Original Article

Effect of Zinc Supplementation on Depression in Selective Serotonin Reuptake Inhibitors-Treated Major Depressive Disorder Patients

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Abstract

Background: *Major Depressive Disorder (MDD) is a major health problem. In Bangladesh, the prevalence of depressive disorder is 4.1%. MDD is the second cause of disability and therefore, alerts physicians of clinical psychiatry. Antidepressants are the treatment of depression. Administration of zinc indicates an important role in mood and depression.* ***Objective:*** *To investigate the role of zinc in MDD.* ***Materials and Methods:*** *A randomized controlled trial; done in the Department of Pharmacology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from March 2019 to August 2020. Placebo group with SSRI was group 'A' (n =35) and zinc supplementation with Selective serotonin reuptake inhibitors (SSRIs) was group 'B' (n=38) for 8 weeks. A baseline visit and a follow-up visit were given after 8 weeks. Then; the severity of depression and serum zinc level was assessed.* ***Results:*** *After 8 weeks, the Depression, Anxiety and Stress Scale (DASS-21) score was found 11.77 ± 4.08 SD and 8.53 ± 4.38 SD in placebo and intervention group respectively. Percentage of decreased DASS-21 score was found 37.68 ± 21.47 SD and 54.48 ± 21.94 SD in placebo and intervention groups respectively. The DASS-21 score was statistically significant. The more significant reduction of DASS-21 score after zinc administration. After 8 weeks, serum zinc levels were found 0.69 ± 0.10 SD in the placebo group and 0.78 ± 0.12 SD in the intervention group. The percentage of changes in the serum zinc level in the placebo group was 0.19 ± 16.17 and in the intervention group 5.88 ± 18.39. The serum zinc levels were significant within the intervention groups. The significant elevation of serum zinc levels after 8 weeks of zinc administration in the intervention group.* ***Conclusion:*** *Zinc supplementation along with SSRI in MDD patients significantly ameliorated the severity of depression.*

Key words: *Depression, Zinc, SSRI, MDD*

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Introduction

Major Depressive Disorder (MDD) is a major global health problem. The number of people suffering from MDD was reported about 4.4% of the world's population. The total number is assumed to increase to 18.4%. Depression is more common in females compared to males. Years lived with a disability resulting from depression occur in about 50 million people due to MDD and this disease has been claimed to be a major cause of morbidity, mortality, and also suicidal death. In Bangladesh, the prevalence of the depressive disorder is about 4.1% and the percentage of total years lived with a disability (DALY) is about 7.1%.[1] Within this number, some people suffer additionally from anxiety disorders and some suffer from both anxiety disorder and MDD. However, MDD has been assumed to occupy the place of the second cause of disability by 2020, and MDD, therefore, demands attention and alerts physicians of clinical psychiatry.[2,3]

According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM- 4), five symptoms need to be present among nine for 2 weeks to diagnose a person suffering from MDD. One such symptom is either depressed mood or loss of interest or pleasure. Other symptoms are fatigue or loss of energy, lack of ability to concentrate, feeling of guilt or worthlessness, significant changes in weight or appetite, changes in sleep patterns, suicidal ideation or recurrent thought of death, and psychomotor retardation.[4] Within the CNS mostly the limbic areas responsible are for maintaining a normal mood. Zinc is present throughout the limbic system. These sites are involved in the regulation of learning, memory, and emotion.[5]

