Section: Psychiatry

Original Research Article

SERUM MAGNESIUM LEVELS IN PATIENTS WITH DEPRESSIVE DISORDERS IN A TERTIARY CARE HOSPITAL IN KARNATAKA- A CASE-CONTROL STUDY

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Abstract

Background: Depression is one of the leading causes of disability worldwide and a major cause of suicide attempts globally. Evidence suggests that magnesium affects the brain physiology and its role in NMDA [N-methyl-D-aspartate] receptor regulation makes it a factor of interest in the pathogenesis of depressive disorder. The aim is to evaluate and compare the serum Magnesium levels in patients with depression and healthy controls. **Materials and Methods:** A cross-sectional study was conducted, where a total of 30 patients with depressive disorder were recruited. MINI International Neuropsychiatric Interview was used to diagnose subjects with depressive disorder according to ICD 10. Blood sample was collected to determine the serum Mg levels. The serum Mg levels were compared with age and sex matched controls. **Result:** Serum magnesium was found to be significantly higher among subjects with depressive disorder than that of healthy controls which was statistically significant [P=0.011]. There was no relationship between serum Mg levels and other clinical variables, like psychomotor retardation, melancholic symptoms, depression severity and psychotic symptoms. **Conclusion:** Serum magnesium levels were found to be higher in subjects with depressive disorders. Further studies should focus on larger sample size and evaluate for serum magnesium levels in homogenous sample of depressive disorders.

INTRODUCTION

Mental health is increasingly recognized as a priority area in global health policies. Depression, a significant public health concern, is characterized by its high prevalence, impact on disability, disruptions to family life, and economic burden.[1] In India, the crude prevalence of depressive disorders was found to be 3.3%, affecting approximately 45.7 million individuals.[2,3] Major depression is considered a complex disorder influenced by genetic, neurological, and environmental factors, yet the specific mechanisms behind these risk factors remain unknown.[4,5]

The primary neurobiological basis for depression lies in the dysregulation of the serotonergic system. However, the response rate to pharmacological treatment for major depressive disorder is less than 60% within the first 12 weeks of treatment initiation.[6,7] Due to relatively low rates of remission, adverse effects associated with medications, and delayed onset of action, there is a need for new therapeutic approaches. Recent studies have explored various neurobiological markers for depression, including brain-derived neurotrophic factors, cytokines, and glutamate.[8]

Among these neurobiological markers, the role of Magnesium [Mg] in depression has received relatively less investigation.[9] Magnesium, the second major intracellular cation and the fourth major element in the body, can be easily measured in routine clinical settings.[10] Calcium, potassium, sodium, and magnesium are recognized as major cations based on their presence in the body and recommended daily allowance [RDA].[11] While the importance of calcium, potassium, and sodium is well understood, magnesium is not widely perceived as clinically significant.[11]

Magnesium serves as a coenzyme in the conversion of tryptophan to serotonin, a neurotransmitter

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implicated in mood disorders.[12] It acts as an endogenous antagonist of the N-methyl D-aspartate receptor (NMDAR), similar to the effects of ketamine in treating resistant depression. Additionally, magnesium exhibits anti-inflammatory properties, which are linked to depression. Therefore, the level of magnesium can be associated with depression, and it is possible that magnesium possesses antidepressant activity.[12]

Hypermagnesemia, an elevated level of magnesium in the blood, is commonly observed in patients with acute or chronic kidney disease. Certain factors, such as proton pump inhibitors (PPI), malnourishment, and alcoholism, can increase the risk of hypermagnesemia in these individuals.[14] Chronic stress, alcohol abuse, and a diet rich in carbohydrates and fats can contribute to magnesium deficiency in humans, and prolonged deficiency may lead to depression.[5,15,16] The use of sertraline and amitriptyline has been shown to increase the concentration of magnesium in red blood cells.[17] Studies have reported that low magnesium intake or deficiency is associated with depression-like behavior in both animals and humans.[18,19]

Research has indicated that patients with depressive disorders and individuals at risk for depression have lower blood magnesium levels compared to controls.[20] However, some studies have suggested an association between higher magnesium levels and depression.[21,22] Overall, the evidence regarding the relationship between magnesium levels and depression remains unclear, with inconsistent results. Therefore, this current study aims to evaluate serum magnesium levels in patients with depressive disorders and explore the relationship between magnesium levels in these subjects compared to a healthy control group.

