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Vitamin D Status and its Correlation with Disease Severity among Patients Presented with Major Depressive Disorders in a Tertiary Health Care Hospital in South India

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Abstract

Vitamin D level has a significant inverse correlation with depressive symptoms. The association of vitamin D level with unipolar or bipolar disorders are inconclusive among Indians. This study was aimed to find the severity of major depressive disorders and their correlation with vitamin D status. A cross-sectional study was conducted among patients (15-65 years old) diagnosed clinically with a major depressive disorder with a known serum 25 (OH) D levels. Mild, moderate, and severe depressive disorders were categorized into groups like vitamin D sufficient (≥75 nmol/L), insufficient (51-74 nmol/L), and deficient (<50 nmol/L). The data were analyzed for correlation. A total of 83 patients (33 males and 50 females) were included. Among the total, only four patients (4.8%) had bipolar disorder, while 79 patients (95.1%) had the unipolar disorder. Three bipolar patients and 68 unipolar patients had 25(OH)D levels below normal. Correlation analysis between the severity of disease and 25(OH)D level found a non-linear negative correlation in males (r= -0.07595, p= 0.7123) and positive correlation in females (r= 0.04234, p= 0.7823). However, correlation of age with 25(OH)D level was positive in males (r= 0.4151, p= 0.035) and negative in females (r= -0.1553, p= 0.3085). A negative correlation was found between the severity of the unipolar disorder and serum 25(OH)D levels in males. Therefore, male patients presented with the unipolar depressive disorder may consider vitamin D supplementation.

Keywords: 25(OH)D, Vitamin D, Bipolar Disorder, Unipolar Disorder, Depression

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Introduction

Vitamin D presents in two primary forms 1) Vitamin D2 (Ergocalciferol) in plants and 2) Vitamin D3 (Cholecalciferol), which is synthesized in the skin of humans after exposure to ultraviolet B radiation (290–310 nm) of the sunlight. Most of the food items rich in vitamin D are of animal origin, and thus the dietary sources have very low vitamin D content. The activation of vitamin D2 and D3 involves sequential hydroxylation such as 25-hydroxylation [25(OH)D] and 1α-hydroxylation in the liver and kidneys, respectively, to form the active 1,25-dihydroxycholecalciferol. The 25(OH)D bounds to the vitamin D binding protein in the bloodstream, constituting the circulating form. The half-life of 25(OH)D in circulation was relatively long (2–3 weeks). Despite the major function of vitamin D in calcium homeostasis, the "non-calcemic" actions are associated with the maintenance of glucose homeostasis, cardiovascular morbidity, autoimmunity, inflammation, and cancer.[1,2]

Vitamin D deficiency is widespread in individuals irrespective of age, gender, race, and geography. Furthermore, Indian socio-religious and cultural practices do not facilitate adequate sunlight exposure, negating plentiful sunshine's potential benefits. Consequently, subclinical vitamin D deficiency is highly prevalent in both urban and rural settings and across all socioeconomic and geographic strata.[3] Based on the serum level of 25(OH)D, patients were grouped as deficient (< 20 ng/mL or <50 nmol/L), insufficient (21–29 ng/mL or 51-74 nmol/L) and sufficient (≥30 ng/mL or ≥ 75 nmol/L). While a desirable and safe range of serum 25(OH)D levels would be ranges from 30 to100 ng/mL (75-250 nmol/L).

Cross-sectional and epidemiologic studies have found that low levels of vitamin D are significantly associated with high levels of depressive symptoms or a depression diagnosis.[4,5]

The standard and disabling mental illness, depression, was one of the cognitive disorders prevalent worldwide irrespective of age, gender, and race. A recent meta-analysis reported that vitamin D deficiency/insufficiency is associated with unipolar and bipolar depression.[6] However, no definite evidence is available to demonstrate the association of vitamin D deficiency as an etiological factor for developing depression.[7-9] Recent clinical trials conducted in subjects (18-70 years of age) with bipolar disorder at the University of Massachusetts Medical School, US, concluded that vitamin D3 supplementation did not improve reduction in mood elevation or anxiety symptoms.[10]

No studies reported the relationship between vitamin D levels and depressive symptomatology in the Indian population. Furthermore, no gender-wise studies were done to determine the correlation between the disease's vitamin D level and severity. Suppose any association could establish between the severity of the major depressive disorder and vitamin D status. The subjects with depressive disorders should be evaluated for their status, and necessary supplementation can be recommended. This study was aimed to find the gender-wise correlation between vitamin D level and severity of major depressive disorder among patients presented in a tertiary care hospital in South India.

Material and Methods

Study Design and Setting

A descriptive cross-sectional study was conducted among patients who presented in the OP/IP Department of Psychiatry between January to December 2020. Patients (aged 15-65 years old) who were diagnosed clinically as having major depressive disorder [according

to International Classification of Diseases and Related Health Problems, Tenth Revision] with a known serum 25 (OH) D levels (estimated by CLIA method and reported in nmol/L) given in their medical records were selected for the study. Patients who were under vitamin D supplements or with malabsorption/ maldigestion syndrome or with any autoimmune diseases or neurological conditions that could contribute to depressive symptoms or patients with chronic liver/renal diseases, or subjects with a genetic defect in vitamin D metabolism or medical records with insufficient data were excluded from the study.

