

Assessment of Depression Symptoms

To assess depression status, the Beck Depression Inventory (BDI) was used [15]. This questionnaire contains 21 items each assessed on a zero (lack of depressive symptoms) to three (severe depressive symptoms) scale. A score of 0–15 indicates no or minimal depression, 15–19 mild depression, 20–29 moderate depression, and 30–63 severe depression [16]. Ghassemzadeh et al. (2005) have validated the Persian

(Farsi) translation of this questionnaire with an acceptable internal consistency (Cronbach's alpha = 0.87) and test-retest reliability ($r = 0.74$) [17].

Statistical Analysis

SPSS version 18 (SPSS Inc. Chicago, IL, USA) was used for all statistical analyses. The normality of the data was assessed using the Kolmogorov-Smirnov test, and the results showed that except for triglyceride and hs-CRP, all variables follow a normal distribution. Chi-square tests were used to compare the qualitative variables. For normally distributed variables, Student's t test was performed. The Mann-Whitney U test was used for non-normal variables. Pearson correlation was applied for assessment of correlation between the following variables: (1) correlation between serum zinc and dietary zinc, (2) correlation between serum zinc concentration and depression score, and (3) correlation between dietary zinc intake and depression score. β-coefficients were calculated using univariate and multivariate linear regression models to assess the association between serum/dietary zinc and depression score. All the analyses were two-sided and a p value < 0.05 was considered as significant.

Results

Participants were stratified for their depression status based on their depression scores [338 (82.8%) subjects with no or minimal and 70 individuals (17.2%) with mild to severe depression symptoms]. The demographic and biochemical characteristics of individuals with no or minimal and mild to severe depression symptoms are presented in Table 1. There were no significant differences in age, height, BMI, FBG, TC, LDL, HDL, TG, hs-CRP, and energy intake between groups. Subjects with mild to severe depression symptoms showed a significantly higher percentage of parental death and parental divorce when compared with those with no or mild depression symptoms (Table 1).

Data regarding serum zinc concentration and dietary zinc intake of individuals with no or minimal or mild to severe depression symptoms are reported in Table 2. The mean serum

Table 1 Demographic and biochemical characteristics of individuals in no or minimal and mild to severe depression symptoms

		Depression severity score		p value
		No or minimal ($n = 338$)	Mild to severe ($n = 70$)	
Age (year)		15.0 ± 1.5	15.2 ± 1.5	0.2
Weight (kg)		54.3 ± 11.3	52.5 ± 10.7	0.3
Height (m)		158.0 ± 6.2	158.4 ± 6.1	0.4
BMI (kg/m^2)		21.7 ± 4.1	20.9 ± 3.7	0.2
FBG (mg/dl)		87.5 ± 10.7	88.2 ± 10.4	0.6
TC (mg/dl)		162.8 ± 26.0	160.4 ± 33.7	0.5
LDL (mg/dl)		99.7 ± 22.4	99.1 ± 26.7	0.8
HDL (mg/dl)		46.9 ± 8.9	46.6 ± 7.8	0.8
TG (mg/dl)		59 (76–100)	85 (58.5–104.5)	0.3
hs-CRP (mg/dl)		0.91 (0.47–1.82)	0.99 (0.60–1.46)	0.9
Energy intake (kcal)		2004.4 ± 626.2	1881.7 ± 621.5	0.1
Father's education	Under diploma, n Upper diploma, n	293 (85.0%) 52 (15.0%)	37 (92.5%) 3 (7.5%)	0.1
Mother's education	Under diploma, n Upper diploma, n	311 (90.4%) 33 (9.6%)	37 (92.5%) 3 (7.5%)	0.4
Passive smoker	Yes, n No, n	68 (20.0%) 273 (80.0%)	10 (25.6%) 29 (74.4%)	0.2
Parental death	Yes, n No, n	3 (1.0%) 325 (99.0%)	7 (10.6%) 59 (89.4%)	< 0.001
Parental divorce	Yes, n No, n	18 (5.5%) 311 (94.5%)	9 (13.6%) 57 (86.4%)	0.02