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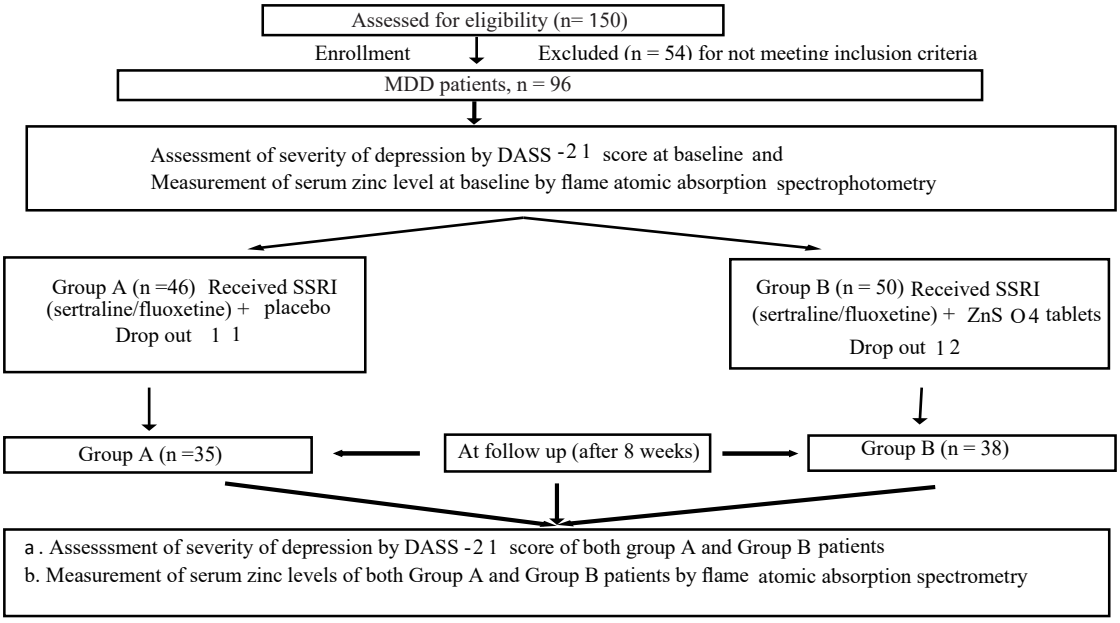
Zinc deficiency has been stated to result in behavioral disturbances and abnormal neurological development.[6,7] Administration of zinc presumably indicates an important role in balancing mood and therefore in counteracting depression. Serotonin is a neurotransmitter that is involved in the regulation of temperature, appetite, emesis, sleep cycle, and sexual behavior. It also regulates mood (anxiety disorders and depression).[8] The role of 5HT in the regulation of mood is well known and well documented in the literature. There may be lower levels of the 5HT in areas related to the regulation of mood, a fact that may intensify the susceptibility to depression following lack of 5HT.[9] Till now, antidepressants (like the TCAs, the SSRIs, and the SNRIs) are the mainstay treatment of depression. About 19-34% of depressed patients have demonstrated improvements by the administration of antidepressants. Supplementation with micronutrients has been attempted along with antidepressants to improve the efficacy of therapy.[10] Researchers have indicated that lower levels or deficiencies of micronutrients like zinc, folic acid, vitamin B1, and vitamin B6 might be associated with depression.[11-13] This point has attracted the attention of the present researcher and hence the present study was designed to investigate the role of zinc, an important micronutrient, as one of the causative factors linking with other major factors to the occurrence of MDD. It was observed that zinc has been associated with mood disorders, alteration of zinc level there developed the depression.[14-16] Now, the present researcher was inclined to explore the role of zinc in patients with MDD in Bangladesh.