MATERIALS AND METHODS

The study employed a cross-sectional hospital-based case-control design. Prior to the study, written informed consent was obtained from the participants, and the study protocol was approved by the institutional ethics committee. Based on a previous study by Aravind et al,[23] which reported a depression prevalence of 5.25% in India, the sample size was determined with an absolute precision of 8% and a 95% confidence interval, resulting in a calculated sample size of 30.

The study included adults with moderate to severe depression, and cases were recruited using a convenient sampling method. Individuals with concurrent alcohol, nicotine, or substance use disorders, as well as those with psychiatric comorbidities such as schizophrenia, bipolar disorder, hypertension, diabetes mellitus, chronic infections, liver and renal diseases, and women during pregnancy and post-partum period, were excluded from the study. Socio-demographic and clinical information, including the history, duration, and frequency of mental illness, were collected using a structured proforma. Diagnosis was established based on the ICD-10 criteria, and the severity of depression was assessed using the Hamilton Depression Rating Scale. Psychiatric comorbidities were ruled out using the MINI 6.0 assessment tool. Controls were selected from the hospital premises in the vicinity of the city. They underwent interviews and assessments to exclude any psychiatric comorbidity using the MINI 6.0, as well as a history of medical comorbidity. Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 22. Continuous variables were analyzed using independent sample t-test, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

Sociodemographic Details

A total of 30 adults with depression were recruited for the study, out of which 15 were males and 15 were females. The mean age of the study sample was 31.37 years [S.D = 8.40]. [Table 1] below presents the sociodemographic profile of the study sample. Among the controls the mean age was 28.27 years [S.D = 5.94]. Among the cases, 43.34% each were from low and middle socioeconomic status. In the control group, majority were from the middle socioeconomic status 73.33% [n = 22] followed by high socioeconomic status 16.66% [n= 5].

Table 1: Socio Demographic Details of the study sample

	Mean Age [YEARS] [SD]	Gender N [%]	Socioeconomic Status N [%]	Background N [%]
Cases	31.37 [8.40]	Male = 15[50%] Female=15[50%]	Low- 13 [43.3%] Middle-13 [43.3%] High- 4 [13.33%]	Urban- 17 [56.67%] Rural-13 [43.33%]
Controls	28.27 [5.94]	Male = 15 [50%] Female = 15 [50%]	Low- 3 [10%] Middle-22 [73.33%] High- 5 [16.66%]	Urban-24 [80%] Rural- 6 [20%]

In the cases, 17 subjects [56.67%] belonged to urban background and among the controls, 80% [n= 24] a large majority were from the urban background.

The control group was not statistically different in terms of age [P= 0.104] and gender. There was no statistically significant difference in the background of the cases and controls [P= 0.053]. A statistically significant difference was found in the socio-economic status of the cases and controls [P= 0.025].

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Table 2: Clinical Details of the cases

Clinical Features	Number [n]	Percentage [%]	Mean HDRS
Episodes			
Single	23	76.7	20.26
Multiple	7	23.3	22.86
Grades			
Moderate	13	43.3	17.54
Severe	17	56.7	23.41
Psychomotor Retardation			
Present	16	53.3	22.63
Absent	14	46.7	18.86
Melancholia			
Present	16	53.3	22.63
Absent	14	46.7	18.86
Deliberate Self Harm			
Present	6	20	21.83
Absent	24	80	20.63
Psychotic Symptoms			
Present	7	23.3	22.71
Absent	23	76.7	20.30

Clinical Details of the Cases

In the study population, the mean Hamilton Depression Rating Scale [HDRS] score was 20.87 ± 4.4. Among the cases, 76.7% [n=23] had first episode of depression with a mean HDRS score of 20.26. Table 2 presents the clinical features of the cases. In the sample, 56.7% [n=17] had severe depression with mean HRDS of 23.41.

In the study subjects, psychomotor retardation and melancholic symptoms were seen in 53.3% [n=16] with a mean HDRS of 22.63 and the remaining 46.7% [n=14] had normal psychomotor activity with a mean HDRS of 18.86.

