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Serum Vitamin D, Mania and Depression-Related Scores: A Comparison among Mixed Bipolar, Mania, and Healthy Subjects

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Abstract

Objective: Manic and mixed episodes of bipolar disorder are important episodes of this disorder. The aim of the current study was to assess serum vitamin D (SVD) levels in patients with mania and mixed bipolar disorder, compared to healthy subjects.
Method: The current cross-sectional study was conducted on 75 subjects, including healthy subjects (n = 25), patients with acute-phase mania (n = 25), and patients with mixed bipolar disorder (n = 25). The SVD levels were measured in all of the enrolled subjects. The Hamilton Depression Rating Scale (HDRS), Young Mania Rating Scale (YMRS), and Clinical Global Impression- Severity (CGI-S) were used to assess disease activity in patient groups. Data analysis was performed using SPSS version 18. For statistical analysis, analysis of variance (ANOVA), independent-sample t test, Pearson correlation, and Chi-square tests were utilized. P-values < 0.05 were considered statistically significant.
Results: The results showed that the mean of SVD was significantly lower in mania and mixed bipolar patients compared to healthy subjects (P < 0.05). In addition, the number of subjects with SVD ≥ 20 ng/ml was higher in the healthy group compared to the patient groups (P < 0.05). Also, SVD was negatively correlated with the CGI-S (r = -0.311; P = 0.028), YMRS (r = -0.464; P = 0.001), and HDRS (r = -0.393; P = 0.005) in the total patient subjects.
Conclusion: Prevalence of low SVD was considerably high in mania and mixed bipolar patients compared to healthy subjects. Additionally, meaningful negative correlations were found between SVD and disease activity-related variables including the HDRS, YMRS, and CGI-S.

Key words: *Bipolar Disorder; Depression; Mania; Vitamin D*

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Mania is an episodic type of bipolar disorder defined by mood, sleep, and behavior disturbances, as well as abnormally elevated levels of energy. During a manic episode, an individual experiences rapid changes in emotions and moods and are highly influenced by surrounding stimuli. The symptoms of mania include hyperactivity, pressure of speech, flight of ideas, as well as decreased desire and need for sleep. These symptoms may be obscured in severe manic episodes by other symptoms and signs of psychosis such as delusions, catatonia, fragmentation of behavior, and hallucinations (1). In a group of bipolar disorder named "acute-phase mania," manic episodes can last days to months and return to a normal situation when symptoms subside. However, in other sub-groups of mixed bipolar disorders, patients experience depression signs and symptoms along with those of manic episode. Each of these episodes are also divided into different subtypes (2).

Regarding recent advances in the field of epidemiological research and neuroscience, there has been a growing interest in nutritional psychiatry and the role of lifestyle in mental disorders. Considerable evidence from observational studies has proposed diet quality as an independent prognostic factor for the prediction of depression risk (3). There are several factors affecting food intake and micronutrient metabolism in patients with bipolar disorders including: 1) the negative effect of bipolar disorder on appetite and satiety, especially in manic-depression cycle, 2) the prevalence of anorexia and binge eating disorders in bipolar patients, and 3) the effect of medications used to treat bipolar disorders on micronutrients metabolism such as vitamin D (4-8).

Vitamin D has multiple roles in several functions of the central nervous system (CNS). Animal data indicate that vitamin D can regulate brain development during early life. Also, the promotion of axogenesis and several neurotrophic factors, especially the nerve growth factor (NGF), is another role found for Vitamin D in the CNS. A link between bipolar disorders and lower vitamin D levels has been reported in different samples of bipolar patients (9, 10). In bipolar disorders, vitamin D deficiency has been reported in manic (11) and psychotic patients (12). In most studies, the average values of vitamin D levels were less than the threshold of vitamin D deficiency in bipolar patients. A high prevalence of vitamin D deficiency in bipolar patients has been shown in a cross-sectional study. Additionally, the mentioned study reported an interaction between vitamin D and cognitive domains. However, this reported effect was modified by age-adjusted analysis. In fact, this age-adjusted interaction was associated with the following outcomes in all participants: 1) verbal fluency, and 2) composite neurocognitive scores. Furthermore, in the younger group, the association was also observed with the processing speed domain (13).