Materials and Methods

This study was a randomized, double-blind, placebo-controlled trial. This study was carried out by the Department of Pharmacology, Faculty of Basic Science and Paraclinical Science, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from March 2019 to August 2020. Ethical clearance was taken from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU). Newly diagnosed moderate major depressive disorder patients according to the Diagnostic and Statistical Manual of Mental Disor ders (DSM-4) criteria, patients were given only SSRI (sertraline/fluoxetine), age 18-55 years, and both genders were included in our study; on the other hand, patients receiving other antidepressants and dietary supplements in the last two months, patients with other psychiatric disorders, patients with other major systemic diseases were excluded. Newly diagnosed mild to moderate MDD patients were selected from the outpatient department of the Psychiatry department of BSMMUA. A total of 150 MDD patients were assessed. 54 MDD patients were excluded by selection criteria, the remaining included patients were 96 in number. Informed written consent from each patient was taken. Then information was recorded in a datasheet. A baseline visit and a follow-up visit were given after 8 weeks of administration of ZnSO4 tablets a placebo. For giving intervention, patients were divided into two groups. Group A (placebo group) and group B (intervention group). Finally, we got 73 patients among the 96 moderate MDD patients were recruited; as 23 patients had been dropped out from both groups. Therefore the placebo group contained (group A, n = 35) and the intervention group contained (group B, n =38). Patients' body weight was obtained at the time of enrollment in the study. At baseline, the DASS-21 score was evaluated by the present researcher and 3 ml blood was collected for the baseline measurement of serum zinc levels. Then patients were assigned their respective groups. Placebo with SSRI (sertraline/fluoxetine) was given to the patient of group A and zinc supplementation with SSRI (sertraline/fluoxetine) was given to the patient of group B for 8 weeks. Regular intake of medicine was confirmed by talking to the patients through telephone and from the compliance sheet of the patients. After 8 weeks of intervention, again the severity of depression was assessed by DASS-21 score and 3 ml blood was collected to measure serum zinc level. Patients were asked to report any unwanted effects of the medication given during the study period. Data analysis was done by using the SPSS software package Version 20.0. The quantitative variables were expressed as the mean (mean± SD). Unpaired t test was done to compare mean values of all data between Group A and Group B. Comparison of mean values before and after treatment of each group was done by using the paired t-test.



Flowchart showing the procedure of the study

Results

Demographic characteristics of Group A and Group B; where baselines were age, sex, educational status, occupation, socio-economic condition, family status, marital status, family history of depressive disorder, BMI at baseline. (Table I, II)

The differences in mean values between the two groups were not statistically significant (p>0.05).

Table I: Demographic characteristics of Group A and Group B in MDD patients (n=73)

Baseline characteristics	Groups		p-value
	Group A Placebo group (n =35)	Group B Intervention group (n = 38)	
Age (years) Mean ± SD	34.66 ± 10.16	29.34 ± 9.54	0.024[b]
Sex			
o Male	20 (57.1%)	22 (57.9%)	0.948[a]
o Female	15 (42.9%)	16 (42.1%)	
Educational status			
o Primary level	14 (40.0%)	10 (26.3%)	
o Secondary level	8 (22.9%)	3 (7.9%)	
o Higher secondary level	3 (8.6%)	11 (28.9%)	
o Graduate and above	10 (28.6%)	14 (36.8%)	
Occupation			
o Unemployed	5 (14.3%)	1 (2.6%)	
o Student	4 (11.4%)	13 (34.2%)	
o Housewife	11 (31.4%)	9 (23.7%)	
o Farmer	1 (2.9%)	1 (2.6%)	
o Day laborer	2 (5.7%)	0 (0.0%)	
o Businessmen	4 (11.4%)	2 (5.3%)	
o Service	8 (22.9%)	11 (28.9%)	
o Retired	0 (0.0%)	1 (2.6%)	
Socio-economic condition			
o Upper	18 (51.4%)	24 (63.2%)	
o Middle	11 (31.4%)	13 (34.2%)	
o Lower	6 (17.1%)	1 (2.6%)	

Table II: Demographic characteristics of Group A and Group B in MDD patients (n=73)