Among the samples, 80% [n=24] did not have any deliberate self-harm attempt during the current episode of depression. Psychotic symptoms were seen in 23.3% [n=7] of the subjects with a mean HDRS score of 22.71.

Association between serum magnesium levels and clinical variables

Table 3: Mean Serum Magnesium levels in the study samples

	Case/Control	N	Mean	Std. Deviation
Serum magnesium	Case	30	2.0663	.24051
	Control	30	1.9343	.13151

As seen in Table 3, the serum magnesium levels were measured across the cases and the controls, mean serum Mg levels in the study sample [n=30] was 2.06 [S.D = 0.24], and the mean serum Mg levels in the control was 1.93 [S.D 0.13]. Serum Magnesium between 1.8-2.4 mg/dl was considered as normal.[24] Above 2.4mg/dl was considered as hypermagnesemia and below 1.8mg/dl was considered as hypomagnesemia. The association between serum Mg levels in cases and controls was calculated using independent t test. With equal variances not assumed, t= 2.638, df= 44.92 which is greater than the critical value [CV= 1.679], p = 0.011. In the current study the serum magnesium levels were significantly higher than that of the control group. Cohen's d was calculated, effect size [Cohen's d] = 0.681 indicating medium effect.

Table 4: Serum Magnesium Levels in the study sample

Case/Control			Magnesium level			Total
			Normal	High	Low	
Case		Male	9	3	3	15
		Female	9	4	2	15
	Total		18	7	5	30
Control		Male	13	1	1	15
		Female	11	0	4	15
	Total		24	1	5	30
Total		Male	22	4	4	30
		Female	20	4	6	30
	Total		42	8	10	60

Table 5: Association between serum magnesium and clinical variables

Clinical variables	Number [n]	Mean [SD]	P value
Episodes			
Single	23	2.02 [0.05]	0.057
Multiple	7	2.21 [0.10]	
Grades			
Moderate	13	1.99 [0.26]	0.131
Severe	17	2.12 [0.21]	
Psychomotor Retardation			

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Present Absent	16 14	2.03 [0.25] 2.10 [0.23]	0.446
Melancholia Present Absent	 16 14	 2.03 [0.25] 2.10 [0.23]	 0.446
Deliberate Self Harm Present Absent	 6 24	 2.08 [0.33] 2.06 [0.22]	 0.865
Psychotic Symptoms Present Absent	 7 23	 2.06 [0.18] 2.06 [0.26]	 0.99

[Table 4] above gives an overview of magnesium levels in the sample. The serum magnesium levels in 70% [42 subjects] of sample was normal, with 16.67% [10 subjects] having hypomagnesemia and the remaining 13.33% [8 subjects] having hypermagnesemia. Out of the cases, 60% [n = 18] had normal serum magnesium levels. In the control group, 80% [n = 24] of the subjects had normal magnesium levels, there was markedly less subjects with hypermagnesemia in the control groups with 3.33% [n =1].

In case of number of episodes and its relationship with serum magnesium levels, the single episode group had a mean of 2.02 [SD = 0.05] and the multiple episode group had a mean of 2.21 [SD 0.10] with t= -1.99, df=28. A trend towards significance for a weak positive correlation with p= 0.057 was observed, Cohen's d= 1.01 which suggests large effect size.

Serum magnesium was compared with the grades of depression i.e., moderate and severe depression and found no statistically significant relationship between the grades of depression and serum Mg levels. The relationship between gender and serum magnesium was measured in cases and controls found no statistically significant relationship between the two groups.

The relationship between presence and absence of psychomotor retardation and melancholic symptoms respectively were measured, and found no statistical significance between the two groups. The study further found no statistical significance between deliberate self-harm attempts and serum magnesium, and the presence and absence of psychotic symptoms.