Values are expressed as mean ± SD for variables with normal distribution, and median and interquartile range for non-normally distributed variables. Categorical data are expressed as number (percentage). *BMI* body mass index, *FBG* fasting blood glucose, *TC* total cholesterol, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, TG triglyceride, hs-CRP high-sensitivity C-reactive protein

Table 2 Serum zinc concentration and dietary zinc intake of individuals in no or minimal and mild to severe depression symptoms

		Depression symptoms		*p* value
		No or minimal ($n = 338$)	Mild to severe ($n = 70$)	
Serum zinc (μg/dl)		95.3 ± 17.8	97.0 ± 17.4	0.5
Zinc deficiency (< 70 μg/dl)	Yes, *n*(%)	27 (8.0)	3 (4.3)	0.2
	No, *n*(%)	311 (92.0)	67 (95.7)	
Dietary zinc intake (mg/day)		8.0 ± 3.0	7.0 ± 4.2	0.03
Insufficient zinc intake (< 7.3 mg/day)	Yes, *n*(%)	165 (48.8)	45 (64.3)	0.02
	No, *n*(%)	173 (51.2)	25 (35.7)	

Values are expressed as mean ± SD. Categorical data are expressed as number (percentage)

zinc concentrations were 97.0 ± 17.4 μg/dL and 95.3 ± 17.8 μg/dL in subjects with no or minimal or mild to severe depression symptoms, respectively ($p = 0.5$). The mean dietary zinc intake was significantly higher in individuals with no or minimal depression symptoms (8.0 ± 3.0 mg/day) when compared with those with mild to severe depression symptoms (7.0 ± 4.2 mg/day, $p = 0.03$). The percentage of subjects with insufficient zinc intake was also significantly higher in the mild to severe group ($p = 0.02$).

As expected, serum zinc concentration was significantly associated with dietary zinc intake ($r = 0.117$, $p = 0.018$) (Fig. 1). The correlations between serum/dietary zinc and depression score are illustrated in Fig. 2 and Fig. 3, respectively. As shown in Fig. 2, there was no significant correlation between serum zinc concentration and depression score ($r = 0.033$, $p = 0.05$). However, there was a significant negative correlation between dietary zinc intake and depression score ($r = 0.133$, $p = 0.008$) in Iranian adolescent girls (Fig. 3).

The β-coefficients examining the association of serum and dietary zinc with depression score are presented in Table 3. Examination of the β-coefficients also indicated that dietary zinc intake is negatively associated with depression symptoms [$\beta = -0.38$ ($p < 0.01$)], even after adjusting for several potential confounding variables known to affect depression symptoms, including age, passive cigarette smoking, BMI, and hs-CRP [$\beta = -0.30$ ($p < 0.05$)].

Discussion

Our results suggest that a higher dietary zinc intake is associated with less severe depression symptoms. However, there

Fig. 1 Correlation between serum zinc (μg/dl) and dietary zinc (mg/day)