Baseline characteristics	Groups		p-value
	Group A Placebo group (n = 35)	Group B Intervention group (n = 38)	
Family status			
o Unitary	15 (42.9%)	15 (39.5%)	
o Combined	9 (25.7%)	10 (26.3%)	
o Disorganized	11 (31.4%)	13 (34.2%)	
Marital status			
o Unmarried	11 (31.4%)	18 (47.4%)	
o Married	22 (62.9%)	17 (44.7%)	
o Separated	0 (0.0%)	1 (2.6%)	
o Divorce	1 (2.9%)	1 (2.6%)	
o Widow/ Widower	1 (2.9%)	1 (2.6%)	
Family history of depressive disorder			
o Yes	6 (17.1%)	10 (26.3%)	0.344
o No	29 (82.9%)	28 (73.7%)	
BMI (kg/m^2) at baseline			
o Under weight	1 (2.9%)	0 (0.0%)	
o Normal	19 (54.3%)	22 (57.9%)	
o Over weight	12 (34.3%)	13 (34.2%)	
o Obese	3 (8.6%)	3 (7.9%)	
Mean ± SD	24.67 ± 3.75	24.30 ± 3.48	0.662

At baseline, the DASS-21 score was found 18.91 ± 1.63(mean ± SD) in the placebo group and 18.37 ± 1.91in the intervention group. The two groups did not differ from each other statistically (p> 0.05). Both group A and B patients were suffering MDD, and both groups showed similar DASS-21 scores at baseline which did not differ from each other.

At follow up after 8 weeks, the DASS-21 score was found 11.77 ± 4.08(mean ± SD) in the placebo group and 8.53 ± 4.38 (mean ± SD) in the intervention group. After 8 weeks the mean DASS-21 score was statistically significant (p<0.01) between the two groups.

The mean percentage (%) of change DASS-21 score was found 37.68 ± 21.47(mean ± SD) in the placebo group and 54.48 ± 21.94(mean ± SD) in the intervention group. After 8 weeks, the mean DASS-21 score was statistically significant (p<0.001) within the placebo and the intervention groups in comparison with baseline. However, the reduction of DASS-21 score after 8 weeks of zinc sulfate (at a dose of 30 mg once daily) administration in the intervention group appeared to have been more significantly reduced compared to those in the placebo group. (Table III)

Table III: Depression Anxiety Stress Scale 21 (DASS-21 score) between two groups

DASS -21 score	Groups		p-value
	Group A Placebo group (n=35)	Group B Intervention group (n=38)	
Baseline (Mean ± SD)	18.91 ± 1.63	18.37 ± 1.91	0.195
At follow up after 8 weeks (Mean ± SD)	11.77 ± 4.08	8.53 ± 4.38	0.002**
Percent of decreased	37.68 ± 21.47	54.48 ± 21.94	
p value	<0.001**	<0.001**	

** Level of significance

At baseline, serum zinc level was found 0.70 ± 0.12 mg/l (mean ± SD) in the placebo group and 0.72 ± 0.09 mg/l (mean ± SD) in the intervention group. The difference was not statistically significant (p>0.05) between the two groups. Both group A and group B patients were suffering from MDD, and both groups showed similar levels of zinc levels at baseline (before starting treatment).

After 8 weeks, serum zinc levels were found 0.69 ± 0.10 mg/l (mean ± SD) in the placebo group and 0.78 ± 0.12 mg/l (mean ± SD) in the intervention group. After 8 weeks mean serum zinc level was statistically significant (p<0.05) between the two groups.

The mean percentage (%) of change in the serum zinc level in the placebo group was 0.19 ± 16.17 and in the intervention group 5.88 ± 18.39.

After 8 weeks, serum zinc levels were statistically significant (p<0.05) within the intervention groups in comparison with baseline. However, the elevation of serum zinc levels after 8 weeks of zinc sulfate (as a dose of 30 mg once daily orally) administration in the intervention group appeared to have been significantly (p<0.05) elevated compared to those in the placebo group (Table IV).

