Zinc monotherapy increases serum brain-derived neurotrophic factor (BDNF) levels and decreases depressive symptoms in overweight or obese subjects: A double-blind, randomized, placebo-controlled trial

Zahra Solati[1], Shima Jazayeri[2], Mehdi Tehrani-Doost[3], Salma Mahmoodianfard[1], Mahmood Reza Gohari[4]

[1]Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran, [2]Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran, [3]Department of Psychiatry, School of Medicine, Roozbeh Psychiatry Hospital, Tehran University of Medical Sciences, Tehran, Iran, [4]Department of Statistics, School of Health Management and Medical Information Sciences, Iran University of Medical Sciences, Tehran, Iran

Objective: Previous studies have shown a positive effect of zinc as an adjunctive therapy on reducing depressive symptoms. However, to our knowledge, no study has examined the effect of zinc monotherapy on mood. The aim of the present study was to determine the effects of zinc monotherapy on depressive symptoms and serum brain-derived neurotrophic factor (BDNF) levels in overweight or obese subjects.

Methods: Fifty overweight or obese subjects were randomly assigned into two groups and received either 30 mg zinc or placebo daily for 12 weeks. At baseline and post-intervention, depression severity was assessed using Beck depression inventory II (BDI II), and serum BDNF and zinc levels were determined by enzyme-linked immunosorbent assay and atomic absorption spectrophotometry, respectively.

Results: The trial was completed with 46 subjects. After a 12-week supplementation, serum zinc and BDNF levels increased significantly in the zinc-supplemented group compared with the placebo group. BDI scores declined in both the groups at the end of the study, but reduction in the zinc-supplemented group was significantly higher than the placebo group. More analysis revealed that following supplementation, BDI scores decreased in subgroup of subjects with depressive symptoms (BDI $\geq$ 10) ($n = 30$), but did not change in the subgroup of non-depressed subjects (BDI $<$ 10) ($n = 16$). Moreover, a significant inverse correlation was observed between serum BDNF levels and depression severity in all participants. Interestingly, a significant positive correlation was found between serum BDNF and zinc levels at baseline.

Conclusion: Zinc monotherapy improves mood in overweight or obese subjects most likely through increasing BDNF levels.

Keywords: Zinc, Brain-derived neurotrophic factor (BDNF), Obesity, Depression

Introduction

In recent decades, many researchers have studied the relationship between obesity and depression. The results of the study by de Wit revealed a significant U-shape association between depression and obesity meaning that underweight and overweight subjects are more likely to have depressive symptoms than normal weight subjects.[1] Depression is a major public health problem and a leading cause of disability worldwide.[2] The World Health Organization has predicted that depression will be the second cause of global burden of disease by 2020.[3] One of the hypotheses in the pathophysiology of depression is the 'neurotrophin hypothesis of depression', which is mainly based on the inverse correlation between stress and brain-derived neurotrophic factor (BDNF) levels.[4] Expression of neurotrophic factors is affected by different stimuli such as stress. Stress significantly down-regulates the expression of BDNF. In contrast,

Correspondence to: Shima Jazayeri, Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, 14155–6117, Iran. Email: sh_jaz@yahoo.com

chronic antidepressant administration increases the expression of BDNF in different parts of the brain.[5] BDNF has critical roles in development, maturation, and function of mature neurons and their plasticity; and is abundant in the brain, serum, and plasma.[6] Despite the fact that the source of circulating BDNF is unknown, previous studies have demonstrated the ability of BDNF to cross the blood–brain barrier;[7] so, it seems that serum BDNF levels are a reflection of brain BDNF levels.[8]

Clear evidence from different studies highlights the role of BDNF in the action mechanisms of antidepressant drugs.[9] Several studies have shown that serum BDNF levels are significantly lower in patients with major depression compared with healthy subjects,[10] and that the depressed levels of serum BDNF can be normalized by successful treatment.[11]