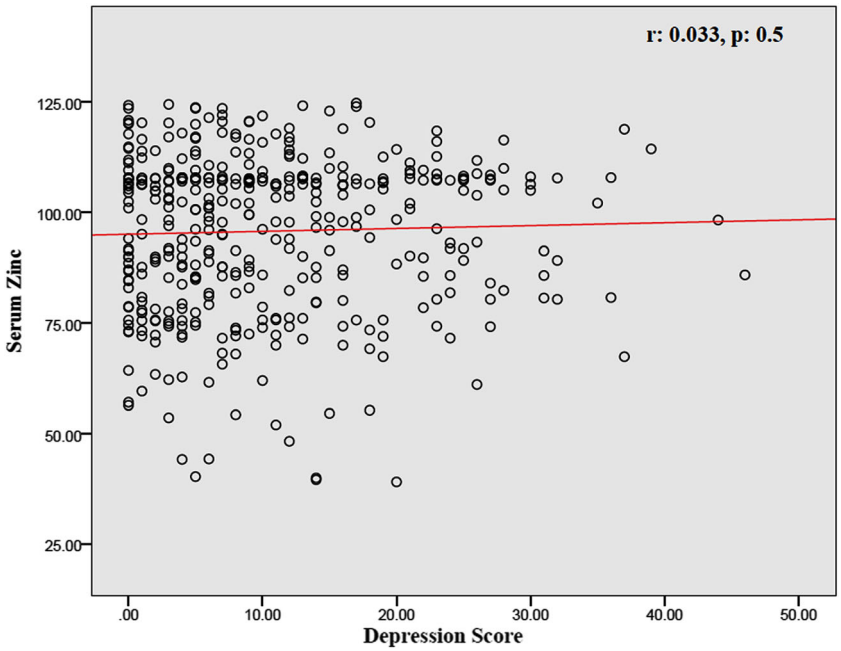

Fig. 2 Correlation between serum zinc (μg/dl) and depression score

was no significant association between serum zinc concentration and depression score.

Some previous studies have similarly shown a negative association between dietary zinc intake and depression [1, 18–20]. Yary et al. conducted a study on 402 postgraduate students including 173 women and 229 men to examine the relationship between dietary intake of zinc and depression. They found an inverse relationship between dietary intake of zinc and depression even after adjusting for age, sex, years of education, smoking status, and physical activity [18]. In another study including 3708 subjects (2163 women, 1545 men), a low dietary or supplemental zinc intake was reported to contribute to depressive symptoms in women, but not in men [19]. Vashum et al. investigated the role of dietary zinc as

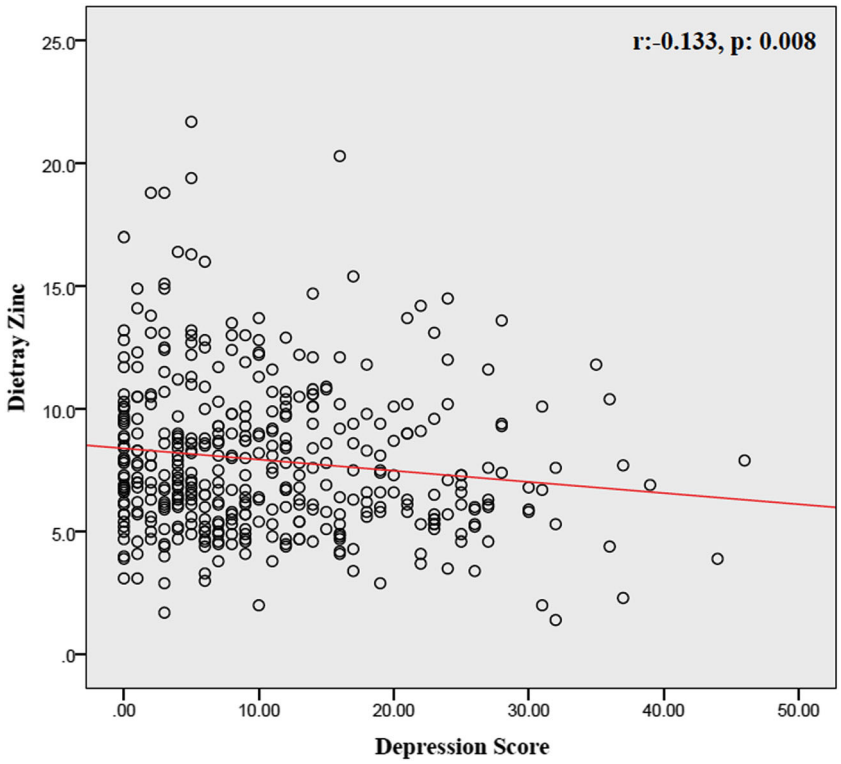

Fig. 3 Correlation between dietary zinc (mg/day) and depression score

Table 3 β-coefficients examining the association of serum and dietary zinc with depression score

	Serum zinc (μg/dl)	Dietary zinc intake (mg/day)
Depression score (crude β)	0.17	− 0.38**
Depression score (adjusted β)	0.02	− 0.30*

β-coefficients obtained from the univariate and multivariate linear regressions. Multivariate analysis was adjusted for age, passive cigarette smoking, BMI, and hs-CRP. *$p < 0.05$; **$p < 0.01$

predictors of incident depression in two large prospective cohorts. The authors observed that a low dietary zinc intake is associated with a greater incidence of depression in both men and women [20]. Amani et al. also found a significant inverse correlation between Beck questionnaire scores and dietary zinc intakes in 23 patients with moderate and severe depression and 23 healthy age-matched controls [1].

