ORIGINAL ARTICLE

SERUM VITAMIN D, CALCIUM AND PHOSPHATE LEVELS IN PATIENTS WITH ACUTE MANIA: A CROSS-SECTIONAL COMPARATIVE STUDY

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ABSTRACT

Objective: To investigate the levels of serum Vitamin D, Calcium and Phosphate levels in the manic phase of bipolar disorder.

Study Design: Cross-sectional study with comparative groups.

Place and Duration of Study: Rawal General Hospital, Islamabad, 10 months (October 2023 to Jul 2024).

Methodology: Forty patients suffering from manic episode according to the Diagnostic and Statistical Manual of Mental Disorders(DSM)- 5 criteria were included in the study, after informed consent. They were compared to 40 age and gender-matched healthy controls who had no previous psychiatric history. The authorization to conduct the study was given by the Ethical Review Board of the medical college vide the ERB permission letter. Young Mania Rating scale was administered to the patients to assess the severity of mania. Venous blood was drawn from all the participants to determine the serum levels of vitamin D, Calcium and Phosphate. Statistical analysis was done with the help of SPSS-23. For numeric variables, descriptive statistics and mean with standard deviation were calculated, whereas frequencies and percentages were calculated for the categorical variables. For the analysis of categorical variables Chi-square test was used, and for the numerical variables, the Independent samples t-test was utilized. The p- value < 0.05 was considered significant.

Results: With respect to demographic details, the cases and controls were homogeneous. The mean Serum vitamin D was 11.52 ± 5.83 ng/ml for the cases and 17.46 ± 6.18 ng/ml for the controls, and this result was statistically significant(P < 0.01).

Conclusion: In our sample, bipolar patients with a manic episode had significantly lower Vitamin D levels, and this purportedly implicated the latter factor in the pathogenesis of bipolar mania.

Keywords: *Bipolar disorder, Inflammation, Mania, Vitamin D.*

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INTRODUCTION

Bipolar disorder (BD), a mental disorder affecting millions of people worldwide, is an incalcitrant condition[1]. The disorder impairs functioning in the biopsychosocial realms, and currently available psychopharmacological agents only provide symptomatic relief [1, 2]. Active exploration and avenues of research include neuroinflammation, oxidative damage and neurodegeneration in its mechanism[3]. Vitamin D (Vit D) is an essential nutrient with pleotropic actions throughout the body, whose relationship with mood disorders has been investigated. In particular, the role of low Vit D levels and major depressive disorder is well-researched, but this association is less well studied in BD [4].

The potential role of inflammation in the development of BD has been well researched, and it is conceivable that stress may trigger neuroinflammation. This is allegedly implicated in the development of BD [5]. In BD, a number of biochemical parameters associated with inflammation have been explored; however, the connection between manic episodes and serum Vit D levels has not been sufficiently studied. While a handful of studies implicate low Vit D in mania, additional work is needed to validate this association [6].

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Biologically, several factors, including inadequate sunlight, poor dietary intake, seasonal variations and increasing age, influence Vit D levels. Across the world, studies show that low Vit D levels, at all ages, are liable for both physical and mental diseases [7]. There is emerging evidence that Vit D is involved in critical brain functions like neurotransmission, neurogenesis, neuroplasticity and neuroinflammation. As such, researchers have turned their attention towards investigating the potential involvement of Vit D in major neuropsychiatric conditions [8].

CAPSULE SUMMARY

The serum levels of Vitamin D, Calcium and Phosphate in the manic phase of bipolar disorder were determined. Patients in the manic episode had significantly lower Vitamin D levels. The differences in Calcium and phosphate levels were not statistically significant.

Major neuropsychiatric disorders like attention deficit hyperactivity disorder (ADHD), BD and schizophrenia show common executive dysfunction, deficits in social behavior and impaired emotional regulation. Serotonin, a monoamine neurotransmitter, performs crucial functions in the brain, and Vit D, among other micronutrients, is required in its synthesis. Relative deficiency of Vit D during critical periods of development supposedly impairs serotonergic transmission in the prefrontal areas and limbic circuit and leads to major neuropsychiatric disorders. Optimizing Vit D intake throughout the development epoch may help modulate brain functioning, and supplementation with this essential nutrient may decrease the psychosocial impairment associated with neuropsychiatric disorders [9].