Although serum vitamin D (SVD) levels are widely and separately assessed in mania and mixed bipolar disorders compared to healthy subjects, to the best of our knowledge, no previous similar study has compared vitamin D status between manic and mixed bipolar patients. This is one of the strengths and novelty of our study. Moreover, the SVD status has not yet been assessed across different subgroups such as gender, disease duration, manic episodes, and depression episodes in psychiatric patients. Considering the importance of vitamin D in the mental health of patients with bipolar disorders and factors affecting vitamin D status in these patients, the current study aimed to assess SVD levels in patients with acute mania and mixed bipolar disorders compared to healthy subjects and across the sub-groups of gender, disease duration, mania, and depression episodes.

Materials and Methods

Participants

The current cross-sectional study was conducted on 75 subjects, including 25 healthy subjects, 25 patients with acute-phase bipolar mania, and 25 patients with mixed bipolar disorder. Structured clinical interviews based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (14) were administered by a psychiatrist to diagnose acute-phase bipolar mania and mixed bipolar disorder. All enrolled subjects passed the same diagnostic interview. The individuals in the control group were included only after it was confirmed that they did not meet the criteria for mania and mixed bipolar disorder.

The written informed consent was obtained from all participants and their guardians. Subjects in the control group were from first-degree relatives of the patients. The convenience sampling method was employed for recruitment of participants from Razi Hospital, Tehran, Iran. The study was approved by the Ethical Committee of University of Social Welfare and Rehabilitation Sciences, Tehran, Iran (Ethical code: IR.USWR.REC.1398.012). The sample size for each study group (n = 25 for each group) was calculated with 95% confidence interval (CI) and statistical power of 80%, considering the serum levels of vitamin D in patients with manic and mixed episode in acute-phase bipolar disorder (15). The main variables assessed were SVD levels, the Young Mania Rating Scale (YMRS), Clinical Global Impression-Severity (CGI-S), and Hamilton Depression Rating Scale (HDRS). Moreover, data on demographic characteristics, disease duration, sun exposure, mania, depression, and mixed episodes number were collected. Demographic characteristics and disease duration were extracted from medical records/files. Data on sun exposure time, mania, depression, and mixed episodes number were gathered by the interviews with patients and their families.

Serum 25(OH) Vitamin D3 Assessment

After an overnight fasting, 5 ml venous blood was collected from all participants. Serum samples were separated from whole blood by centrifugation at 2000 rpm for 10 min at 4°C. Aliquots were then stored at -70°C until biochemical analysis. The concentration of serum 25(OH) D3 was determined by a radioimmunoassay technique utilizing the Architect i2000 (Abbott Laboratories).

Assessment of Mental Related Variables

In addition to the SVD, in the current cross-sectional comparative study, the CGI-S, YMRS, and HDRS were also assessed in all participants. In the CGI-S, a 7-point scale, the clinician rates the severity of the illness at the assessment time. The clinician's question is as follows: "Considering your total clinical experience with this particular population, how ill is the patient at this time?" Possible ratings are as follows: 1) Normal, not at all ill, 2) Borderline mentally ill, 3) Mildly ill, 4) Moderately ill, 5) Markedly ill, 6) Severely ill, and 7) among the most extremely ill patients. The validity of the questionnaire was previously assessed in the Iranian population (16). The presence and severity of mania and associated symptoms were measured by the YMRS.

The items are 1) elevated mood, 2) increased motor activity or energy, 3) sexual interest, 4) sleep, 5) irritability, 6) speech (rate and amount), 7) language (thought disorder), 8) content, 9) disruptive or aggressive behavior, 10) appearance, and 11) insight. The validity of the questionnaire was also assessed in the Iranian population (17). In the current study, the 17-item HDRS was used to provide an indication of depression. Eight of the seventeen items rated on a 5-point scale are as follows: 0 (absent), 1 (doubtful or mild), 2 (mild to moderate), 3 (moderate to severe), 4 (very severe). The remaining nine items are rated on a 3-point scale: 0 (absent), 1 (doubtful or mild), 2 (clearly present), yielding a minimum total score of 0 (least severe) and a maximum score of 52 (most severe). The validity of the questionnaire was assessed in the Iranian population (18).

