Original Article

Effects of Zinc Supplementation in Patients with Major Depression: A Randomized Clinical Trial

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Objective: Major depression is a mood disorder that causes changes in physical activity, appetite, sleep and weight. Regarding the role of zinc in the pathology of depression, the present study was aimed to investigate the effects of zinc supplementation in the treatment of this disease.
Methods: This study was a double-blind randomized clinical trial. Forty four patients with major depression were randomly assigned to groups receiving zinc supplementation and placebo. Patients in Zinc group received daily supplementation with 25 mg zinc adjunct to antidepressant; Selective Serotonin Reuptake Inhibitors (SSRIs), while the patients in placebo group received placebo with antidepressants (SSRIs) for twelve weeks. Severity of depression was measured using the Beck Depression Inventory at baseline and was repeated at the sixth and twelfth weeks. ANOVA with repeated measure was used to compare and track the changes during the study .
Results: The mean score of Beck test decreased significantly in the zinc supplement group at the end of week 6 ($P<0.01$) and 12 ($P<0.001$) compared to the baseline. The mean score of Beck Depression Inventory reduced significantly compared to the placebo group at the end of 12th week ($P<0.05$)
Conclusion: The results of the present study indicate that zinc supplementation together with SSRIs antidepressant drug improves major depressive disorders more effectively in patients with placebo plus antidepressants (SSRIs).

Key words: *Major depressive disorder; Zinc supplement; placebo and Selective Serotonin Reuptake Inhibitors (SSRIs)*

Iran J Psychiatry 2013; 8:2: 73-79

According to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), major depressive disorder (MDD) is a psychiatric disorder with genetic, biological, and environmental risk factors. This disorder is one of the most common diseases in the world, with high levels of associated mortality. It affects people of every region in every ethnic group (1, 2) to the extent that one out of every 5 people referred to a physician is affected by depression (3).

About 19-34 % of patients with depression do not respond to antidepressants, and 15-50 % of them have a recurrence; therefore, other medications or supplementation with micronutrients are increasingly adjunct to antidepressant drugs to improve their therapeutic effects (4).

Zinc is one of the micronutrients involved in behavior, learning and mental functions. The first clinical studies in the field of serum zinc level in depressed patients have been published by Hansen and colleagues (5). The first report on the relationship between zinc status and brain function in humans has been published in 1998 by Sand stead and colleagues (6). Various studies have identified the effects of zinc in the pathophysiology of depression and antidepressant drugs mechanisms of action. Also, other clinical studies have shown low serum zinc concentrations in patients with depression (7).Furthermore, Long-term treatments with zinc in laboratory animals have had the same mechanisms and effects as the antidepressant drugs (8) .

In previous studies, the dietary micronutrients as confounding factors have not been studied. However, the present study was designed to examine the effects of zinc supplementation in patients with major depression, while assessing and controlling dietary intake. The present study was the first randomized clinical trial in Iran designed to examine the effects of zinc supplementation in patients with major depression.

Material and Methods

Participants and Procedure

This study was a double blind randomized clinical trial that was performed on 44 patients with major depression. Study population was among people with depression who were referred to the psychiatric clinic of Imam Hussein, Tehran. Sampling started after obtaining approval from the ethics committee of Nutrition Research Institute, Shahid Beheshti University of Medical Sciences (No. t/1/044).

The patients were aged 18-55 years. The inclusion criteria included diagnosis of major depressive disorder by a psychiatrist based on DSM-IV-TR, obtaining informed consent from the patients, no supplements usage at least four weeks before the study, not taking any medication except for those associated with depression status. The exclusion criteria included pregnancy or lactation, severe psychotic symptoms, changing drug class, symptoms requiring hospitalization including suicidal thoughts and actions.

Patients were randomly assigned in to two groups. One group received 25-mg zinc supplement daily with Selective Serotonin Reuptake Inhibitors (SSRIs) antidepressants (citalopram 20-60mg per day or fluoxetine 20-60mg per day), and the other group received placebo (containing Malto-dextrose) plus an antidepressant SSRI (citalopram 20-60mg per day or fluoxetine 20-60mg per day). The groups were blinded to the researchers and patients.