DISCUSSION

This study aimed to investigate the association between serum magnesium levels and depression by comparing them in patients with depression to age and sex matched healthy controls. The findings of the study revealed that the serum magnesium levels in the cases were significantly higher than those in the healthy controls, which aligns with the results of previous studies on the subject.[21,25-30]

Sociodemographic Variable in Cases and Control Group

In our study, the mean age of the cases and controls were 31.37 years and 28.27 years, respectively. The participants in our study were relatively young when compared to previous studies, with Singh et al [2011],[31] having a mean age of 39.65 ± 7.0 years in cases and 41.65 ± 7.97 years in controls. Imada et al,[30] had a mean age of 48.3 ± 12.8 years in MDD group and 43.1 ± 12.1 years in the control group. Bhatia et al,[32] had a mean age of 49.6 ± 19.4 years. The reason for this relatively younger cohort is due to stricter inclusion criteria which exclude patients with comorbid medical and psychiatric disorders. In our study there was a significant difference in the socio-economic status and the background of the cases and controls. Subjects were coming from lower socioeconomic and rural background significantly more than that of the control group. It has been often observed that there is a change in the dietary and lifestyle pattern between different socioeconomic status and the background which may have influenced the findings of the current study.[33] The presence of more participants from rural background and lower socioeconomic status, could be the reason for the high prevalence of hypomagnesemia in the cases. Similarly, the consumption of soft drinks and beverages containing phytates amongst the urban population could explain the high prevalence of hypomagnesemia amongst the controls.[34]

Clinical Details of Study Sample

In our study, Mean HDRS score of the cases was 20.87 ± 4.40. Similar to the studies by Cubala et al. 2016,[35] who had a mean HDRS score of 22.5, while Camardese et al,[36] reported a mean HDRS score of 18.88 ± 5.18. In the present study, the mean HDRS score was 20.87 ± 4.4, with 76.7% [n=23] had first episode of depression, mean HDRS = 20.26, and 23.3% [n=7] had recurrent depressive episodes, mean HRDS = 22.86. In cases, 56.7% [n=17] had severe depression with mean HRDS of 23.41. Psychomotor retardation and melancholic symptoms were seen in 53.3% [n=16] with a mean HDRS of 22.63.

Cubala et al,[21] found that the severity of depressive symptoms in individuals with major depressive disorder (MDD) was significantly higher in patients with melancholia compared to those with non-melancholic MDD (P=0.002). However, in our study, we did not find a significant relationship between melancholic symptoms and the mean Hamilton Depression Rating Scale (HDRS) score.

In a study by Bhatia et al,[32] they observed that there was no significant change in serum magnesium levels across different age groups of depression patients. This finding is consistent with

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our study, where we also did not find a relationship between age and serum magnesium levels.

Among the samples, 20% [n=6] had attempted deliberate self-harm and had a mean HDRS of 21.83. Psychotic symptoms were seen in 23.3% [n=7] of the subjects with a mean HDRS score of 22.71. To the best of our knowledge, there are no studies that have looked at the relationship between the depression with psychotic symptoms and serum magnesium levels. In our study, the mean HDRS score was comparable with other studies and there was no significant difference in clinical variables of our sample compared with previous studies.

Association between serum magnesium levels and clinical variables:

Syedmoradi et al,[37] reported a prevalence of 4.6% for hypomagnesemia in the total population, with a higher prevalence observed in females (6.0%) compared to males (3.2%). Additionally, the overall prevalence of hypermagnesemia was found to be 3.0%. In a separate study conducted by Rajizadeh et al,[38] the mean serum magnesium level was reported as 2.1 ± 0.26 mg/dl. The prevalence of hypomagnesemia in that study was 13.7%, while hypermagnesemia was observed in 8.3% of the participants. Furthermore, the suboptimal prevalence of magnesium levels in women (28.1%) was higher than that in men (26.2%). Notably, a significant relationship between depression and serum magnesium levels was observed (P=0.02).

In our study, 16.67% of the subjects had hypomagnesemia and 13.33% had hypermagnesemia, which is high compared to the study by Syedmoradi et al.[37] Among the study sample, cases constituted of 16.67% of hypomagnesemia and hypermagnesemia was seen in 23.3% of the cases. The higher prevalence of hypo and hypermagnesemia seen in our study could be due to the smaller sample size, which could be overestimating its prevalence. Dietary preferences of the population studied also has a role in serum magnesium levels. The dietary patterns of the study sample were not assessed. Secondary to decreased food intake, the patient maybe malnourished which could the reason for the high prevalence of hypermagnesemia seen in our study.