Statistical Analyses

Data analysis was performed by the SPSS software (version 16, IBMSPSS statistics, IL, Chicago, USA) and P-value < 0.05 was considered statistically significant. Quantitative and qualitative variables were summarized as mean ± SD and frequency (percent), respectively. The normality of the study variables was assessed by the Kolmogorov–Smirnov test. Data analysis was conducted using the independent sample t-test and Analysis of Variance (ANOVA) for quantitative variables, and the chi-square test for qualitative variables. The correlations between the main variables of the current study were assessed by the Pearson correlation test.

Results

The current study was designed to assess vitamin D status in manic, mixed bipolar, and healthy subjects. General characteristics of the study groups are summarized in Table 1.

Table 1. General Characteristics of the Study Population and Comparison of Them between Mania, Mixed Bipolar, and Healthy Subjects

Variables		The study groups			P-value
		Mania (n = 25)	Mixed bipolar (n = 25)	Healthy subjects (n = 25)	
Age (Year)		37.08 ± 8.10	37.88 ± 11.96	39.07 ± 8.77	0.678*
Gender	Male	15 (60)	16 (64)	18 (72)	0.662**
	Female	10 (40)	9 (36)	7 (28)	
Sun exposure	zero time*	4 (16)	6 (24)	1 (4)	0.062**
	1-3 times*	11 (44)	10 (40)	6 (24)	
	≥ 3 times*	10 (40)	9 (36)	18 (72)	
Disease duration	< 10 years	16 (64)	20 (80)	-	0.173**
	≥ 10 years	9 (36)	5 (20)	-	
Mania	< 10 episodes	8 (32)	17 (68)	-	0.011**
	≥ 10 episodes	17 (68)	8 (32)	-	
Depression	< 10 episodes	20 (80)	21 (84)	-	0.500**
	≥ 10 episodes	5 (20)	4 (16)	-	

Quantitative and qualitative variables were presented as mean ± SD and frequency (%), respectively. * Data analysis was done using the Independent Sample T test. ** Data analysis was conducted using the Chi-square test.

The mean age in manic, mixed bipolar, and healthy subjects were 37.08 ± 8.10, 37.88 ± 11.96 and 39.07 ± 8.77, respectively (P = 0.678). The assessment of gender distribution across the study groups revealed that 15 (60 %) participants in the manic group, 16 (64 %) participants in the mixed bipolar group, and 18 (72 %) participants in the healthy group were male (P = 0.662). Additionally, the statistical analysis showed that there were no significant differences between manic and mixed bipolar patients in terms of disease duration and number of depression episodes (P > 0.05). However, the number of patients with equal or more than 10 depression episodes were significantly higher in manic patients compared to those in the mixed-bipolar group (P = 0.011).

Vitamin D status among the study groups is shown in Figure 1. The quantitative statistical analysis indicated that the mean value of SVD was significantly lower in mania and mixed bipolar patients compared to the healthy subjects. Additionally, the number of subjects with SVD ≥ 20ng/ml was higher in the healthy group compared to the other groups (P < 0.05). After gender-specific data analysis, the differences between patient groups compared to the healthy group remained significant only in male subjects (P < 0.05; Figure 2). On the other hand, sub-group data analysis showed that there were no significant differences in terms of SVD levels between the sub-groups of categorical mania episode number and depression episode number (< 10 episodes vs. ≥ 10 episodes; Figure 3; P > 0.05). Data analysis across the sub-groups of disease duration (< 10 years vs. ≥ 10 years) revealed that among patients with a disease duration of ≥ 10 years, SVD was significantly lower in mixed bipolar patients compared to patients in the mania group (P < 0.05). However, there was no significant difference between the patient groups with a disease duration of < 10 years (Figure 4; P > 0.05). The correlation assessment between the assessed variables in this study demonstrated that the SVD levels were negatively correlated with CGI-S, YMRS, and HDRS scores in total patient subjects. Furthermore, the YMRS was directly correlated with the number of mania and depression episodes (Table 2).