Over the last decade, there has been a burden of proof suggesting a link between zinc and depression. The results of different studies suggest that serum zinc concentration might be a sensitive and specific marker of depression.[12–14] Furthermore, clinical data imply that zinc supplementation maybe considered as an adjunctive therapy for major depressive disorder.[12,15]

One of the antidepressant-like activities of zinc is increasing BDNF gene expression. This effect of zinc is similar to antidepressant drugs, which induce neurogenesis by increasing BDNF.[16]

Many researchers have reported that obese subjects are more likely to have depressive symptoms,[17] and lower serum BDNF[18,19] and zinc levels.[20,21] No study has examined the effects of zinc monotherapy on serum BDNF levels and depression severity. However, some researchers have examined the effect of zinc supplementation on BDNF gene expression in animal models. Few human studies have investigated the effect of zinc supplementation as an adjunctive therapy in major depressive disorder,[12,15] and just one study has examined the effect of zinc plus multivitamin on mood states.[22] Therefore, the aim of this study was to examine the effects of zinc monotherapy on serum BDNF levels and depression severity in overweight or obese subjects.

Materials and methods

Trial design

This was a double-blind, randomized, placebo-controlled trial conducted between January and July 2011 in Tehran, Iran. After obtaining informed consent, eligible subjects were randomly divided into two groups receiving 30 mg zinc supplements as zinc gluconate or placebo daily for 12 weeks. Pharmavite Company supplied zinc gluconate tablets containing 30 mg elemental zinc with the brand name of Nature Made, (made in USA); placebo was made from starch, and prepared by School of Pharmacy, Tehran University of Medical Sciences, and was identical to supplements in shape and size. Randomization was done with a random number table. The protocol of the study was congruent with the Declaration of Helsinki, and was approved by the Ethics Committee of Tehran University of Medical Sciences (number 13515-27-03-90). This trial was registered in Iran Registry of Clinical Trials (IRCT ID: IRCT201106122394N5).

Participants

Fifty overweight or obese subjects (15 men and 35 women, body mass index (BMI) between 25 and 44 kg/m^2, age between 18 and 35 years), were recruited through public announcement at Tehran University of Medical Sciences to assess the effects of zinc supplementation on serum BDNF levels and depressive symptoms in overweight or obese subjects. They were included in the study if they had not taken any supplements including vitamins, minerals, or antidepressant drugs during the 3 months prior to enrollment. Exclusion criteria included substance abuse, pregnancy and lactation, and occurrence of important adverse effects of supplements or disease during the study. Participants were instructed not to change their diet or physical activity during the study. In the zinc group, two subjects were excluded from the study as they did not take the tablets, and two subjects were excluded from the placebo group due unwillingness to participate in the study. No important adverse effects were observed during the study. Compliance was assessed by measuring serum zinc concentrations, and counting the remaining tablets.

Outcomes and other covariates assessment

A member of the study group who was blind to the intervention assignment measured weight and height in the beginning and the end of each intervention period. Weight was measured using the Seca Scale with an accuracy of 0.5 kg in the fasting state with minimal clothing without shoes in the beginning and at end of the study. Height was measured with an accuracy of 0.5 cm without shoes in the beginning of the study.

We used the validated Persian version of Beck depression inventory II (BDI-II)[23] to assess the depression severity at baseline and after 12 weeks of supplementation.

At baseline and after 12 weeks of supplementation, 10 ml venous blood samples were collected after 10–12 hours of fasting between 8 am and 9 am. Then, blood samples centrifuged at 3000 *g* for 10 minutes and serums were isolated and frozen at −80°C until analysis. Zinc concentrations were measured using atomic absorption spectrophotometry. BDNF was assessed

by enzyme-linked immunosorbent assay at baseline and after 12 weeks.

Intake of energy, macronutrients, and micronutrients were assessed using a 3-day food record method in the beginning and at the end of the study. At the end of recording, an expert interviewer reviewed the records with the respondent.