Demographic data form was completed at the baseline. Inclusion and exclusion criteria and disease background were evaluated by research team. The Beck Depression Inventory (9), physical activity questionnaire, three-day dietary recall, and anthropometric indices were completed in the beginning, middle and end of the study. Nutritionist IV software was used to analyze a three-day dietary recall. Macro and micronutrients intake was derived from the three-day dietary recall and compared between the two groups.

Also, at the beginning and end of the study, a blood sample of 5 ml was taken after a 12-hour fasting state. Serums were separated and zinc concentrations were measured by flame atomic absorption spectrophotometry.

Statistical Analysis

Sample size was determined so that 11 score difference in the mean of Beck score could be detectable, while comparing zinc and placebo groups with α=0.05 and 1-β=80%. In all, a sample size of 18 was detected to be sufficient. However, to cover at least 20% drop out which is common in clinical trials, a sample size of 22 subjects was determined for each group.

Data analysis was performed using SPSS version 16. The Kolmogorov - Smirnov and chi-square tests were used to determine the normal distribution of quantitative data and to compare qualitative variables between the two groups, respectively. In the case of quantitative variables with normal distribution for comparison between the beginning and end of the intervention within each group, paired t-test, and for comparison between the two groups at the beginning or end of the intervention, t-test were used. The Wilcoxon and Mann-Whitney tests were used in the case of quantitative variables with non-normal distribution. To compare and track the change of means of quantitative variables that were measured three times during the study period, analysis of variance (ANOVA) with repeated measure was done. Covariance analysis was performed to adjust for quantitative confounding factors.

The IRCT number was 201110187836N1

Result

In this study, 6 out of 44 patients were excluded voluntarily or due to lack of medication. Therefore, 21 patients in the group receiving zinc supplements and 17 in the placebo group remained in the study (Figure 1). Furthermore, when serum zinc concentration was assessed, one subject was dropped out in zinc group due to loss of blood sample .The mean age in the zinc group was 37±9 and in the placebo group was 37.5±8 years, which was not significantly different.

The two groups were alike with respect to gender, education level, income, smoking, and no significant difference was observed between them (Table 1). Both groups received the same SSRI antidepressants. Furthermore, the groups were statistically similar in terms of sleep duration, physical activity, weight, BMI, and serum zinc concentration during the study (Table 2).

No significant difference was observed between the two groups regarding dietary intake of energy, carbohydrate, protein, cholesterol, and fiber (Table 3). However, intake of total fat, saturated fatty acids and Monounsaturated Fatty Acids (MUFA) in the zinc group was significantly lower in the sixth week ($p<0.05$) and twelfth week ($P<0.01$) compared to the placebo group(table 3). Also, intake of Polyunsaturated Fatty Acids (PUFA) was significantly lower in the zinc group compared to the placebo group in the twelfth week ($p<0.05$) (Table 3).