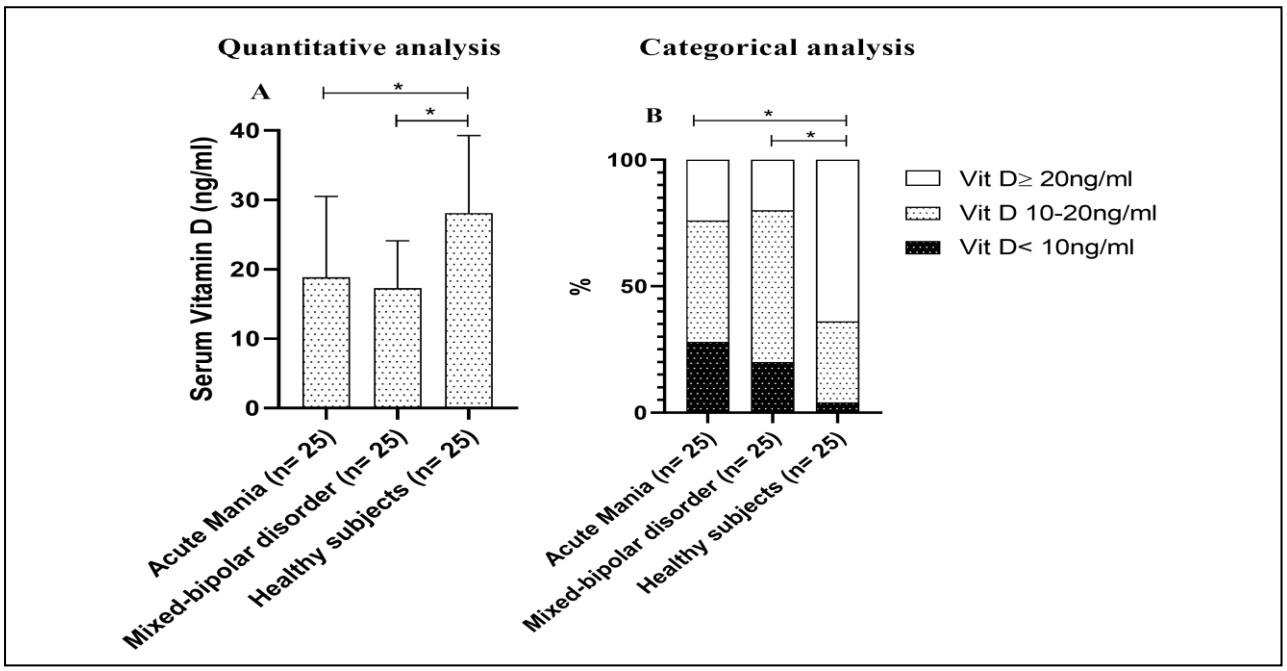

Figure 1. Quantitative (A) and Qualitative (B) Comparison of the Serum Vitamin D Levels between Mania, Mixed Bipolar, and Healthy Subjects

The data are represented as mean ± SD and percentage for quantitative and qualitative variables, respectively. Data analysis was done by ANOVA and chi-square tests. * P-value < 0.05.