The study procedure was approved by Institutional Research Committee and done after getting approval from the Institutional Ethics Committee (Ref. No.10/IEC/20/ AIMS-01).

Sample Size Calculation

Results of the recent study revealed an 83.7% prevalence of vitamin D deficiency/ insufficiency among depressive patients.[11]

$$n = z_a^2 pq/d^2$$

$z_a = 0.05 = 1.96$

Using the prevalence (p) of 83%, q of 17%, relative precision (d) as 10% of p, the minimum sample size was 82.

Study Procedure

Informed consent was taken from the patient or their parents or guardians to select their medical records. The medical records of patients who were enrolled in the study were reviewed. Details such as age, sex, type of major depressive disorder, and serum 25 (OH) D levels were taken and subjected to analysis. Patients (males and females) were categorized according to the serum levels of 25(OH) D as vitamin D sufficient (≥75nmol/L), insufficient (51-74nmol/L), and the deficiency (≤50 nmol/L) as per the previous study.[3] Each category was sub-grouped into mild, moderate, and severe based on the severity of the depressive disorder. The data were statistically analyzed.

Statistical Analysis

Data were analyzed using SPSS (v16, IBM, US) software package. A comparison of serum 25(OH)D levels between males and females was made using an unpaired t-test. Linear regression analysis was done to find the correlation between the continuous variables, vitamin D (dependent variable) and age (independent variable). Spearman Rank correlation, a non-parametric test, was used to evaluate the gender-wise correlation of vitamin D level with the severity of the depression. P <0.05 was considered significant.[12]

Results and Discussion

A total of 83 patients (33 males and 50 females)were included in the study. The mean age of patients was 43.6 ± 17.2 years, with female dominance. Among the total patients with bipolar/unipolar disorders, 12 patients had serum 25(OH)D level sufficient, above 75 nmol/L. Among the total patients, only four patients (4.8%) were presented with bipolar disorder, while 79 patients (95.1%) were with the unipolar disorder. Among the patients with bipolar disorder, 3/4 had vitamin D below the sufficient level. The age and gender-wise distribution of patients with serum 25(OH)D level is described in Table 1.

Of 79 patients with unipolar disorders, 68 (86.0%) had 25(OH)D below the sufficient level. Among the total 68 patients with a below adequate level of 25(OH)D, 12 (17.6%) had mild, 50 (73.5%) had moderate, and 9 (13.2%) had severe depression.

Table 1. Distribution of Serum Vitamin D Level and Severity of the Unipolar Disorder

Groups based on Vit. D status	Gender	Age (years)	Severity of Disease	Serum 25 (OH)D level (nmol/L)	P value (Unpaired t test)
Deficient (N=43)	Male (N=11)	38.1 ± 16.6	Mild= 2 Moderate= 8 Severe= 1	34.54 ± 12.38	0.1723
	Female (N=32)	43.2 ± 15.8	Mild= 4 Moderate= 22 Severe= 6	30.71 ± 11.15	
Insufficient (N=25)	Male (N=14)	49.4 ± 18.6	Mild= 5 Moderate= 8 Severe= 1	59.73 ± 6.88	0.3988
	Female (N=11)	37.3 ± 16.5	Mild= 1 Moderate= 9 Severe= 1	59.0 ± 7.11	
Sufficient (N=11)	Male (N=6)	50.5 ± 12.3	Mild= 2 Moderate= 2 Severe= 2	85.58 ± 12.52	0.0198
	Female (N= 5)	45.2 ± 28.7	Mild= 1 Moderate= 4 Severe= 0	125.05 ± 38.20	

Values are mean ± SD

Gender-wise analysis of 68 patients presented with unipolar disorders with below sufficient level of 25(OH)D, 43 were females, and 25 were males. Linear regression analysis found a statistically significant positive correlation between the age of male patients and 25(OH) D level, while a negative insignificant correlation for female patients (Table 2). Correlation analysis between the level of 25(OH)D and the severity of the disease among female patients found a statistically insignificant (Table 3). At the same time, the severity of disease among the males showed an insignificant negative correlation.