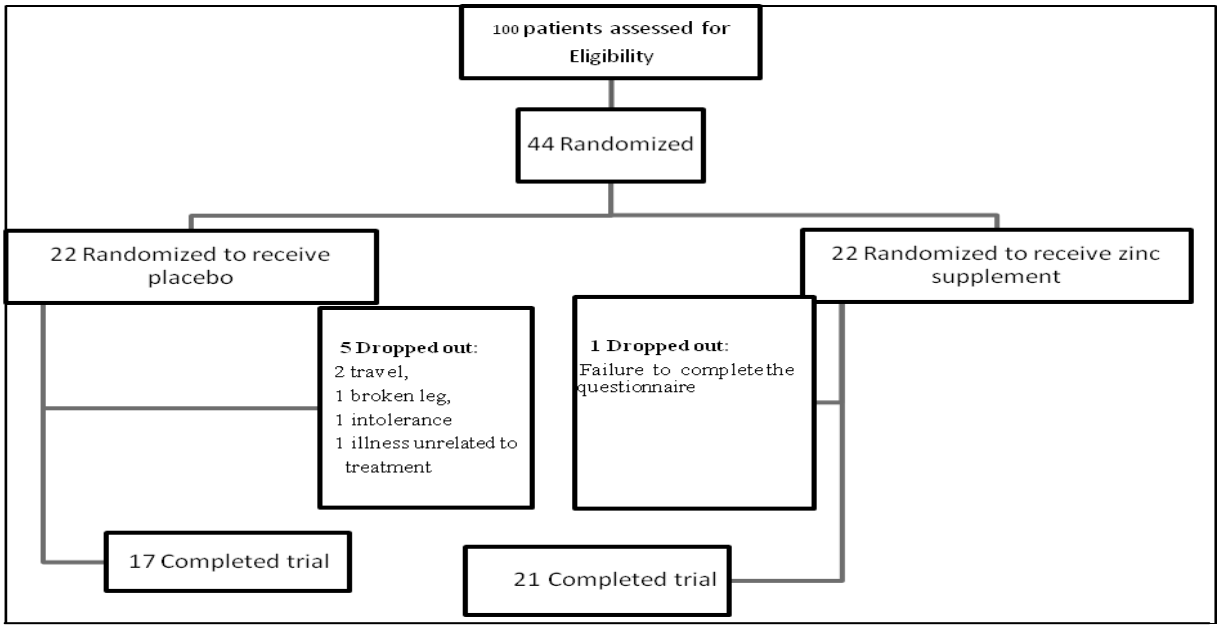

Figure 1: Flow chart of the study

Table 1: General characteristics of Zinc and Placebo groups

Variables		Zinc group (n=21) n (%)	Placebo group (n=17) n (%)
Gender	Female	20(95%)	14(82%)
	Male	1(5%)	3(18%)
Education Level	Elementary school	3(14%)	5(29%)
	Secondary school	8(38%)	2(12%)
	High school	7(34%)	5(29.5%)
	Academic	3(14%)	5(29.5%)
Smoking	No	18(86%)	15(88%)
	Yes	3(14%)	2(12%)
Marital Status	Single	2(9.50%)	2(12%)
	Married	19(90.50%)	15(88%)
Income	Less than 200 thousand	2(9%)	1(6%)
	200 to 400 thousand	6(29%)	2(12%)
	400 to 600 thousand	7(33%)	10(59%)
	More than 600 thousand	6(29%)	4(23%)

Table 2: Mean and standard deviation of sleep duration, physical activity, anthropometric indices and serum zinc concentration in patients with depression receiving zinc supplementation or placebo

Variables	Study groups	N	Study period		
			Baseline	Sixth Week	Twelfth week
Sleep duration (hours per day)	Zinc	21	7±1	7±1	7±1
	Placebo	17	7±1	7±1	7±1
Physical activity (d/MET/h)	Zinc	21	16.5±3	17±3	17±3
	Placebo	17	18±3	18±4	18±3
Weight (kg)	Zinc	21	71±17	72±17.5	71±18
	Placebo	17	68.5±10	69±10	70±10.5
Height (cm)	Zinc	21	161±6	-	-
	Placebo	17	162±9	-	-
BMI (kg/m^2)	Zinc	21	27±6	28±7	27.5±6
	Placebo	17	26±5	26±5	27±5
Serum zinc concentration (µg/dL)	Zinc	20†	100±15	-	107±11
	Placebo	17	106±17	-	106±14

†: When serum zinc concentration was assessed, one subject was dropped out in zinc group due to loss of blood sample

Table 3: Mean and standard deviation of energy intake, dietary macronutrients and fiber in patients with depression receiving zinc supplementation or placebo