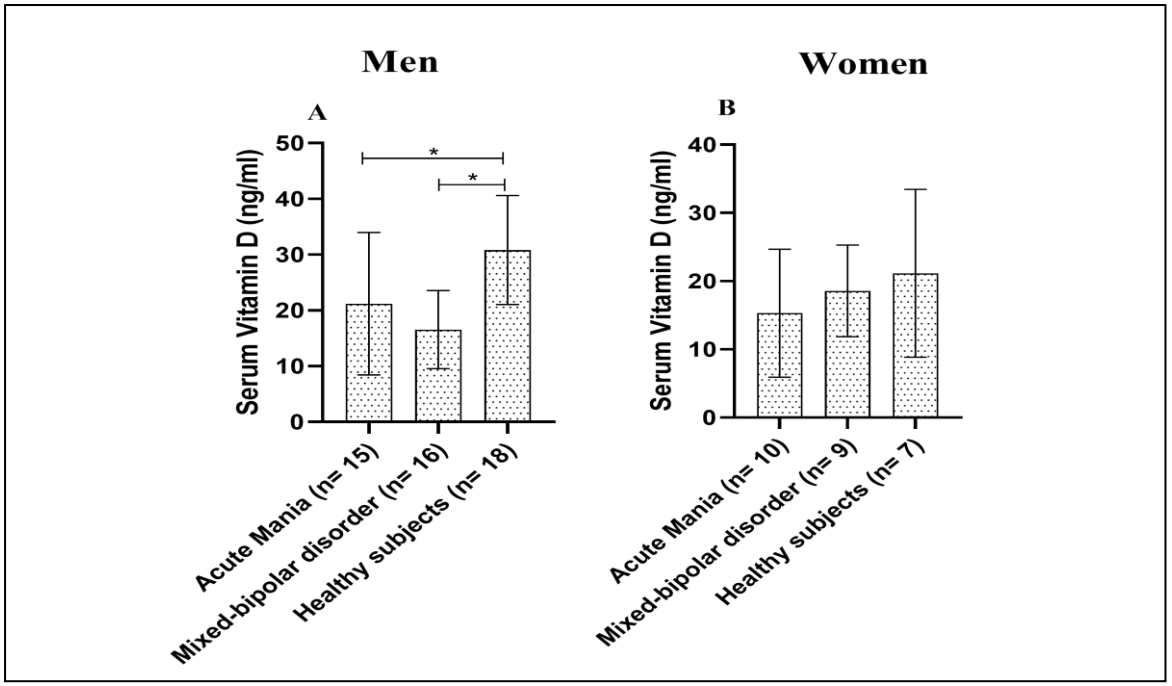

Figure 2. The Comparison of Serum Vitamin D Between Mania, Mixed Bipolar, and Healthy Subjects According Men and Women.

The data are represented as mean ± SD. Data analysis was done using the ANOVA test. * P-value < 0.05.

Table 2. The Correlation of Serum Vitamin D and Other General Characteristics with the YMRS, CGI-S and HAMD in Patient Population

		YMRS	CGI-S	HDRS
Serum vitamin D	r	**-0.464**	**-0.311**	**-0.393**
	P	**0.001**	**0.028**	**0.005**
Age	r	-0.095	**-0.371**	-0.021
	P	0.512	**0.008**	0.882
Disease duration	r	0.112	-0.151	0.144
	P	0.440	0.296	0.317
Mania episode number	r	**0.365**	-0.026	-0.167
	P	**0.009**	0.860	0.247
Depression episode number	r	**0.351**	-0.054	-0.133
	P	**0.013**	0.711	0.358

Data analysis was done by Pearson correlation.
HDRS: Hamilton Depression Rating Scale; CGI-S: Clinical Global Impression- Severity; YMRS: Young Mania Rating Scale.