In BD, there is acute disturbance during the manic episode, and it is highly desirable to examine the status of Vit D and related parameters of Calcium (Ca) and Phosphate (P) in the peripheral blood. In this regard, only a handful of studies have assessed peripheral levels of Vit D, Ca and P in BD patients. In a review published a few years ago, the authors performed a literature search, investigating Vit D status in BD subjects. They found 10 original studies on this subject, and the overall results showed that there was sub-threshold Vit D deficiency in BD cases, which had an association with the status of symptoms. In addition, Vit D supplementation helped decrease both manic and depressive symptoms [10].

A recent study used novel parameters to examine Vit D status in BD. The researchers measured 25 (OH) D, 24, 25 (OH) D and Vit D metabolite ratio (VMR) [VMR = 100×(24,25(OH)2D/25(OH)D)] in cases and controls. Their findings demonstrated a negative correlation between Vit D parameters and severity of symptoms of mania as calculated by the Young Mania Rating Scale(YMRS). The authors concluded that keeping in view the limitations of the cross-sectional study, a significant inverse relationship occurred between the severity of mania and Vit D levels, and this required further investigation [11]. The aim of our study was to investigate serum Vit D, Ca and P in acute mania and compare those to healthy individuals to examine any association between these variables.

METHODOLOGY

Approval for the study was obtained from the Institution Review Board of Rawal Institute of Health Sciences (RIHS), Islamabad.

In this cross-sectional study with comparative groups, study subjects were patients seen in the outpatient section of the department of Psychiatry of Rawal General Hospital, which is the teaching hospital of RIHS, Islamabad, Pakistan. The duration of the study was from 01/10/2023 to 31/07/2024, a period of 10 months. Patients with BD, suffering from a manic episode, were included in the study through non-consecutive sampling, after an informed consent. Sample size was calculated using open epi calculator for comparing means between two independent groups. The calculations were based on a 95% confidence interval, 80% power and previously reported Vit D levels in group 1, 14.58±11.27 and group 2, 30.97±17.87 mg/ml [12]. The sample size required was calculated to be 14 participants per group. We inducted 40 individuals into each group. A large sample helps mitigate the potential effect of dropouts or outliers and generalizability of the results. The patients in the study group could have an index or recurrent episode of mania, while the comparative group consisted of healthy individuals, matched for age and gender and having no previous psychiatric history.

Inclusion criteria included patients diagnosed as having BD type I, current episode manic according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria, giving informed consent, patients of either gender and ages between 18 and 60 years. Exclusion criteria included patients with bone disorders and endocrinological conditions affecting Vit D metabolism, those cases who took Vit D supplementation for 03 months prior to evaluation, pregnant and lactating mothers, patients with acute medical conditions, e.g. infections, patients with chronic medical conditions, for example, diabetes mellitus.

The participants with BD were administered the Young Mania Rating Scale (YMRS) to confirm the diagnosis of mania and rate its severity [13]. This is a well-validated instrument with a high level of reliability. It is the preferred instrument in research work and has been used innumerable times in both national and international studies. To differentiate between cases and non-cases, a cut-off score of 20 on the YMRS was utilized. Demographic variables of the cases and controls were recorded with the help of a separately designed proforma.

With the help of sterile technique, 5 ml of blood from the antecubital vein of all of the subjects was drawn and collected into vacutainer tubes . The samples were centrifuged for 10 min at 2500 revolutions per minute, and the serum was separated. It was analyzed to determine the 25-OHD levels. Serum Vit D levels were interpreted in the following manner [14]:

- normal - 20–100 ng/mL

- insufficient - 10–20 ng/mL
- deficient - <10 ng/mL

From the same sample, serum Ca and P were also determined.

Statistical analysis was done with the help of SPSS-23. For numeric variables, we used descriptive statistics and derived the mean with standard deviation, whereas frequency and percentage were calculated for categorical variables. For the analysis of categorical variables Chi-square test was used, and for numerical variables Independent samples t-test was utilized. The p- value < 0.05 was considered significant throughout the statistical measures.

RESULTS

There was no statistically significant difference between the demographic variables (age, gender, residence, level of education and employment status) of cases and the comparative group (Table 1) The biochemical variables(serum Vit D, Ca and P) of patients and the comparative group are compared in Table 2, which demonstrates that serum Vit D levels are significantly lower in cases with mania as compared to healthy individuals ($p < 0.01$), while serum Ca and P values did not reach statistical significance.