There are also several reports of the efficacy of zinc supplementation in the treatment of depression [6, 21–23]. In a randomized double-blind placebo-controlled clinical trial by Ranjbar et al., forty-four patients with major depression were randomly assigned to groups receiving zinc supplementation or placebo, in addition to the usual antidepressant therapy. They found that zinc supplementation together with selective serotonin reuptake inhibitors (SSRIs) improves major depressive disorders more effectively in comparison with patients with placebo plus SSRIs [21]. In another study, forty-four patients aged 18–55 years were randomly assigned to zinc-supplemented and placebo groups. Subjects in the zinc-supplemented group received zinc sulfate (25 mg elemental Zn/day) orally in addition to their usual SSRIs for 12 weeks. Zinc supplementation significantly reduced Hamilton Depression Rating Scale (HDRS) scores compared to placebo [22]. In another study, zinc supplementation (25 mg of Zn^{2+} once daily) significantly reduced scores in both HDRS and BDI after a 6- and 12-week supplementation when compared with placebo treatment [6]. The results of the study conducted by Siwek and colleagues revealed that zinc supplementation (25 mg/day for 12 weeks) augments the efficacy and speed of the onset of therapeutic response to imipramine treatment, particularly in patients previously nonresponsive to antidepressant pharmacotherapies [23].

In contrast to our findings, several studies reported an inverse association between serum zinc concentration and depression score. Tahmasebi et al. conducted a cross-sectional study on a random sample of 100 representative high school female students and found that serum zinc levels are negatively correlated with BDI and the Hospital Anxiety Depression Scale (HADS) [24]. In another study, serum zinc concentration was significantly lower in 144 depressed patients than that in 161 age- or sex-matched healthy controls [25]. Amani et al. also observed a linear inverse correlation between BDI scores and serum zinc concentrations in all of the investigated students [1]. Maes et al. suggested that the low serum zinc concentration in major depression might be related to the activation of cell-mediated immunity [26].

Chronic zinc deficiency increases inflammation and enhances the production of pro-inflammatory cytokines, influencing the outcome of a large number of inflammatory diseases [27]. We have previously supported the role of inflammation and immune dysfunction in the etiology of depression [28, 29]. Therefore, it is likely that inadequate zinc intake increases depression severity by enhancing the inflammatory state. Furthermore, depression disorder is associated with elevated levels of oxidative stress and reduced antioxidant defenses [30, 31]. Since zinc is a necessary factor in a variety of antioxidant enzymes [32], reducing oxidative stress may be another potential mechanism responsible for antidepressant effects of this mineral. However, it seems that the modulation of glutamatergic neurotransmission [via the NMDA receptor, α-amino-3-hydroxy-5-methyl-4isoxazolepropionic acid (AMPA) receptor or metabotropic glutamate receptor (mGluR)] and modulation of the serotonergic system, especially of 5-HT1A receptor activity, is the most important mechanism involved in the antidepressant-like activity of zinc [5].

The strengths of our study include considering both serum zinc concentration and dietary zinc intake, and using a standardized tool for assessment of depression severity. We also conducted this study on adolescent girls who are a highly vulnerable population to zinc deficiency. We acknowledge the limitations in our study, including (a) a lack of generalizability of findings to men, (b) using self-administered tools instead of more accurate face-to-face interviews, and (c) the fact that the cross-sectional design of the study limits determination of causative relationship.

In conclusion, we found that dietary zinc intake, but not serum zinc concentration, is inversely associated with depression symptoms. Therefore, controlled clinical trials are needed to determine the efficacy of zinc supplementation in the treatment of depression disorders.

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Compliance with Ethical Standards

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

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