The study revealed that unipolar disorder was prevalent among the patients presented in the psychiatric clinic during the one year of the study. Among the patients presented with the unipolar disorder, 86% had vitamin D below the sufficient level. No significant difference was found in the serum 25(OH) D levels between the male or female patients with a mild, moderate, or severe grade of symptoms and below sufficient level of vitamin D. Despite a negative correlation found between the severity of symptoms in male and serum 25(OH)D levels, the data was found statistically insignificant. However, the

Table 2. Correlation Analysis between 25(OH)D Level and Age among Patients with Unipolar Disorder and Vitamin D Level

Gender	Pearson correlation coefficient	P value
Male	r = 0.4151 (95% CI 0.03292 to 0.6913)	0.0350
Female	r = -0.1553 (95% CI -0.4293 to 0.1449)	0.3085

Table 3. Correlation Analysis between 25(OH)D Level and Severity of Unipolar Disorder among Patients with Vitamin D Levels below the Reference Value

Gender	Pearson correlation coefficient	P value
Male	r = -0.07595 (95% CI -0.4597 to -0.3317)	0.7123
Female	r = 0.04234 (95% CI -0.2628 to 0.3398)	0.7824

positive correlation found between the age of male patients and serum 25(OH)D levels were significant. A little positive correlation was found between the grading of symptoms in females and serum 25(OH)D levels.

The prevalence of vitamin D deficiency obtained in this study is consistent with the study of Woo et al.[12] The inverse association of vitamin D and severity of disease obtained in this study among male patients was also correlated with the study conducted among the community-dwelling European men in which an inverse association between depression and vitamin D level was reported.[13]

Despite no correlation could establish between the vitamin D level and depression score, a study done in Swedish depressed adolescents concluded that subjects with a low level of vitamin D (mean level of 41 nmol/L) were improved from depression after the supplementation of vitamin D.[14] Study in Iranian pregnant mothers, Vazari et al.[15] demonstrated that vitamin D supplementation was beneficial to perinatal depression at 4 and 8 weeks after birth. The age of the male patients in this study was not found to be a confounding factor in the inverse correlation of vitamin D levels with the severity of the disease. This is due to the linear significant positive correlation exhibited between the age of male patients and vitamin D levels. While in female patients, age and vitamin D level showed an insignificant inverse correlation.

Furthermore, no such inverse correlation was observed between disease severity and vitamin D level in female patients. The underlying mechanism for the different results observed between male and female patients is unknown. No previous studies reported a gender-wise correlation between disease severity and vitamin D level among patients with depressive disorders.

Although population-based studies on the correlation between vitamin D levels and depression are debatable, the current scientific evidence can support the role of vitamin D in cognitive function. Previous studies demonstrated that vitamin D supplementation might render additional therapeutic benefits in subjects with depression due to its receptor distribution in the brain region and its role in calcium homeostasis.[16] Kim et al[17] demonstrated that vitamin D supplementation could regulate neurotransmitter synthesis, enhancement of nerve growth factors, and antioxidant and anti-inflammatory activities.

Vitamin D3 exhibits neuroprotective effects by inhibiting the synthesis of nitric oxide, a free radical that can damage the cells.[18] Furthermore, vitamin D3 was found to stimulate the synthesis of the antioxidant glutathione indirectly and may act as a neurotrophic factor by stimulating nerve growth factor, glial cell line-derived neurotrophic factor, and neurotrophin 3.[19-21]

The role of serotonin in various cognitive disorders was studied, including bipolar disorder, attention deficit hyperactivity disorder, schizophrenia, and impulsive behavior activation.[22] Deficits in serotonin, regulation of dopamine, and nor-epinephrine were associated with the etiology of mood disorders.[23]

Supplementation of vitamin D was adequate to maintain an optimum level of serotonin as the enzyme for serotonin synthesis from tryptophan is transcriptionally activated by vitamin D.[24] Furthermore, inflammation was found to be associated with the etiology of depression, and thus anti-inflammatory agents were promising agents for the therapy.[25] The antioxidant and anti-inflammatory properties of vitamin D might be related to mood swing among subjects with depression.

The deficiency of vitamin D prevails in epidemic proportions all over India. Vitamin D deficiency was widespread in individuals worldwide irrespective of gender, age, race, or geography. The prevalence was 70–100% in the general population. A previous study among healthy Indians in 18 states reported the prevalence of vitamin D deficiency as 79%.[3] This may probably be due to widely consumed dairy products that are rarely fortified with vitamin D. Prevalence of vitamin D status was not evaluated among subjects in this population, which remains one of the major limitations of this study. The required dose of vitamin D supplements varies between individuals depending on baseline 25(OH)D level, seasonality, latitude, ethnicity, nutrition, adiposity, dosing, and vitamin D analog used for supplementation.[26] The optimal approach for vitamin D supplementation as an effective adjunct in patients with psychological diseases has to be established. Furthermore, the study included only a small sample size and no etiological factors for vitamin D deficiency among the studied population. The evaluation was undergoing to know whether supplementation of vitamin D should be considered an augmentation strategy with antidepressant drugs.

Conclusion

A negative correlation between the severity of depression and serum 25(OH)D levels in male subjects presented with unipolar disorders. However, a statistically significant positive correlation was found between age and vitamin D status in males. This suggests that age is not a confounding factor in the exhibited negative correlation. The results indicate the need for evaluating the vitamin D status among male patients presented with depressive disorders and supplementing vitamin D if found deficient.

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Conflict of Interest

None declared

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