Original Article

Association between Serum Magnesium Level and Depression in Selective Serotonin Reuptake Inhibitors Treated Major Depressive Disorder Patients

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ABSTRACT

Depression, a common mental health disorder, contribute to burden globally as well as in Bangladesh despite availability of many treatment modalities. Evidence showed improvement of depressive symptoms after magnesium supplementation but could not report consistent significant results. A randomized, double-blind, placebo-controlled trial was conducted in Bangladesh Medical University (BMU), Dhaka, Bangladesh, between March 2020 and January 2022, to relate serum magnesium with the level of depression. Serum magnesium level was estimated by using spectrophotometric method in Beckman Coulter autoanalyzer (AU 680) at Department of Biochemistry & Molecular Biology of the same institution. Level of depression was measured using Bangla Version of the Depression Anxiety Stress Scale 21 items (DASS-21)-BV. In this randomized controlled trial on 90 moderate and severe major depressive disorder (MDD) patients, respondents were given a treatment of 200 mg of magnesium glycinate or placebo tablets twice daily orally for the 8 weeks with selective serotonin reuptake inhibitors (SSRIs). Between 2020 and 2022, serum magnesium level was measured as the primary indicator at baseline, and after 8 weeks of intervention. DASS-21-BV was completed as the primary outcome at baseline and 8 weeks intervention. The study found a difference in serum magnesium from baseline to 8 weeks ($p<0.05$) and from the control arm ($p<0.05$). As serum magnesium was increased from baseline, DASS-21 items were decreased from baseline to 8 weeks ($r= –0.6$). The results of the regression suggested that serum magnesium explained 38% of the variance and significantly predicted DASS-21 (–12.37 points/mg/dL; $t= –4.79$; $p=0.00$). In this trial, lower serum magnesium levels were found to be linked to depressive symptoms suggesting serum magnesium may help identify the biological basis of depressive symptoms and select patients who could respond to magnesium supplementation.

Keywords: *Depression, serum magnesium, SSRIs, DASS-21, intervention*

Mugda Med Coll J. 2025; 8(2): 138-144.
DOI: https://doi.org/10.3329/mumcj.v8i2.85808

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INTRODUCTION

Depression, a recurrent mental health disorder, presents with persistent depressed mood, loss of interest or pleasure, and decreased energy. About 322 million people live with depression worldwide where the South-East Asia regions have largest number (85 million). It is ranked as the single largest contributor to non-fatal health loss (7.5% of all YLD, years of healthy life lost due to disability). In Bangladesh 4.1% was the estimated prevalence in 2015.[1] However, in 2018-19, it was increased to 6.7%.[2] The long time to get symptomatic relief, social stigma about mental health diseases, and a lack of awareness are responsible for this increasing prevalence.[3] It is predicted to be the primary contributor of disability globally by 2030.[4]

Though the exact etiology is unclear to date, some factors in the pathogenesis have been identified, such as genetic, environmental, and psychosocial.[5] The most commonly accepted theory "monoamine hypothesis" proposes that a deficiency of monoamines in the brain is responsible for depression.[6] Glutamate, the main excitatory neurotransmitter in the brain binds with its receptors N-methyl-D-aspartate receptors (NMDARs). Several pieces of evidence have suggested that excess functioning of glutamate and NMDA receptor disturbances causes synaptic dysfunction, excessive excitation, and neuronal cell death, which ultimately leads to behavioral and mood disorders, including depression.[7] Reduced levels of macro-minerals and trace elements (iron, magnesium, calcium, copper, zinc, manganese, and selenium) have been shown as contributing factors to the pathophysiology of MDD; the serum magnesium level has been identified as crucial.[8,9]

Treatment modalities for depression include antidepressant medications, non-pharmacologic treatments such as cognitive behavioral therapy. So far, SSRIs and SNRIs are still first-line antidepressants.[10] Medications can take 2 weeks or more to have an effect,[11] side-effects,[12] and often fail to achieve complete remission.[13] Different dietary supplements have a role in depression. Well-documented associations have been linked depression to low magnesium intake around the world and depression supports its use.[14-16]