Physical activity levels were assessed using the International Physical Activity Questionnaire[24] at baseline and at the end of the study.

Statistical analysis

The main outcome variables were changes in BDNF levels and depression severity after intervention. Continuous variables were reported as mean and standard deviation. The normal distribution of the variables was checked using Kolmogorov–Smirnov test. Paired *t*-test was used to compare changes in each group, and comparisons between the two groups were performed using *t*-test. Analysis of covariance (ANCOVA) was performed to adjust for potential confounders. Pearson's correlation was utilized to examine the potential associations between continuous variables. Chi-square test was used to compare categorical variables between the two groups at baseline. All analyses were conducted using SPSS software (version 16.0; Spss, Inc. chicago). P values <0.05 were considered significant.

Results

Baseline description

Counting the remaining tablets and serum zinc levels at the end of the study showed that the compliance was excellent. All of the participants took more than 95% of the tablets.

Analysis was performed for 46 subjects who completed the study. The characteristics of the participants are demonstrated in Table 1. No significant differences in age, weight, BMI, sex, serum BDNF levels, depression severity, and serum zinc concentrations were observed between the two groups at baseline. Moreover, analysis of 3-day food record showed no significant differences in the intake of energy, macronutrients, and micronutrients at baseline and at the end of the study.

Table 1 Characterization of participants at baseline

	Zinc ($n = 22$)	Placebo ($n = 24$)	P value
Age (years)	29.77 ± 4.21	31.29 ± 3.81	0.209†
Weight (kg)	84.99 ± 12.82	83.78 ± 15.68	0.792†
BMI (kg/m^2)	31.43 ± 3.78	31.38 ± 4.59	0.969†
Gender (male/female)	8/14	7/17	0.418‡
BDI (score)	12.77 ± 9.59	16.5 ± 10.91	0.224†
Serum zinc (mg/dl)	71.93 ± 24.88	79.55 ± 23.13	0.290†
Serum BDNF (ng/ml)	15.37 ± 8.28	16.20 ± 7.15	0.720†

†Independent sample *t*-test.
‡Chi-square test.
BDI, Beck depression inventory.

Treatment response

Analysis of data in all participants ($n = 46$) revealed that after supplementation, serum BDNF levels increased significantly in subjects who received zinc supplement (mean increase = 6.46 ng/ml, $P = 0.001$), whereas no significant increase was observed in serum BDNF levels of subjects in the placebo group from baseline to week 12 (mean increase = −0.53 ng/ml, $P = 0.57$). Furthermore, ANCOVA, adjusted for baseline BDNF levels, showed that serum BDNF levels were significantly higher in the zinc-supplemented group compared with the placebo group at the end of the study ($P = 0.003$, Fig. 1).

Paired *t*-test showed that BDI scores decreased significantly in both the intervention (mean decrease = −4 score, $P = 0.003$) and the placebo groups (mean decrease = 1.08, $P = 0.03$), but ANCOVA revealed that the BDI score was significantly lower in the zinc-supplemented group than the placebo group at the end of the study ($P = 0.01$). The repeated measure analysis also revealed that time × group interaction adjusted for baseline BDI score was significant ($P = 0.002$).

The result of paired *t*-test demonstrated that serum zinc concentration also increased in the zinc-supplemented group ($P = 0.001$). Furthermore,