Variables (Energy and food components)	Study groups	N	Study period		
			Baseline	Sixth Week	Twelfth week
Total energy intake (Kcal/d)	Zinc	21	1667±261	1686±425	1665±433
	Placebo	17	1787±259	1819±239	1851±289
Total carbohydrate intake (g /d)	Zinc	21	251±53	280±49	272±42
	Placebo	17	240±62	259±53	261±62
Total protein intake (g / d)	Zinc	21	57±19	58±17	60±11
	Placebo	17	66±23	63±23	67±27
Total fat intake (g / d)	Zinc	21	49±26	46±16[a]	46±15 [b]
	Placebo	17	59±33	65±34	65±21
Saturated fatty acid intake (g / d)	Zinc	21	17±8	18±6[a]	17±6 [a]
	Placebo	17	21±7	24±9	25±9
MUFA fatty acids intake (g / d)	Zinc	21	13±6	13±4[a]	13±4 [b]
	Placebo	17	16±7	18±8	19±5
PUFA fatty acid intake (g / d)	Zinc	21	9±14	9±8	8±7 [a]
	Placebo	17	18±24	17±25	17±17
Cholesterol intake (g / d)	Zinc	21	224±120	178±87	210±131
	Placebo	17	254±152	208±153	238±177
Fiber intake (g / d)	Zinc	21	13±5	16±4	14±3
	Placebo	17	14±4	14±4	13±4

For comparison in each group paired t-test and for comparison between two groups independent sample t-test was used. Statistically significant difference compared with Placebo: a) $p<0.05$ b) $p<0.01$

Table 4: Mean ± SD dietary micronutrient intake in patients with depression receiving zinc supplementation or placebo

Variables (Energy and food components)	Study groups	N	Study period		
			Baseline	Sixth Week	Twelfth week
Zinc intake (mg/d)	Zinc	21	6.5±2.1	7.5±1.7	7.5±1.7
	Placebo	17	7.6±2.2	7.4±2.5	7.3±2.5
Magnesium intake (mg/d)	Zinc	21	193±55[a]	227±63	234±85
	Placebo	17	249±75	255±83	254±63
Iron intake (mg / d)	Zinc	21	11±4	12.5±5	12±4
	Placebo	17	13±4	13±4	13±4
Vit. B_1 intake (mg / d)	Zinc	21	1.4±0.5	1.5±0.5	1.6±0.4
	Placebo	17	1.7±0.5	1.7±0.4	1.5±0.3
Vit. B_2 intake (mg / d)	Zinc	21	1.2±0.4	1.5±0.6	1.5±0.5
	Placebo	17	1.5±0.5	1.5±0.7	1.4±0.4
Vit. B_3 intake (mg / d)	Zinc	21	17±5	17±6	18±5
	Placebo	17	18±5	18±5	19±8
Vit. B_6 intake (mg / d)	Zinc	21	1.5±0.8	1.5±0.6	1.5±0.6
	Placebo	17	1.5±0.4	1.5±0.3	1.6±0.4
Folic acid intake (µg / d)	Zinc	21	198±119	239±110	228±106
	Placebo	17	246±114	234±130	270±120
Vit. B_{12} intake (µg / d)	Zinc	21	2±1.2	2.4±1.4	2.6±1.1
	Placebo	17	2±0.9	2.6±1.4	2.7±1.8

Statistically significant difference compared with Placebo: a) $p<0.05$
* Vit.= Vitamin

During the study, dietary intakes of micronutrients such as zinc, magnesium, iron, vitamins B1, B2, B3, B6, B12 and folic acid were not significantly different between the two groups (Table 4). Only dietary intake of magnesium in the group receiving zinc supplementation was significantly lower ($p<0.05$) than the placebo group at the baseline (Table 4).

The Beck score decreased in the placebo group, but this reduction was not significant compared to the baseline. Depression scores decreased significantly in the zinc group in the sixth week ($P<0.01$), and the twelfth week of the study ($P<0.001$) compared to the baseline, but this difference was not statistically significant compared to the 6th and 12th week values.

At the end of the study, Beck scores was significantly lower ($p<0.05$)in zinc group compared with the group receiving the placebo. Even after adjusting for the effect of dietary confounding factors, including intake of total fat, saturated fatty acids, MUFA and PUFA fatty acids and magnesium, this difference still remained significant (Figure 2).