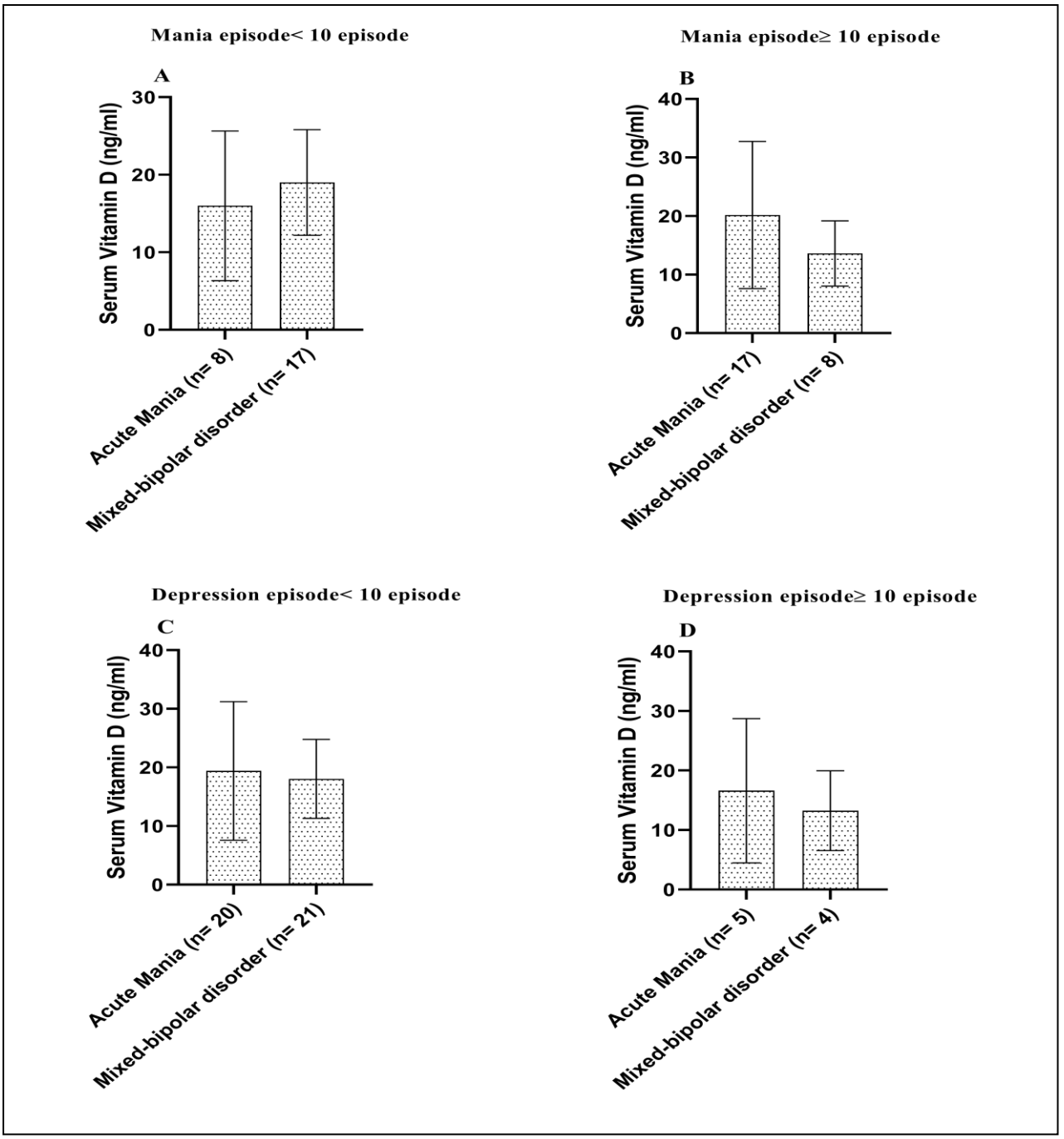

Figure 3. The Comparison of Serum Vitamin D between the Study Groups Considering Sub-Groups of Mania (A, B) and Depression (C, D) Episodes.

The data are represented as mean ± SD. Data analysis was done using the ANOVA test.