DISCUSSION

The studies examining the link between Vit D and BD are scarce. Relying on the current literature, it can be said that there exists a tentative connection between clinical symptomatology and serum Vit D levels. A comprehensive review, published a few years ago, addressed this matter; an exhaustive search revealed that 10 original studies examined Vit D blood levels in both the manic and depressive phases of BD. Compared to other diagnostic groups, BD cases had no significant differences in serum Vit D levels; nonetheless, the average values of Vit D were in the insufficient range in the BD population. Additionally, it was seen that there existed a relationship between Vit D levels and clinical symptomatology in BD patients, but this could not be regarded as a fully characterized biomarker. Rather, it was a feature shared with other psychiatric disorders, including schizophrenia and major depressive disorder (MDD). Importantly, the addition of Vit D to the treatment regimen was accompanied by a reduction in both depressive and manic symptoms [10]. In our study, the population was homogeneous in the demographic variables. A significantly low serum Vit D was observed in BD patients presenting with mania. These results were in line with previously published studies, and strengthened the general assumption that Vit D had an immunomodulatory and anti-oxidant role, and that its relative deficiency resulted in neuropsychiatric disorders [15].

Table 1: Demographic characteristics of study participants

Variables	BD group n = 40	Healthy individuals n = 40	p-value*
Age (mean ± SD)	31.63±7.49	29.27±8.45	0.358#
Male n(%)	26 (65)	28 (70)	0.154
Female n(%)	14 (35)	12 (30)	0.368
Urban residence n(%)	30 (75)	32 (80)	0.712
Rural Residence n(%)	10 (25)	8 (20)	0.471
No education n(%)	6 (15)	8 (20)	0.217
Matric n(%)	20 (50)	18 (45)	0.761
Higher n(%)	14 (35)	14 (35)	0.358
Employed n(%)	28 (70)	30 (75)	0.269
Unemployed n(%)	8 (20)	8 (20)	0.752
Student n(%)	4 (10)	2 (5)	0.183

P* - Pearson's Chi-square; P# - Independent samples t-test; SD – Standard deviation

Table 2: Comparison of Vit D levels, Ca and P levels between patients with acute mania and healthy individuals

Variable	Manic cases n = 40 mean ± SD	Healthy individuals n = 40 mean ± SD	t-value	p-value
Vit D (ng/ml)	11.52 ± 5.83	17.46 ± 6.18	**2.708**	**< 0.01**
Ca (mg/dL)	9.11 ± 0.83	9.51 ± 0.72	**1.195**	**0.47**
P (mg/dL)	3.19 ± 0.68	3.74 ± 0.68	**1.211**	**0.38**

Ca – Serum Calcium; P – Serum Phosphate; SD. – Standard Deviation; p* – independent samples t-test

An accumulating body of evidence demonstrates that Vit D performs essential functions in the brain. Vitamin D, a neuroactive steroid, has been suggested to modify neurotransmitter pathways in the central nervous system. It is surmised that aberrant neurotransmission is involved in the pathogenesis of principal neuropsychiatric diseases such as schizophrenia, BD and MDD. Vit D performs important actions of calcium homeostasis, and supposedly the amyloid-peptide clearance as well, in addition to having antioxidant and anti-inflammatory functions. Furthermore, it acts as a likely protective factor against the progression associated with Alzheimer's disease, schizophrenia and neurodevelopmental disorders. Several studies indicate that Vit D has a shielding role in neuropsychiatric disorders, such that its regular intake helps in the prevention of these disorders and also reduces the severity of psychiatric ailments. Hence, the bulk of extant research indicates that timely supplementation, keeping Vit D concentrations at adequate levels, is critical in slowing, averting or improving decline in the neurocognitive status [16].

A recently published systematic review highlighted the beneficial effects of regular Vit D intake in neuropsychiatric disorders. A wide-ranging search of the literature was supportive of adding Vit D to the treatment regimens in mood disorders, psychotic disorders, neurodevelopmental and neurodegenerative disorders. The salutary effects of this pleotropic hormone were evident across the spectrum of neuropsychiatric illnesses, such that the monitoring of Vit D levels and its administration were highly recommended [17]. An interesting study was recently published from the People's Republic of China, investigating serum 25-hydroxy Vit D levels in patients diagnosed as suffering from bipolar depression. Vit D levels were measured at the start of the study and 2 weeks after treatment; three sub-groups were identified through latent profile analysis. The study found that participants with adequate levels of Vit D demonstrated a significant improvement in the severity of depression. However, the patients who had low levels of Vit D went on to remain significantly depressed, specifying a requirement for directed Vit D supplementation. The results of this study highlighted the importance of planned and personalized Vit D supplementation to manage the deficiency of Vit D in patients with BD [18].