Magnesium is the second most abundant cation in the cell and fourth most plentiful mineral. It is a co-factor for over 300 enzymes and has a role in many of the pathways, enzymes, hormones, and neurotransmitters involved in mood regulation. It plays a crucial role for the functioning of central nervous system properly. Cardiovascular, neuromuscular, neurological, psychiatric, and electrolyte abnormalities are all linked to hypomagnesaemia.[17,18] Magnesium increases synthesis of the brain-derived neurotropic factor (BDNF). The function of magnesium as a voltage-dependent blocker of the N-methyl-D-aspartate (NMDA) receptor and a calcium antagonist may be related to BDNF. Thus, it serves as a physiological blocker of calcium channels in the N-methyl-D-aspartate (NMDA) receptor as calcium flow into the neuron is controlled by NMDA. Depression may arise when high glutamate and calcium levels deregulate synaptic activity in low magnesium situations.[7] Oral magnesium is safe and magnesium glycinate (magnesium bisglycinate) has good absorption.[19] For adult men the recommended dietary allowance (RDA) is 400 mg to 420 mg per day and for women 310 mg to 320 mg per day.[20]

Meanwhile, biomarkers and neuroimaging markers including magnetic resonance imaging (MRI) are developing which may provide a guide for the objective diagnosis of major depressive disorders (MDD).[21] However, the development of biomarkers that can be reliable is still insufficiently sensitive and specific for clinical use.[22] Although magnesium levels in the blood do not accurately reflect its status, the serum level is the most common and practical test in clinical settings among all other tests.[23] In a study showed those patients with high normal magnesium levels had a rapid response to antidepressants than who had normal magnesium levels.[24] It is unclear, whether those with higher serum magnesium level responded more to antidepressant treatment,[25] and a strong correlation was evident.[26,27]

The most suitable options may be found with the help of biomarkers, leading to more individualized treatment plans. However, additional data are needed to identify the practical and effective biomarkers.[28] Thus, the present trial was designed and conducted to determine if serum magnesium levels and depression are correlated in selective serotonin reuptake inhibitors (SSRIs) treated MDD patients.

METHODS

This Randomized, double-blind, placebo-controlled trial was conducted in Bangladesh Medical University (BMU), Dhaka, Bangladesh, between March 2020 and January 2022. One hundred forty patients were recruited for the baseline screening from Psychiatry outpatient department (OPD) of BSMMU Hospital. Potential ninety patients with moderate to severe depression were enrolled after screening and assigned to one of the two study arms. Our inclusion criteria were: i) patients aged ≥18 years as newly diagnosed with major depressive disorders (MDD), according to the DSM-5,[29] ii) moderate to severe MDD, according to the DASS-21 (scores of 14–27), and iii) patients prescribed with only SSRIs. Exclusion criteria were: i) patients having any other psychiatric disease, kidney disease, or gastrointestinal disease,

ii) taking dietary supplements in the last two months, iii) taking fluoroquinolones, aminoglycosides, tetracyclines, calcium channel blockers, bisphosphonates, and skeletal muscle relaxants, and iv) pregnant and lactating women.

One senior faculty member from the Department of Biochemistry and Molecular Biology, of the same institution has done randomization by online graph pad software using a computer from the website (http://www.graphpad.com/quickcales/ranMenu), which automatically generated two distinct sets of random numbers after giving necessary inputs. Patients were randomly provided with either magnesium or placebo treatment containing package with proper instructions on a compliance sheet: i) 200 mg magnesium glycinate tablet or ii) 200 mg placebo tablet for 8 weeks. 45 patients were randomized to magnesium treatment and 45 to placebo treatment. Investigators and all subjects were blind to the assigned treatment and remained blinded until unblinding the codes during data analysis.

Patients were instructed to take 1 tablet twice daily after meals for 8 weeks along with SSRI treatment. Tablets were provided free of charge. Also instructed not to change their food, physical activity habits, prescription medicine usage habits or not to use any magnesium-containing dietary supplements while remaining in the experiment. Regular intake was confirmed over the telephone by audio call or text message, pill count, and compliance sheet.

The original 42-item DASS developed by Lovibond and Lovibond was modified into a shorter version consisting of 21-items. To get the final score, the sum of the score was multiplied by 2.[30] The DASS-21 item is a set of three self-report questionnaires to assess the severity of depression. Here, depression subscale scores range from 0 to 21, with the following severity: 0–9 normal; 10–13 mild; 14–20 moderate; 21–27 severe; 28+ extremely severe.[31] It is validated in Bangla and is considered to be a reliable tool for depression.[32] At baseline, a preformed questionnaire was completed, which included the required demographic data, BMI, concomitant or recently taken medications, and nutritional supplements. After that, the completion of DASS-21 items was done for the assessment of the severity score of depression symptoms and 3ml blood had drawn to measure baseline serum magnesium level on every enrolled patient. The DASS-21 items were completed again at the end of 8 weeks treatment, the serum magnesium was measured at the end of 8 weeks treatment and patients were discharged from the study.