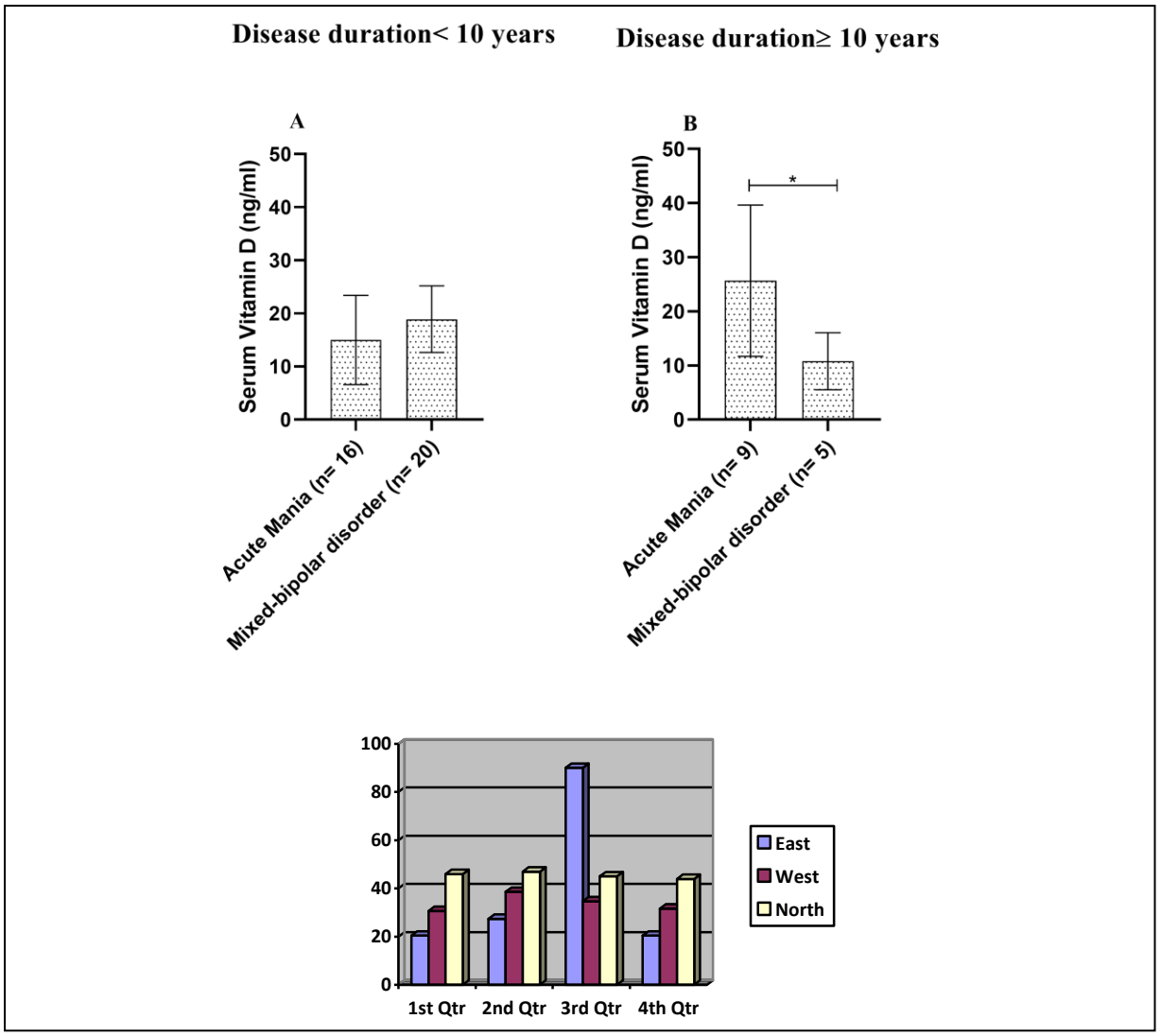

Figure 4. The Comparison of Serum Vitamin D Between Mania, Mixed Bipolar, and Healthy Subjects Based on Disease Duration

The data are represented as mean ± SD. Data analysis was conducted using the ANOVA test. SVD: serum vitamin D. * P-value < 0.05.

Discussion

In the current cross-sectional study, SVD levels in manic and mixed bipolar patients were assessed compared to the healthy subjects. The study results showed that SVD levels in patient groups were considerably lower compared to the healthy subjects. In addition, in terms of SVD, there was no meaningful difference between the patient groups. The indirect and considerable correlations of SVD with the CGI-S, YMRS, and HDRS scores were another important finding of this study.