In an effort to study the part played by inflammation, a recently published study examined the link between serum Vit D levels, C-reactive protein (CRP) and psychiatric illnesses with psychotic symptomatology. The investigators had three clusters of cases, including schizophrenia, psychotic mania and methamphetamine-induced psychosis. In the 3 sets of cases, CRP levels were significantly higher and serum Parathyroid hormone (PTH) levels were significantly lower, compared to the healthy control group ($p < 0.001$). As regards blood levels of Ca, P and Vit D, the differences did not reach statistical significance when patient and control groups were compared. However, in patients with chronic psychosis, serum CRP levels were significantly higher ($p < 0.031$) and Vit D levels significantly lower ($p < 0.044$) compared to patients who had first-episode psychosis. These results proposed that Vit D levels were decreased in subjects with chronic psychosis in comparison to patients with first-episode psychosis, and conceivably, this finding had pathophysiological and therapeutic implications[19]. Neuropsychiatric disorders, including BD are characterized by subtle impairments in cognitive functioning, and it would be interesting to know if Vit D plays a role in this regard. A comprehensive review published recently addressed this issue in the main psychiatric illnesses, including Schizophrenia, mood disorders, Alzheimer's disease and ADHD. The authors noted that while there were many studies specifying the key role of vitamins in cognition, it was still too early to unambiguously assume that Vit D had an effect in the development of cognitive symptoms. More study was needed to confirm this putative association, together with the necessity of improving on the biological veracity of animal prototypes, better defining the key cognitive deficits accompanying the disorders, while determining the optimum way, Vit D is taken [20].

Finally, seasonal affective disorder (SAD) is an illness characterized by depressive episodes in fall and winter, with resolution of the affective symptoms in spring and summer. These patients have an illness where mood episodes occur in a seasonal form for two or more years consecutively. It is surmised that a decrease in sunlight hours during winter months plays an etiological role in SAD, and Vit D status in these patients has been investigated as exposure to sunlight is essential for the synthesis of this substance in the body. A recently published review on the subject of fat and water soluble vitamins in the prevention and treatment of SAD underlined that vitamins taken in the diet, as well as added vitamins, had encouraging effects in both prevention and treatment. However, clinicians dealing with psychiatric ailments faced ambiguity because of the variations present in the study designs, such that any definitive conclusions were hard to make. The authors concluded that there was evidence to support the roles of vitamins B, C and D in the prevention and treatment of mood disorders; nonetheless, additional work was required to explain their modes of action and to find out the most effective means of supplementing these micronutrients [21].

LIMITATIONS

1. Cross-sectional design of the study introduces bias in the interpretation of the results.
2. The fact that many patients were receiving psychopharmacological agents was not controlled for in the study.
3. Dietary habits and exposure to sunlight have an influence on serum Vit D levels, and these factors could have introduced bias in the results.

CONCLUSION

The results of this study can be regarded as preliminary; nonetheless, these are still valuable as it was shown that Vit D levels were unequivocally reduced in BD patients with manic episodes. It is known that immunologic and inflammatory mechanisms are important players in the manic phase of bipolar disorder, and Vit D, with its myriad functions in the CNS, plays a contributory part in the onset and maintenance

of BD. Additional research, which adequately controls for diet, exposure to sunlight and medications, can further elucidate the role of Vit D in the bipolar diathesis.

ETHICAL APPROVAL: *Reference number:* RIHS/IRB/08/2023*, Date: 01-08-2023*

CONSENT FOR PUBLICATION: *Written, informed consent was obtained from the study participants.*

AVAILABILITY OF DATA: *Data is available from the corresponding author on a justified request.*

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AUTHORS' CONTRIBUTION

- ***Ather Muneer:*** *Acquisition of data, Aanalysis and interpretation of data, Drafting the article*
- ***Nargis Muneer:*** *Acquisition of data, Drafting the article*
- ***Mahwish Ahmad:*** *Aanalysis and interpretation of data, Drafting the article*
- ***Zara Inam:*** *Drafting the article, Acquisition of data, Critical revision*

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