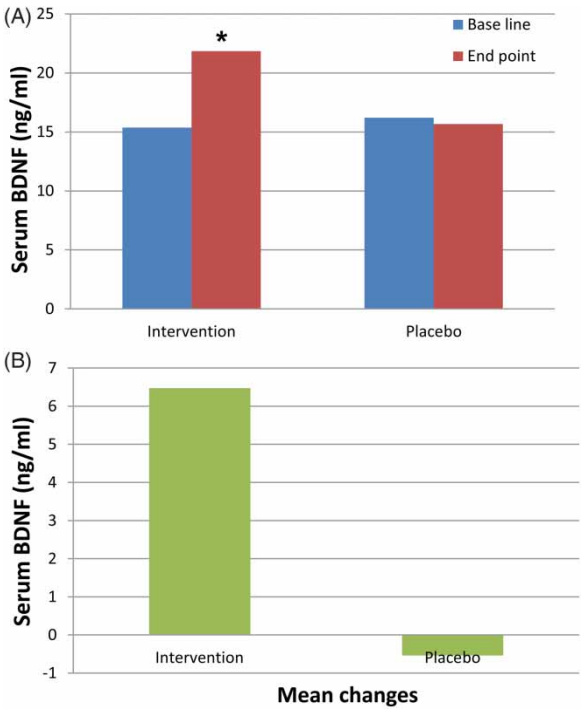

Figure 1 (A) Serum BDNF level at baseline and after 12 weeks supplementation in the two groups. (B) Mean changes in serum BDNF level through 12 weeks zinc supplementation. *statistically significant.

ANCOVA analysis revealed that serum zinc concentration was significantly higher in the supplemented group compared with the placebo group. ($P = 0.001$) (Table 2).

For more in-depth clinical assessment, BDI scores (BDI $\geq$ 10) were considered as a screening tool to identify subjects with depressive symptoms.[25] Therefore, based on this cutoff point, subjects were categorized into two groups of non-depressed subjects ($n = 16$) and subjects with depressive symptoms ($n = 30$).

In the subgroup of non-depressed subjects ($n = 16$), paired *t*-test showed that BDNF levels did not change significantly in neither group at the end of the study ($P > 0.05$). ANCOVA, adjusted for baseline BDNF levels, revealed that BDNF levels changed significantly between the two groups at the end of the study ($P = 0.003$). However, paired *t*-test showed no significant differences in the BDI score in the two groups at the end of the study ($P > 0.05$). ANCOVA, adjusted for base line BDI score, showed no significant differences between the two groups at the end of the study ($P = 0.13$). Similarly, repeated measure analysis also revealed no significant differences in time $\times$ group interaction ($P = 0.184$). The result of paired *t*-test revealed that serum zinc concentration increased in the zinc-supplemented group (mean increase = 38.4 μg/dl, $P = 0.001$). Furthermore, ANCOVA showed that zinc concentration was significantly higher in the zinc-supplemented group compared with the placebo group ($P = 0.03$).

In the subgroup of subjects with depressive symptoms ($n = 30$), paired *t*-test showed that serum BDNF levels increased significantly in the zinc-supplemented group at the end of the study (mean increase = 6.54 ng/ml, $P = 0.002$). Moreover, ANCOVA revealed that BDNF levels increased significantly in the intervention group compared with

Table 2 Serum BDNF, BDI score, and zinc levels at baseline and after 12 weeks

	Baseline	After 12 weeks	*P* value[a]
All people			
Serum BDNF			
Zinc group	15.37 ± 8.28	21.84 ± 6.87	0.001*
Placebo	16.2 ± 7.1	15.66 ± 6.36	0.574
P value[b]	0.72	0.003*	
BDI score			
Zinc group	12.77 ± 9.59	8.77 ± 6.71	0.003*
Placebo	16.5 ± 10.91	15.41 ± 10.53	0.033*
P value[b]	0.22	0.014*	
Serum zinc			
Zinc group	71.93 ± 24.88	101.04 ± 28.53	0.001*
Placebo	79.55 ± 23.13	86.13 ± 7.30	0.133
P value[b]	0.28	0.026*	
Non-depressed subjects			
Serum BDNF			
Zinc group	18.66 ± 10.0	25.00 ± 3.6	0.57
Placebo	18.05 ± 8.1	16.62 ± 5.7	0.44
P value[b]	0.89	0.003*	
BDI score			
Zinc group	3.62 ± 3.1	2.25 ± 2.3	0.13
Placebo	4.5 ± 3.9	4.1 ± 4.08	0.08
P value[b]	0.62	0.18	
Serum zinc			
Zinc group	72.72 ± 35.1	111.1 ± 46.2	0.001*
Placebo	72.58 ± 15.8	86.91 ± 5.7	0.08
P value[b]	0.99	0.03*	
Subjects with depressive symptoms			
Serum BDNF			
Zinc group	13.5 ± 6.8	20.04 ± 6.8	0.002*
Placebo	15.27 ± 6.7	15.18 ± 6.7	0.937
P value[b]	0.47	0.003*	
BDI score			
Zinc group	18.00 ± 7.9	12.5 ± 5.3	0.008*
Placebo	22.5 ± 7.76	21.06 ± 7.77	0.058
P value[b]	0.12	0.002*	
Serum zinc			
Zinc group	71.48 ±18.3	95.27 ± 8.09	0.001*
Placebo	83.03 ± 25.77	85.75 ± 8.13	0.605
P value[b]	0.17	0.001*	