To the best of our knowledge, vitamin D status in mixed-bipolar disorders has not been examined until now. However, vitamin D deficiency in acute manic patients has been reported by several studies. Marazziti *et al*. in a cross-sectional study examined serum levels of vitamin D in patients with bipolar disorders. The study results showed that serum levels of vitamin D in patients were considerably lower compared to the normal value (> 30 nmol/L). In Marazziti *et al*. study, there was no control group to examine along with patients with bipolar disorders (1). There is a lot of evidence on vitamin D deficiency in mood disorders, especially in depression. Findings on vitamin D status in bipolar disorder is limited to a study by Atunsoy and colleagues (11). Atunsoy *et al*. in a cross-sectional study examined vitamin D status in healthy controls, bipolar disorder patients in remission, and acute manic episode. The study results indicated that SVD in acute manic patients was considerably lower compared to the healthy subjects. On the other hand, there was no meaningful difference between patients in remission and healthy subjects. Further, negative correlation was reported between SVD and disease activity-related scores

including the YMRS and CGI-S in acute manic patients. It should be noted that although the authors claimed that the HDRS was also examined, the related results were not reported (11). The study conducted by Atunsoy *et al.* (11) was the most similar study to ours. However, in our study, mixed bipolar disorder patients were enrolled instead of acute manic patients in remission, and as mentioned before, the results from HDRS assessment were not reported by Atunsoy and colleagues (11). On the other hand, Marsh *et al.* in a randomized-controlled trial evaluated 12-week supplementation of vitamin D with daily dose of 5000 IU on YMRS in patients with bipolar depression. The reported results revealed that vitamin D supplementation compared to the placebo had no significant effects on the YMRS. Low dose of vitamin D was reported as the main reason for the non-significant effects on the mentioned outcome. The authors claimed that although daily dose of 5000 IU significantly increased SVD, it was not enough to reduce vitamin D deficiency in the study population (19).

Despite the well-established role of vitamin D in pathophysiology and treatment of depression, the possible association between vitamin D status and mania has not been elucidated until now. Glutamatergic abnormalities are suggested defects in bipolar disorder. Disruption in glutamatergic neurons and neurons producing gamma aminobutyric acid (GABA) leads to an increment in the concentration of intracellular calcium and cause mania. It has been shown that vitamin D is associated with a reduction in calcium levels.

Thus, a decrease in vitamin D levels may be related to the increment of calcium concentration. This can harm GABA producing neurons and lead to manic symptoms (20, 21). Sikoglu *et al.* reported that bipolar patients had improvement in their mood symptoms after 8-weeks supplementation with vitamin D3 (22).

As mentioned before, serum levels of vitamin D in mania and mixed-bipolar disorders were considerably lower compared to the control group. After sub-group analysis, the meaningful difference remained only in men. To the best of our knowledge, there is no similar study examining SVD levels in gender sub-groups. However, interventional studies have indicated that bipolar symptoms significantly improved in women compared to men after vitamin D supplementation (23, 24). It should be noted that disappearing meaningful difference after gender sub-group analysis in the women sub-group may be related to the female sample size (25). In the current study, the female sample size was ≥ 10 subjects (in each group) which can affect statistical significance. In fact, SVD in female patients with mania and mixed bipolar disorders were lower than female controls, but the differences were not statistically significant.

Comparing the number of mania and depression episodes, no significant differences were found between the mania and mixed bipolar disorder in terms of SVD. Also, among patients with a disease duration of 10 years or more, SVD was considerably lower in the mixed bipolar group compared to the mania group. This finding may be related to the more severe nature of mixed bipolar disorder compared to the manic condition.

Limitation

Although the sample size calculation in the current study was performed according to the previous similar works, a higher sample size is needed for further sub-group analysis. Therefore, similar studies with higher sample sizes are suggested. Moreover, assessing SVD levels in the remission phase after the disease attack could provide us with more insights into vitamin D metabolism in patients with bipolar disorders.

Conclusion

In the current study, vitamin D status was assessed in patients with mania and mixed bipolar disorders compared to healthy subjects. The prevalence of low SVD was considerably high in patients compared to healthy subjects. Furthermore, the meaningful negative correlation was found between SVD and disease activity-related variables including the HDRS, YMRS, and CGI-S. Future studies with higher sample sizes are needed to focus on the role of low SVD in the development of mixed bipolar and manic disorders for a more conclusive analysis.

Acknowledgment

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Conflict of Interest

None.

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