Indian Journal of Basic and Applied Medical Research; March 2020: Vol.-9, Issue- 2. P. 86 - 94
DOI: 10.36848/IJBAMR/2020/12165.51220

Original article:

Study on Clinical Co relation between Vit D deficiency and depressive disorders

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Abstract:

Background: High prevalence of depression as well as Vitamin D deficiency in general population, potential impact of Vitamin D deficiency on treatment and outcome of depression, lack of Indian data on this association, and wider acceptability, negligible side effects and cost effective approach with Vitamin D supplementation have given us impetus to study in this area and to fill the research gap with Indian data.

Aim and Objectives: The present study aimed to assess Vitamin D status in patients with depression and to see role of Vitamin D supplementation in outcome of depressive disorders.

Material and Methods: The study was carried out at the psychiatry outpatient clinic of a tertiary care hospital in Lucknow, North India. Totally 120 patients with depressive disorders were consecutively recruited and assessed for their severity of depression, functionality score, physical and nutrition habits score, obesity (as per Asian criteria body mass index (BMI) ≥25) and serum Vitamin D level. They were followed up monthly for 1 year. Out of 120 patients, only 100 patients continued regular follow-ups for 1 year. Therefore, we have used the data of those 100 patients for final analysis.

Results: The mean age of onset of depression, duration of depressive disorder, and monthly sun exposure were 32 years, 39 months, and 48 h, respectively. First episode depressive episode was the most common psychiatric disorder (75%), followed by recurrent depressive episode and dysthymia. Nearly one-third of patients were obese (BMI ≥ 25) (35%). Mean serum Vitamin D level was 10.95 ng/ml.

Conclusion: Majority (80%) of patients with depression had Vitamin D deficiency. It was seen more in unemployed or homemaker, females, patients with smaller height, and from nuclear family. These all factors were also found significant predictors for hypovitaminosis D. Vitamin D deficient patients took significantly longer time in remission than nondeficient patients.

Keywords: Depression, Hypovitaminosis D. Time to remission, Vitamin D.

Background:

Depression is a major public health problem and is projected to be the second most important cause of disability worldwide in 2020.[1] This trend is accompanied by soaring costs for treatment and reduced productivity.[2] Depression aetiology and pathophysiology have not yet been fully elucidated. Recent

advances in basic and clinical research highlighted the potential role of new biological factors that may affect mood in combination with the more traditional neurochemical and neuroendocrine mechanisms.

Furthermore, stigma, poor acceptability of psychiatric treatment, side effects of antidepressants are resulting in poor treatment adherence and high relapse rate of depression. Nutritional deficiency, especially of Vitamin D, is highly prevalent and potentially modifiable.[3] Globally about 1 billion people have Vitamin D deficiency.[4] Vitamin D is involved in numerous brain processes including neuroimmunomodulation, neuroprotection, neuroplasticity, regulation of neurotrophic factors, and making it biologically plausible to be associated with depression.

Several Indian studies have reported high prevalence of Vitamin D deficiency across India, including in healthy, middle-aged health care professionals (79%).[5] High prevalence of depression as well as Vitamin D deficiency in general population, potential impact of Vitamin D deficiency on treatment and outcome of depression, lack of Indian data on this association, and wider acceptability, negligible side effects and cost effective approach with Vitamin D supplementation have given us impetus to study in this area and to fill the research gap with Indian data.

Aim and Objectives:

The present study was aimed to:

- Assess Vitamin D status in patients with depression.
- Its association with time to remission.
- Role of Vitamin D supplementation in the outcome of patients with depressive disorders.

Material and Methods:

The study was approved by the Institutional Ethics Review Committee of Career Medical college and Hospital. The study was carried out at the psychiatry outpatient clinic of a tertiary care hospital in Lucknow, North India. The study sample comprised consecutive patients, of either gender aged between 18 and 60 years, with depressive disorders (first episode depression, recurrent depressive disorder, and dysthymia) as per International Classification of Diseases, Tenth Revision (ICD-10)[6] consulted to Psychiatry outpatient clinic from January to June 2018. Diagnostic confirmation was done by Mini International Neuropsychiatric Interview (MINI).[7] All the patients with depressive disorder were approached, excluding patients with bipolar depression, psychotic depression, and any other comorbid psychiatric or chronic physical disorders. Written informed consent was sought from all the patients. The assessment was done at their first visit to psychiatry outpatient clinic.