*Statistically significant.
[a]Paired *t*-test was used.
[b]ANCOVA adjusted for baseline values was used.
BDI, Beck depression inventory.

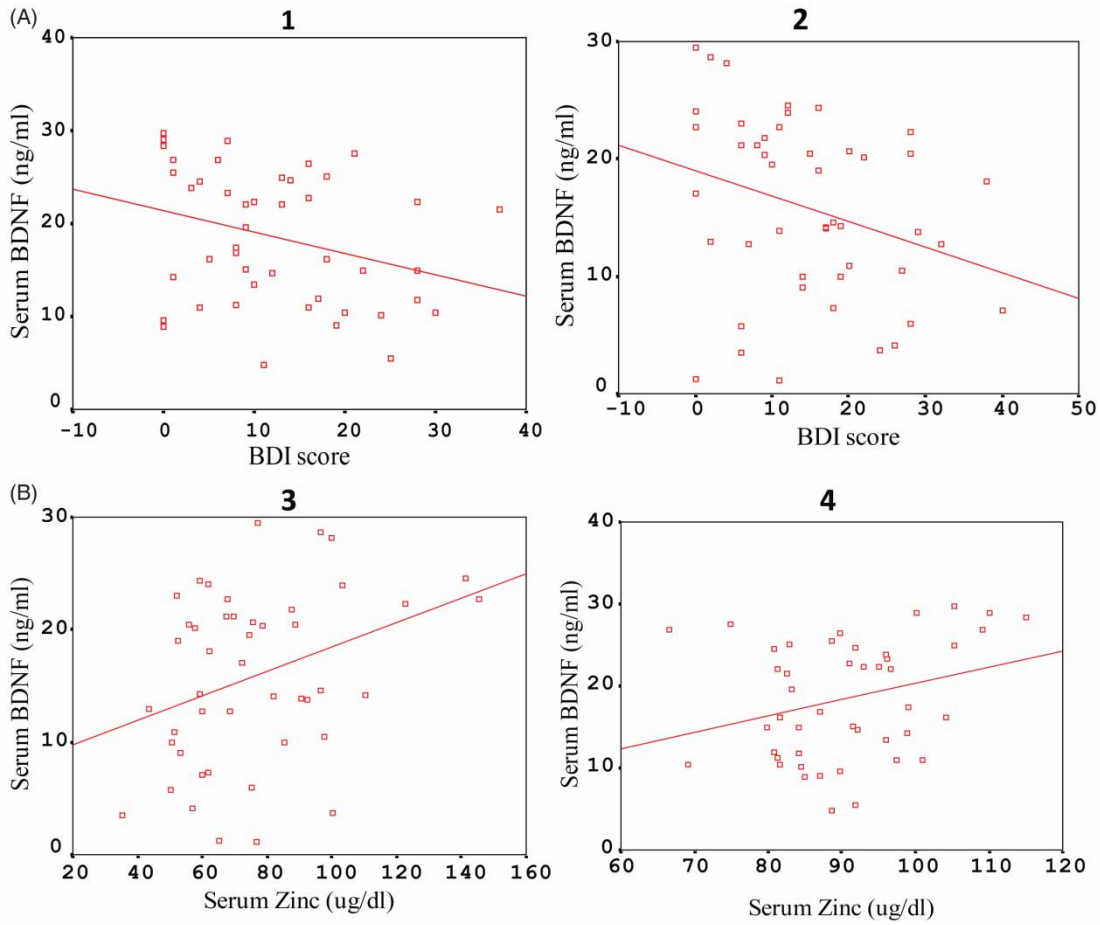

Figure 2 (A) Correlation between serum BDNF and BDI score at baseline (1) and endpoint (2). (1): $r = -0.297$, $P = 0.045$; (2): $r = -0.299$, $P = 0.044$. (B) Correlation between serum BDNF and serum zinc at baseline (3) and endpoint (4). (3): $r = 0.34$, $P = 0.02$; (4): $r = 0.289$, $P = 0.054$.

the placebo group at the end of the study ($P = 0.003$). Moreover, paired *t*-test showed a significant reduction in the BDI score in the zinc-supplemented group at the end of the study (mean decrease = −5.5 score, $P = 0.008$). ANCOVA, adjusted for baseline BDI score, revealed that BDI scores decreased significantly in the intervention group compared with the placebo group at the end of the study ($P = 0.002$). Repeated measure analysis also showed that time × group interaction, adjusted for baseline BDI score, was significant ($P = 0.002$). According to paired *t*-test, serum zinc concentration also increased in the zinc-supplemented group (mean increase = 23.79 μg/dl, $P = 0.001$), and ANCOVA showed that serum zinc concentration was significantly higher compared with the placebo group ($P = 0.001$).

Relationships between serum BDNF levels and other variables

In this study, a significant inverse correlation was found between BDNF levels and BDI scores in all subjects at baseline ($r = -0.297$, $P = 0.045$) and after intervention ($r = -0.299$, $P = 0.044$) it is repeated. In addition, a significant positive correlation was observed between serum BDNF and serum zinc levels at baseline ($r = 0.34$, $P = 0.02$) in all subjects (Fig. 2).

Discussion