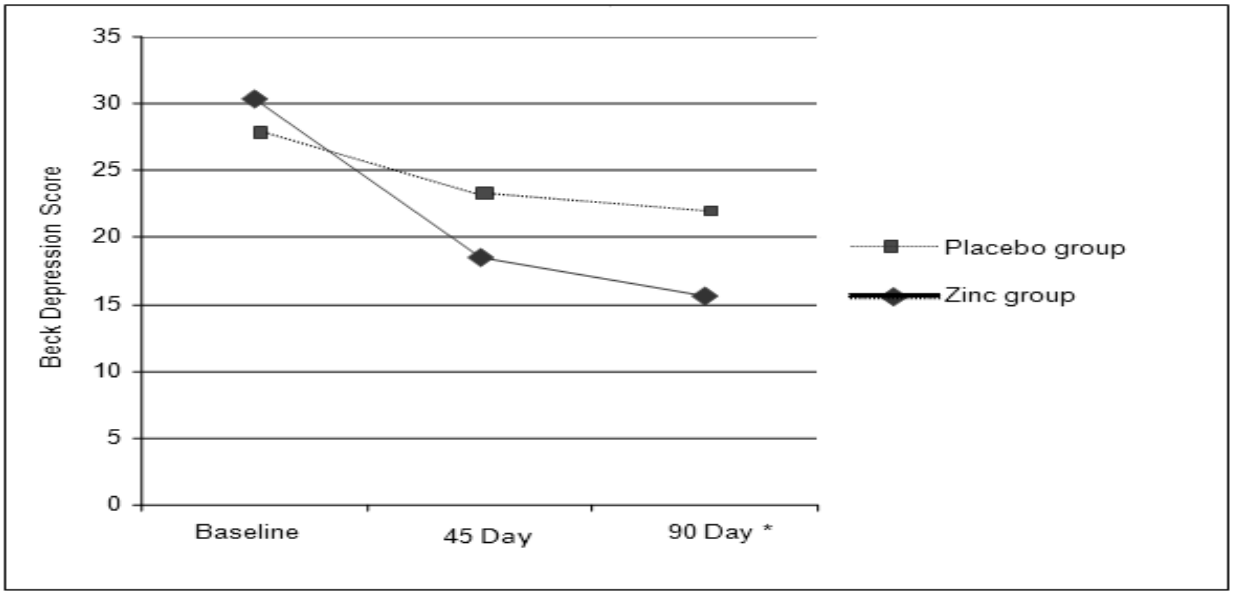

Figure 2: Changes in mean Beck depression scores in the groups receiving zinc compared with placebo using ANOVA with repeated measure. * Statistically significant difference compared with Placebo after 90 day: p<0.05

Discussion

Zinc is an essential micronutrient which is responsible for the different biological roles. Some of these functions are involvement in some enzymes activation, gene expression, synthesis and release of insulin, and cardiovascular homeostasis. The amount of zinc stored in the adults' body is 2-3 grams; most of which, is in skeletal muscle and bone. Only 0.1% of the total zinc pool is present in plasma. The plasma levels of zinc are used to evaluate the nutritional status of zinc (10).

In the present study, mean serum zinc concentration in the group receiving zinc supplements increased by 6.5 µg/dL. However, this increment was not significant compared with placebo. Mean serum zinc concentrations at baseline were 100 ±15 and 106 ±17 µg/dl in the zinc and placebo groups, respectively. These amounts were similar to the mean serum zinc concentrations in healthy adults in Shiraz 104 ±18 µg/dL (11), and Ahvaz (7)111 ± 18 µg/dL, respectively. Some studies have shown the low serum zinc levels in depressed patients which are resistant to treatment (12, 13).Other studies have also shown that low serum zinc levels are normalized during treatment with antidepressants (14) which is consistent with our findings. In the present study, the mean dietary zinc intake in patients with major depression was about 6.5-7 mg per day. While in the study of Ghasemi and colleagues, the mean dietary zinc intake in men and women were 15.8 ± 11 and 14.7 ± 11 mg/day, respectively (15). The less zinc intake in these patients may be due to some antidepressants and lack of appetite as one of the symptoms of depression. Serum zinc level was normal in the current study. Therefore, despite the low intakes of zinc, we can infer that the increased serum zinc up to normal levels may be due to antidepressants. The antidepressants may stimulate releasing zinc from the body's stores such as muscles and bones. Also, zinc supplementation on these patients has restored the zinc pools .