Totally 120 patients with depressive disorders were consecutively recruited and assessed for their severity of depression, functionality score, physical and nutrition habits score, obesity (as per Asian criteria body mass index (BMI) ≥25)[8] and serum Vitamin D level. They were followed up monthly for 1 year. Out of 120 patients, only 100 patients continued regular follow-ups for 1 year. Therefore, we have used the data of those 100 patients for final analysis.

Including demographic and clinical profile sheet following instruments were used:

Mini International Neuropsychiatric Interview : The MINI is a clinician based, brief structured interview for diagnosis of a major axis I psychiatric disorders in Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) and ICD-10 and divided into modules corresponding to

diagnostic categories. MINI is compared with Structured Clinical Interview for DSM-III-R-patient version and Composite International Diagnostic Interview for ICD-10 and found to have high validity and reliability.[7]

Hamilton Depression Rating Scale: It is a clinician-rated scale, with 17 items and each item is rated from 0 to 4, according to intensity and frequency of symptoms in the past few days.[9]

Health Promoting Lifestyle Profile-II: It has been used extensively to explore health promoting lifestyle variables and found to have high construct validity and reliability. It is a 52-item self-report instrument, on likert scale from 1 to 4 with 1 = never, 2 = sometimes, 3 = often, and 4 = routinely. We have used two subscales, that is, physical activity and nutritional habit containing 8 and 9 items, respectively, with total score ranging from 17 to 68.[10]

Global Assessment of Functioning Scale: It was developed to rate Axis-V of DSM diagnostic system. It measures overall functional status in relation to psychiatric symptoms.[11]

Vitamin D status was measured by assessing circulating levels of serum 25-hydroxyvitamin D3 (25(OH) D) level, which reflects total Vitamin D from dietary intake and sunlight exposure, and including the conversion of Vitamin D from adipose stores in the liver. Therefore, it is the best indicator of overall Vitamin D status.[12] Fasting blood samples were obtained in the morning from 10 am to 1 pm and kept frozen at 80°C and never thawed before analysis. Serum 25(OH) D was measured using chemiluminescence essay by DiaSorin.

Vitamin D deficiency is defined as a level <20 ng/mL.[13] The number of sunlight hours in the 12 weeks preceding blood drawing was assessed, as a possible factor affecting serum Vitamin D level. As a standard protocol, we have prescribed antidepressants to all the study participants, commonly selective serotonin reuptake inhibitor (SSRI), with escitalopram being most common agent. Patients with hypovitaminosis D were given Vitamin D supplementation as per standard protocol one sachet of cholecalciferol (Vitamin D3) 60,000 units weekly for 8 weeks and later once a month to maintain the level.[14]

Results:

We have analysed the data of 100 patients who continued regular follow-up for 1 year. As depicted in Table 1, mean age was 35 years. More than half of patients were females, unemployed or homemaker, from extended or joint families, and urban locality. The majority of patients were married, and Hindu by religion.

Variable	**Mean ± SD (range)**
Age (in years)	35±10.05(18-60)
Education (in years)	8.7±5.76(0-18)
Monthly family income	23500±3452(3000-100,000)
Variable	**Frequency %**
Sex	
Male	40 (40%)
Female	60 (60%)
Marital status	
Single	15 (15%)

Married	85 (85%)
Occupation	
On paid jobs	45 (45%)
Unemployed	55 (55%)
Religion	
Hindu	70 (70%)
Muslim	30 (30%)
Type of family	
Nuclear	35 (35%)
Extended/ joint	65 (65%)
Locality	
Urban	57 (57%)
Rural	43 (43%)

Table 1: Socio demographic profile of study population (n=100)

The mean age of onset of depression, duration of depressive disorder, and monthly sun exposure were 32 years, 39 months, and 48 h, respectively. First episode depressive episode was the most common psychiatric disorder (75%), followed by recurrent depressive episode and dysthymia. Mean Hamilton Depression Rating Scale score was 17 with moderate to severe depression in nearly half of the patients [Table 2].Nearly one-third of patients were obese (BMI ≥ 25) (35%). Mean serum Vitamin D level was 10.95 ng/ml. The majority of patients were Vitamin D deficient (80%).