This study revealed that the serum BDNF levels increased in all participants and in the subgroup of subjects with depressive symptoms following zinc supplementation. Within-group analysis showed no significant changes in serum BDNF in the intervention group in the subgroup of non-depressed subjects. However, considering that ANCOVA showed significant differences between the two groups in this subgroup, it seems that the results of within-group analysis would be significant if our sample size were larger. Previous human studies have shown that treatment with antidepressants increases serum or plasma BDNF levels in depressed subjects,[6] but no study has evaluated the effect of zinc supplementation on the serum BDNF levels. However, some animal studies have addressed the effect of zinc administration on BDNF gene expression. Cieślik *et al.* investigated the effect of chronic combined treatment with zinc (15 mg/kg zinc hydroaspartate) and imipramine (5 mg/kg) on BDNF mRNA levels in rats with chronic unpredictable stress. In their study, they

found a significant increase in the BDNF mRNA levels in the hippocampus in rats treated with zinc and rats treated with a combination of zinc and imipramine, while imipramine therapy did not show the same effect.[26] Also, Corona *et al.*[27] found that zinc supplementation significantly increased the levels of BDNF in a transgenic mouse model of Alzheimer's disease. Sowa-Kućma *et al.* examined the effect of zinc therapy on brain BDNF protein and mRNA levels in rats with chronic mild stress. Their study revealed that chronic treatment with zinc induced a 17–39% increase in the BDNF mRNA and protein levels in the hippocampus. In 2008, Franco *et al.* investigated the effect of zinc on rats, and administered zinc acutely during 7 days, or chronically during 30 days in the forced swimming test. They found that chronic zinc treatment increased BDNF expression in the cerebral cortex.[28] Nowak *et al.*[29] also reported that chronic treatment with zinc increased the levels of BDNF mRNA in the rat cerebral cortex.