Estimation of serum magnesium level was done with Beckman Coulter autoanalyzer (AU 680) by spectrophotometric method in the Department of Biochemistry and Molecular Biology of the same institution. This autoanalyzer required Chemistry Calibrator (Cat#DR0070) and Mg^{++} reagent for estimation. After calibration, controls should be performed with each lot of reagents. Here, the colour xylidyl blue was used and Mg^{++} forms a colored complex with xylidyl blue in a strongly basic solution. It estimates every determination at the same time interval automatically. The produced colour is measured chromatically at 520/800 nm. This measured color is proportional to the Mg^{++} concentration. Results are automatically printed out for each sample in mg/dL at 37° C.

Data was analyzed by using MS-Excel and Statistical Package for the Social Sciences (SPSS) software version 16.0 for Windows. Data was presented as frequency and percentage as well as mean±SD, as applicable, in tabulated form. Simple linear regression, Unpaired and Paired Student's t-tests and Chi-square test were employed to determine the association between variables. A p-value <0.05 was considered as the level of significance.

Ethical approval was received from the Institutional Review Board (IRB) of Bangladesh Medical University (BMU), Dhaka, Bangladesh. This trial was also registered in the ClinicalTrials.gov (Trial ID number: NCT04880460).

RESULTS

In this trial, 7 patients from the control arm and 5 patients from the intervention arm dropped out before analysis. Therefore, 78 patients completed all 8 weeks of the trial and were finally analyzed (Fig. 1). Considering all baseline characteristics, the two arms were similar in terms of age, gender, BMI and DASS-21 score (p>0.05). The distribution of DASS-21 scores reflects a screening population with most subjects scored "severe" (Table-I). We found a significant increase in serum magnesium level in the intervention arm (from 1.90±0.23 to 2.20±0.24 mg/dL; p=0.00) after 8 weeks of magnesium treatment; however, serum

magnesium level was found decreased (from 1.98±0.17 to 1.96±0.14 mg/dL; p=0.08) in the control arm (Table-II). As serum magnesium increased from baseline to end of the treatment, the DASS-21 score decreased from baseline to end of the treatment; there was found a moderate negative relation (*r*= –0.61) between the serum Mg and the DASS-21 score (Fig. 1). To investigate whether serum magnesium predicts depression a simple linear regression was conducted. The predictor variable was found to be statistically significant [β= –12.37, 95% CI (–17.58,–7.15), p=0.00]. The model explained approximately 38% of the variability [R^2=0.38] (Table-III).

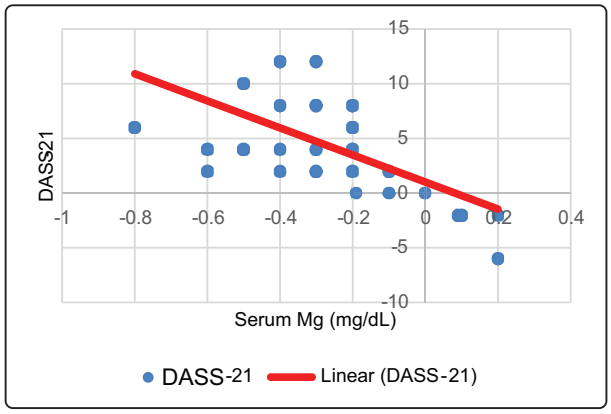

Fig. 1. . *Association of serum magnesium with DASS-21 scores in 40 MDD patients. Bangla Version of Depression Anxiety Stress Scale 21 items (DASS-21-BV) was used.*

Table-I: *Baseline characteristics of the study subjects (n=90)*

Characteristics		Control (n=45)	Intervention (n=45)
Age (years)	Mean ± SD	32.56±11.79	30.68±10.22
	Range	19–60	18–50
Gender	Male	16/45 (35.56%)	14/45 (31.11%)
	Female	29/45 (64.44%)	31/45 (68.89%)
BMI	Mean ± SD	22.76±2.64	23.16±2.73
	Range	17.60–29.70	16.40–31.10
DASS-21 Score	14–20 (Moderate)	23/45 (51.11%)	21/45 (46.67%)
	21–27 (Severe)	22/45 (48.89%)	24/45 (53.33%)

p-value reached from Unpaired Student's t-test and Chi-square test; p>0.05.