Variable	**Mean ± SD (range)**
Age at onset of depression (years)	32.6±10.45 (15-60)
Duration of illness (months)	38.9±48.72 (1-240)
Monthly sun exposure (hours)	48.05±40.08 (1-176)
Depression severity score (HDRS)	17.52±6.58 (8-31)
Serum Vit D levels	10.95±6.5 (4-28)
Variable	**Frequency %**
Diagnosis	
First episode of depression	75 (75%)
Recurrent depressive disorder	15 (15%)
Dysthymia	10 (10%)
Depression severity	
Mild HDRS (10-13)	25 (25%)
Mild to Moderate HDRS (14-17)	20 (20%)
Moderate to severe HDRS (>17)	55 (55%)
Obesity (BMI≥25)	35 (35%)
Vit D deficiency (<20ng/ml)	80 (80%)

Table 2: Clinical Profile of patients (n=100)

www.ijbamr.com P ISSN: 2250-284X, E ISSN: 2250-2858

Patients with hypovitaminosis D had a greater proportion of females, unemployed or homemaker, and were from nuclear family, smaller in height, and took longer time in remission of depression, compared to patients with normal Vitamin D level [Table 3].

Variables	**Frequency %**		**Chi Square p value**
	Patient with vitamin D deficiency (n=80)	**Patient without vit D deficiency (n=20)**	
Gender			
Male	35 (43.75)	05 (25)	**4.67 (0.04)**
Female	45 (56.25)	15 (75)	
Occupation			
Employed	34 (42.5)	11 (55)	**5.9 (0.010)**
Unemployed	46 (57.5)	09 (45)	
Family			
Nuclear	30 (37.5)	05 (25)	**5.56 (0.018)**
Joint	50 (62.5)	15 (75)	
Religion			
Hindu	60 (75)	10 (50)	0.90 (0.22)
Non Hindu	20 (25)	10 (50)	
Locality			
Urban	42 (52.5)	15 (75)	2.4 (0.08)
Rural	38 (47.5)	05 (25)	
BMI >25 Kg/mt sq	30 (37.5)	05 (25)	1.25 (0.51)

Table 3: Comparison of demographic profile of patients for having Vit D deficiency.

Variables	**SE**	**OR**	**Significance**	**CI**
Gender-female	0.60	3.45	0.041	1.04-12.02
Occupation-unemployed	0.62	4.41	0.021	1.23-15.74
Nuclear family	1.05	8.65	0.043	1.06-70.05
Height	0.05	0.88	0.001	0.82-0.95

Table 4: Important predictors of Hypovitaminosis D.

Predictors of hypovitaminosis D were assessed by using simple binary logistic regression analysis. As shown in Table 4, significant predictors of hypovitaminosis D were female gender, unemployment, nuclear family and smaller height.

Majority of patients with hypovitaminosis D were given Vitamin D supplementation as per standard protocol-one sachet of cholecalciferol (Vitamin D3) 60,000 units weekly for 8 weeks and followed by once a month dose to maintain the level. Their blood sample for Vitamin D estimation was drawn at first visit, but owing to reporting time and monthly follow-up, Vitamin D supplementation was started nearly 1 month after their first contact. Time to remission in patients with Vitamin D deficiency after

supplementation was longer than patients with normal Vitamin D levels, but the difference was statistically not significant (1.95 months [standard deviation (SD) 2.24 months] vs. 1.35 months [SD 0.57 month], Mann– Whitney value = 160.0, P = 0.36).

Discussion:

Baseline low Vitamin D level is found to be associated with developing depression over the time[7,8] and the same is also supported by several systematic reviews and meta-analysis.[15-17] Meta-analysis of data from more than 50,000 study participants found a significant inverse association between serum 25(OH) D levels and the risk of depression.[17] The odds ratio for having a current depressive episode was 1.8-fold higher in individuals with deficient Vitamin D compared to those with sufficient Vitamin D.[18] A systematic review and meta-analysis of cohort studies by Anglin et al.[15] reported significantly increased risk of developing depression with low Vitamin D levels (hazard ratio = 2.21, P < 0.001). On the other side, depression may also be a risk factor for developing Vitamin D deficiency, as depressed people may consume less nutritious diet, stay indoors, and exercise less; all these health behaviours contribute to hypovitaminosis D.[6]

Given the high prevalence of both Vitamin D deficiency and depression, their association has significant public health implications. Vitamin D supplementation could play a significant role in the treatment of depression, and it has been supported by world literature,[7-8,15-17] but we don't have enough study from India. Index study is an attempt to fill this gap in literature.