In our study, the mean serum magnesium level in the cases was 2.06 mg/dl (S.D = 0.24), while in the control group, the mean serum magnesium level was 1.93 mg/dl (S.D = 0.13). The association between serum magnesium levels in cases and controls was found to be statistically significant with a p-value of 0.011. However, there were no significant differences in magnesium levels between sexes in our study.

Cubala et al. [2016] conducted a study that was similar to ours, and they reported a mean magnesium level of 0.71 mmol/L (equivalent to 1.73 mg/dl) in cases. They observed significantly higher magnesium levels (P=0.016) in individuals with major depressive disorder (MDD) compared to controls.

In another study by Cubala et al,[21] they found significantly higher magnesium concentrations in depressed patients with melancholic MDD (P=0.029) compared to controls. However, in non-melancholic MDD patients, a significant difference in magnesium levels was not observed (P=0.082).

Bhatia et al,[32] revealed significant hypomagnesemia in the subjects compared to the normal population, similar to the study by Rajizadeh et al,[10] and suggested for magnesium supplementation in patients with depression as an adjunct to antidepressants. Contrary to this finding, in our study we observed a positive correlation between magnesium levels and depression.

Ruljancic et al,[39] conducted a study that revealed a significant difference in serum magnesium levels between depressive patients with attempted suicide (mean serum Mg: 0.89 mmol/L, SD ± 0.16) and depressive patients without attempted suicide (mean serum Mg: 0.96 mmol/L, SD ± 0.12). However, in our study, no statistically significant relationship was found between magnesium levels and deliberate self-harm attempts (P=0.865).

Camardese et al,[36] conducted a study and did not find a significant correlation between plasma magnesium levels and anhedonia. They did observe a weak positive correlation between plasma magnesium levels and psychomotor retardation, although the relationship did not reach statistical significance (P=0.076). On the other hand, Cubala et al,[21] reported a significant positive correlation between plasma magnesium concentrations and psychomotor retardation in individuals with major depressive disorder (MDD). They also observed hypermagnesemia in MDD patients but found no correlation between magnesium concentrations and other psychopathological features. In our study, we did not find a relationship between serum magnesium levels and melancholic symptoms or psychomotor retardation. Additionally, Camardese et al,[36] observed that MDD patients with higher plasma magnesium levels at baseline had a significantly higher response rate to antidepressant treatment compared to those with lower magnesium levels. However, this specific aspect was not evaluated in our present study.

Strengths

One notable strength of this study is the inclusion of a control group that was carefully matched for age and sex. Additionally, the study employed a strict inclusion criterion, excluding individuals with any medical or psychiatric co-morbidities, which helped to eliminate confounding factors that could influence serum magnesium levels. The research utilized structured interviews to identify psychiatric disorders and conducted comprehensive assessments of various symptom domains of depression, which were then analyzed in relation to serum magnesium levels.

Limitations

The study suffered from a small sample size, which may limit the generalizability of the findings.

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Furthermore, important factors such as dietary supplementation, specific pharmacotherapy (e.g., PPI), and levels of physical activity were not evaluated in the current study. The assessment of multivitamin supplement consumption also lacked detail. Additionally, the evaluation of comorbidities in the control group relied solely on self-reported information provided by the subjects. It should be noted that serum magnesium levels may not accurately reflect magnesium concentrations in the brain, and future studies should consider measuring magnesium levels in the cerebrospinal fluid (CSF) and exploring their correlation with different symptom domains.

CONCLUSION

Subjects with depressive disorder exhibited significantly elevated serum magnesium levels, indicating a potential association between magnesium and depression. However, previous studies have presented conflicting findings regarding magnesium levels in different body fluids, leading to ambiguity. To gain more clarity, it is crucial to conduct further prospective studies with larger sample sizes to comprehensively explore the relationship between serum magnesium and depression. In addition to serum magnesium levels, future investigations should consider assessing magnesium levels in cerebrospinal fluid (CSF) and erythrocytes. Incorporating newer techniques like phosphorus magnetic resonance spectroscopy, which enables the measurement of brain magnesium concentrations, could provide valuable insights into the role of magnesium in the pathophysiology of depressive disorders.

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