Table-II. *Serum magnesium level within the control and intervention arms*

Variables	Serum magnesium level (mg/dL)			p-value*
		Control (n=38)	Intervention (n=40)	
Baseline	mean±SD	1.98±0.17	1.90±0.23	0.10^{NS}
	Range	1.60–2.30	1.50–2.41	
End of 8 week	mean±SD	1.96±0.14	2.20±0.24	0.000^{S}
	Range	1.60–2.20	1.80–2.80	
P-value**		0.08^{NS}	0.000^{S}	

p-value reached from Unpaired* and Paired** Student's t-test; S=significant, NS=not significant.

Table-III: *Univariate regression analysis between serum magnesium level and Bangla version of depression anxiety stress scale-21 items (DASS-21-BV)*

	DASS-21-BV score (n=40)		
Serum magnesium level (mg/dL)	β	95% CI	p-value
	–12.37	–17.58, –7.15	0.00

β=the independent regression coefficient when controlling for all the other variables in the model.

DISCUSSION

Depression, a mood disorder is now far more common that adversely affects both health and functioning and playing a significant impact on suicide and ischemic heart disease. It creates a high economic burden by contributing to the overall burden of 3.8% of global disability-adjusted life years (DALY)[6] and non-fatal health loss. The majority (80%) of this loss occurred in low and middle-income countries. Also, the prevalence is increasing in Bangladesh.[1]

Existing data showed the connection between depression and hypomagnesemia,[33-36] but the results were inconclusive.[25,37] Previous studies found that serum magnesium levels increases after magnesium Supplementation.[36,38] However, another study reported no association.[39] Unfortunately, research trying to assess the association between serum magnesium and depression by applying magnesium as a treatment option could not show significant results consistently. Identifying total body magnesium deficiency is difficult due to the limitations of serum magnesium levels.[39,40] The primary purpose of the study was to determine the association of serum Mg with depression in a double-blind, randomized trial.

In present study control and intervention arms were comparable as there were no significant differences in demographics. The present study revealed a significant increase in serum magnesium level in response to 8 weeks of oral magnesium glycinate supplementation. Similarly, in some other trials, serum Mg levels increases after magnesium supplementation for different duration (ranging from 7 days to 12 weeks), regardless of the initial serum magnesium level;[34,35] however, another trial revealed no rise,[41] which was possibly due to a lower sample size.[41]

The present study demonstrated a diminution of depression score with an increased serum magnesium level. The changes in the DASS-21 score were negatively correlated with the changes in the serum magnesium level, which suggests an improvement in depression symptoms and adds further evidence towards the effect of magnesium in depression. Many clinical trials report similar findings of magnesium on the reduction of depression symptoms in subjects with known hypomagnesaemia.[36,42] Also, studies that did not limit the subjects with known hypo-magnesaemia report similar findings of Mg on the reduction of depression symptoms.[34,39,41,43] Also found that those patients who had high normal magnesium levels at baseline had more responses to antidepressants.[24] Further research is needed to establish the association between the baseline magnesium level and treatment outcome after supplementation with magnesium.

Currently, there is a lack of biological markers to identify individuals who would develop treatment resistance to conventional therapies and forecast the effectiveness of interventions. Finding a biological marker that can predict treatment resistance could result in safer, faster, and more effective treatments, better guidelines for treatment, and minimized suffering.[44] However, for diagnosis of depression, reliable biomarkers development is still inadequate in terms of specificity and sensitivity for practical application. Findings from this study suggest that measuring a serum magnesium levels could be a cost-effective means to determine which patients would benefit from taking magnesium. On the other hand, serum magnesium may serve as a marker for patients with treatment-resistant depression,[45] or may identify a subgroup of patients of altered metabolisms of magnesium, who respond differently to treatment than anticipated.[24] In this context, additional research is required to find biomarkers with higher sensitivity and specificity for diagnosis of depressive disorders.

CONCLUSION

Our data suggests that the lower the serum magnesium levels, the greater was depressive symptoms suggesting a biologic reason for the effectiveness of magnesium supplementation in treating depression. These findings were in line with previous research. Serum magnesium levels may be measured safely, affordably, and easily, and they may aid in individualizing treatment.

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