Table IV: Serum zinc levels between two groups

Serum zinc level (mg/l)	Groups		p-value
	Group A Placebo group (n = 35)	Group B Intervention group (n = 38)	
At Baseline (Mean ± SD)	0.70 ± 0.12	0.72 ± 0.09	0.575
At follow up after 8 weeks (Mean ± SD)	0.69 ± 0.10	0.78 ± 0.12	0.001**
Percentage of change	0.19 ± 16.17 (decreased)	5.88 ± 18.39 (increased)	
p value	0.494	0.009**	

** Level of significance

Discussion

In our study baseline characteristics of both groups like age, sex, educational status, occupation, socioeconomic condition, family status, marital status, family history of depressive disorder, BMI at baseline were similar. DASS-21 BV (Depression Anxiety Stress Scale-21 score Bangla Version) is the easiest and most reliable for assessing the severity of depression which was translated and validated by an author.[17] The present study has attempted to assess improvements in depression through a comparison between two groups using DASS-21 scoring at baseline and after 8 weeks of treatment.

In the present study, both groups of patients were suffering from MDD and both groups showed similar DASS-21 scores at baseline. And also at follow-up after 8 weeks, the mean DASS-21 score was improved in SSRI with zinc supplementation group after zinc supplementation at a dose of 30 mg compared to SSRI without zinc supplementation group.

In this study, the reduction of the mean percentage (%) change of DASS-21 score after 8 weeks of zinc sulfate supplementation in the SSRI with zinc supplementation group appeared to have been more significantly reduced compared to those in the SSRI without zinc supplementation group.

In our study, both groups of patients were suffering from MDD, and both groups showed a similar level of serum zinc at baseline (before starting treatment). Also after 8 weeks of follow-up in SSRI without zinc supplementation group, serum zinc level was decreased and decrement was statistically not significant within the same group; but we found in our study; the significant elevation of serum zinc levels after 8 weeks of zinc sulfate supplementation in the SSRI with zinc supplementation group compared to those in the SSRI without zinc supplementation group.

In this study, zinc supplementation significantly reduces depression severity and facilitated the outcome of antidepres

sant therapy. Taking into account these observations, the present study showed that after zinc supplementation, serum zinc level is increased significantly from the baseline in the SSRI with zinc supplementation. Findings indicate that the supplementation of zinc may be beneficial when used as an adjunctive drug to the conventional antidepressant drug therapy for depressive symptoms.

This result was supported by the augmentation effect of zinc adjunctive therapy that comes from clinical studies and zinc supplementation significantly reduced depression scores compared with placebo treatment.[10,12,18] Also, a study reported that zinc monotherapy reduces depression severity in patients with coexisting obesity.[19]

On the other hand, a study assessing the effects of zinc supplementation on mood and depression symptoms among psychogeriatric patients. It also concluded that zinc deficiency is quite common among psychogeriatric patients.[20] several factors were found regarding depression or MDD that may contribute to MDD development, among them the serum level of zinc is one of the factors that play a role in the development of depression.[21]

The mechanism of action of zinc and its effect on mood is not completely revealed in our study. Some hypotheses may explain the relationship between zinc and depression.[15, 22-26]

There are a limited number of trials that examine the effect of zinc supplementation on depressive symptoms and the presented available evidence is insufficient to reach a conclusive decision due to heterogeneity of the target population, intervention, and outcome measures used. The present findings in the study may have significant implications in public health.

Future research should be adequately toward developing well-designed randomized controlled trials that would examine the effect of supplementation of zinc on depressive symptoms. The limitation was a single-centered study, short duration of treatment, and, the sample size was limited.

Conclusion

It is being concluded that in the present study, zinc supplementation along with SSRI in MDD patients significantly ameliorated the severity of depression.

It is recommended for future additional research on bigger populations of depressed patients to explore the role of zinc in the treatment of depression. As zinc supplementation is a safe and inexpensive applicable intervention, future clinical studies should examine the potential benefits of zinc supplementation along with SSRIs in MDD patients for a longer period. A positive outcome may indicate a new horizon of application of zinc sulfate and betterment of MDD patients in the future compared to the present modes of treatment and their outcomes.

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