Studies on dietary factors and their relation to depression have shown that consumption of meals containing high amounts of carbohydrates cause insulin release. Insulin causes glucose entrance into the cells, and on the other hand make more amino acids such as tryptophan to cross the blood - brain barrier. This may increase neurotransmitter levels, especially serotonin, in the brain which can lead to improved mood (16). Amino acid tryptophan can be converted to serotonin in the body and can cause sleep and mental calmness (17). Tyrosine amino acid can be synthesized from the amino acid phenylalanine and may enter into the biochemical pathways of dopamine and norepinephrine (18). Dietary omega-3 fatty acids are provided from some especial plant and animal sources (especially some marine animals). Omega-3 fatty acids are involved in regulating corticotropin factor, stimulating the serotonergic pathway, preventing neuronal apoptosis, improving blood flow to the brain and regulating gene expression (19). Folate and B12 deficiency are associated with depression. About 10 to 30% of depressed patients have low serum folate levels and their response to antidepressants is weak. Early vitamin B12 deficiency leads to depression. This is due to the reduced synthesis of S-Adenosyl Methionine (20). S-Adenosyl Methionine is associated with mood. The low concentrations in cerebrospinal fluid of depressed patients have been observed and it was found that increasing its plasma concentrations have improved the depressive symptoms (21). So far, clinical trials published in this field have not assessed

the mentioned dietary confounding factors. However, the present study was the first experiment which evaluated the effects of dietary confounding factors in patients with depression. As shown in the results, the effects of dietary factors on depression during the study were similar between the two groups. In cases where there was statistical difference between the two groups, the confounding effects were adjusted using ANCOVA.

In the present study, zinc supplementation significantly decreased the Beck depression scores compared with the placebo. Findings of this research were similar to the study by Nowak and colleagues on 20 patients with major depression. Nowak supplemented the antidepressants with 25 milligrams of zinc in one group and the other group was given a placebo with antidepressants. Beck depression scale at baseline and the second, sixth and twelfth weeks were measured. Nowak showed that reduction in Beck scores at week 6 and 12 in the group receiving the supplement were significant compared with placebo (22).

In a study on patients with major depression, Siwek and colleagues gave imipramine combined with 25 mg zinc supplement to one group and placebo combined with imipramine to another group. Siwek findings revealed no significant change in depression scores of the two groups. However, zinc supplementation significantly reduced the rate of depression in patients resistant to medication and may facilitate treatment with antidepressants (12). One of the possible causes of the differences in the results of Siwek study with ours may be due to different type of antidepressant medication prescribed.

Antidepressants may exert their effect through the zinc-containing neurons. Zinc is located in the presynaptic vesicles of neurons of the cortex, amygdala, hippocampus, and spinal cord. These neurons are mainly glutaminergic. The majority of zinc-containing neurons in the spinal cord is gamma-amino butyric acidergic or GAB Aergic and partly Glycinergic; perhaps zinc inhibits glutamate receptors such as N-Methyl-D-Aspartic (NMDA) (23, 24).

Another hypothesis in this field is the role of the protein Brain-Derived Neurotrophic Factor (BDNF). Some recent studies have shown that the BDNF may be involved in mechanism of zinc antidepressant effect. Chronic high doses of zinc increases BDNF gene expression in the cerebral cortex of rats, while a low dose of zinc may increase BDNF gene expression in hippocampus (25, 26).

Limitations

The limited number of patients did not allow subgroups analysis based on type of SSRI drugs.

Conclusion

The results of this study reveal that zinc supplementation combined with antidepressant drugs can be effective in the treatment of patients with major depression.

Recommendations

We suggest evaluating the effects of different doses of zinc on depression in future studies.

Acknowledgements

We would like to thank the Center for Neuroscience Research for financial support, Imam Hussein Laboratory personnel, and Endocrine Research Center of Shahid Beheshti University of Medical Sciences.

Conflict of interest

Authors have nothing to declare.

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