This effect of zinc in inducing BDNF gene expression is similar to antidepressants mechanism of action. Most of the antidepressants induce BDNF gene expression in the hippocampus.[8,9] Adachi *et al.*[30] suggested that the therapeutic effect of antidepressants was mediated by the increasing levels of the BDNF in the hippocampus,, which is particularly involved in the neurogenesis.[31,32] Although BDNF is highly concentrated in the brain, it is found peripherally, especially in the serum.[33.34] The source of the circulating BDNF is not clear. However, BDNF can cross the blood–brain barrier in both directions, and the circulating BDNF could originate from neurons of the brain.[10] Karege *et al.*[35] reported a positive correlation between serum and brain BDNF levels. Considering the fact that previous studies demonstrated the ability of BDNF to cross the blood–brain barrier,[7] it seems that serum BDNF levels are the reflection of brain BDNF levels.[8]

In our trial, similar to previous studies,[8,35–37] a significant inverse correlation was observed between serum BDNF levels and the depression severity. In addition, BDI scores decreased in the intervention group following zinc supplementation. However, we found that the depression severity decreased in the placebo group although it was less than the reduction in the zinc group, which may be related to the placebo effect that is common in psychological studies.[38,39] More analyses revealed that BDI scores decreased just in the subgroup of subjects with depressive symptoms, but not in the non-depressed participants. These results were similar to those of previous studies. Nowak *et al.* examined the effect of zinc supplementation on patients with unipolar depression. Participants received antidepressants with zinc supplements or placebo. In their trial, 12 weeks of supplementation with 25 mg zinc in six unipolar depressed patients resulted in more decrease in depressive symptoms.[12] In another double-blind placebo-controlled trial, adjunctive therapy with 30 mg zinc decreased depressive scores in 60 antidepressant-resistant patients.[15] The results of a study by Sawada *et al.* are consistent with our findings. Sawada and Yokoi[22] showed that supplementation with 7 mg zinc plus multivitamin improved anger–hostility score and depression–dejection score in the Profile of Moods States in young women after 10 weeks. However, their study had some limitations. They used zinc plus multivitamin (not zinc only) to improve mood states, which may raise the possibility of interactions. In addition, improving the mood states in this group was not significant compared with the multivitamin group.

Interestingly, we found a significant positive correlation between serum BDNF and zinc levels at baseline. However, it was very close to significance at the end of the study ($P = 0.054$). This correlation would have been significant with the larger sample size. Although the serum zinc levels are under close homeostatic control,[40] more than 50% of our participants were zinc deficient (serum zinc level $<70\ \mu g/dl$) at baseline and their dietary intake of zinc was lower than the recommended dietary intake.

Zinc exerts antidepressant-like behavior through different mechanisms. One aspect of this effect is the increasing BDNF synthesis in brain, especially in the hippocampus. This region of the brain contains high zinc concentrations.[16] Hwang *et al.*[41] suggested that zinc therapy activated the tropomyosin-related kinase receptors through activation of matrix metalloproteinases, leading to pro-BDNF release from cells and its change to mature BDNF.

Based on our information, this study is the first to examine the effects of zinc monotherapy on the serum BDNF levels and depression severity. To date, no study has examined the effects of zinc supplementation on serum BDNF. In relation to antidepressant-like activity of zinc, previous studies examined the effects of zinc adjunctive therapy or zinc plus vitamins for improving mood states (not zinc only), but one cannot directly attribute those finding to zinc.

This study had some limitations that should be considered. We determined and assessed the depression severity only by a self-report questionnaire.

In conclusion, our study showed that zinc supplementation increased serum BDNF and decreased BDI score in our participants, suggesting that zinc monotherapy maybe an effective and safe treatment option for decreasing the depression severity in people with depressive symptoms.

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