Similar to earlier study by Dana-Alamdari et al.,[19] majority of our patients had Vitamin D deficiency (80%). In the present study, hypovitaminosis D was seen more in unemployed or homemakers, female patients, with smaller height, and from nuclear family. To elaborate further, unemployed or homemaker patients and females were less exposed to sun, patients with smaller height were having lesser body surface area, therefore having lesser production of Vitamin D with sun exposure. Patients from nuclear family might have lesser dietary intake of Vitamin D rich food. Other association of Vitamin D status was found with religion, but it might be associated with dietary pattern directly or indirectly. Collin et al.[20] reported lower probability of recurrent depressive symptoms with ≥10 ng/mL level of 25(OH) D. In index study, we did not find such association on comparing our patients with first episode versus recurrent episode of depression. Grudet et al.[21] found significantly lower Vitamin D level in suicide attempters compared to depressed nonsuicidal patients. We could not find such association of Vitamin D level in our patients with suicidal ideation, as the majority of them had suicidal ideas but very few of them had suicide attempt in past. Milaneschi et al.[22] and Polak et al.[23] reported inverse association of Vitamin D with depression severity. While similar to Dana-Alamdari et al.,[19] index study could not find such association. Milaneschi et al.[22] reported greater risk (1.74 times) of developing depression in Vitamin D deficient patients and greater duration of depressive symptoms, compared to patients with normal Vitamin D levels. Similar to Milaneschi et al.,[22] index study reported longer time to remission in Vitamin D deficient patients.

Augmentation strategies in depression treatment are being used commonly in patients with incomplete remission[24] or the presence of subsyndromal symptoms.[25] Co-administration of nutraceuticals or nutritional agents may also enhance antidepressant effects, either by synergistically augmenting effects of

antidepressants or by other biological effects.[26] Many nutraceuticals are cost effective, safe and evidence-based augmenting agents for depression treatment including Vitamin D supplementation. Similar to earlier evidence,[21] we have found Vitamin D supplementation safe and effective as an adjunctive treatment in depressive disorder with hypovitaminosis D.

Conclusion:

Majority (80%) of patients with depression had Vitamin D deficiency. It was seen more in unemployed or homemaker, females, patients with smaller height, and from nuclear family. These all factors were also found significant predictors for hypovitaminosis D. Vitamin D deficient patients took significantly longer time in remission than nondeficient patients. All the patients with Vitamin D deficiency received supplementation and subsequently their time to remission was comparable to nondeficient group. Therefore it highlights the need for timely assessment and treatment of hypovitaminosis D for effective management of depression to avoid delay in response, treatment resistance, incomplete remission, or residual symptoms.

Limitations:

The present study has following limitations: Hospital based sample, smaller sample size for patients with normal Vitamin D status, causal association cannot be determined between Vitamin D levels and depression and due to logistic issues Vitamin D supplementation was started nearly 1 month after their first contact and we could not repeat Vitamin D serum levels after the supplementation. Future studies should be conducted in larger sample from hospital and community, with healthy controls, prospective and multicentric study design, and detailed exploration of physical activity, dietary patterns, sun exposure and other health promoting lifestyle behaviours and future research should attempt to overcome above limitations.

Acknowledgement:

We are thankful to Dr Abhishek Arun and his team for assistance in medical writing. We are also thankful to staff and resident doctors of department of Psychiatry Career Institute of Medical sciences and Hospital. Above all we are thankful to all those who participated in this study.

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Date of Submission: 01 January2020
Date of Peer Review: 03 February 2020
Date of Acceptance: 27 February 2020
Date of Publishing: 12 March 2020
Author Declaration: Source of support: Nil , Conflict of interest: Nil
Ethics Committee Approval obtained for this study? Yes
Was informed consent obtained from the subjects involved in the study? Yes
For any images presented appropriate consent has been obtained from the subjects: NA
Plagiarism Checked: Urkund Software

DOI: 10.36848/IJBAMR/2020/12165.51220