



INCIDENCE OF COMORBIDITY OF VITAMIN D3 DEFICIENCY IN PATIENTS WITH DEPRESSIVE DISORDER AND CORRELATION OF THE DEFICIENCY WITH DEPRESSIVE SYMPTOMATOLOGY: A CROSS-SECTIONAL HOSPITAL-BASED STUDY

Dr. Shubham Fojdar¹, Dr Anu Meena², Shubham Jhanwar^{3*}, Alka Meena⁴

¹Assistant Professor, Psychiatry, ESIC Medical College and Hospital, Address: ESIC Medical College and Hospital, Desula, MIA, Alwar, Rajasthan, E-mail: fojdarshubham@gmail.com

²Assistant professor, OBGY, OBGY, ESIC Alwar, E-mail: anu13.doc@gmail.com

^{3*}Assistant Professor, Psychiatry, ESIC Medical College and Hospital, ESIC Medical College and Hospital, Desula, MIA, Alwar, Rajasthan, E-mail: shubhamjhanwar03@gmail.com

⁴Senior Resident, Psychiatry, ESIC Medical College and Hospital, ESIC Medical College and Hospital, Desula, MIA, Alwar, Rajasthan, E-mail: dralkameena013@gmail.com

***Corresponding Author:** Shubham Jhanwar

Designation: Assistant Professor
Department: Psychiatry
Institution: ESIC Medical College and Hospital
Address: ESIC Medical College and Hospital, Desula, MIA, Alwar, Email: shubhamjhanwar03@gmail.com*

Abstract

Background: Depressive disorder is a significant global public health issue with very high morbidity, mortality and socioeconomic cost. Recent studies anticipate the possibility of the relationship between the deficiency of Vitamin D3 and depressive disorders; nonetheless, the data on Indian clinical populations is insufficient.

Aim: To evaluate the comorbidity of Vitamin D3 deficiency in patients with depressive disorder and to assess the correlation between serum Vitamin D3 levels and severity of depressive symptomatology.

Methods: This hospital-based cross-sectional study was conducted among 54 patients diagnosed with depressive disorder who attended the Psychiatry Outpatient Department of a tertiary care centre. The severity of depression was evaluated using the Hamilton Depression Rating Scale (HDRS), while serum Vitamin D3 levels were estimated and classified into appropriate categories. Descriptive statistical methods and correlation analysis were then used to explore the association between Vitamin D3 status and the severity of depressive symptoms.

Results: A high prevalence of suboptimal Vitamin D3 levels was observed, with Vitamin D insufficiency being the most common category. An inverse relationship was noted between serum

Vitamin D3 levels and severity of depressive symptoms, with lower Vitamin D3 levels associated with greater depression severity.

Conclusion: Depression disorder is a disease with high levels of vitamin D3 deficiency and correlates with more severe depressive symptoms, which implies the possibility of using Vitamin D3 assessment in the clinical environment.

Keywords: Depression; Vitamin D3 deficiency; Hamilton Depression Rating Scale; Comorbidity; Cross-sectional study

1. INTRODUCTION

Depressive disorder is a very common and debilitating mental health disorder in the world, and it affects all age groups, gender and sociocultural backgrounds. The worldwide statistics show that in 2015, the number of people in the world with depression was about 4.4% and thus the most common cause of disability in the world (Depression, 2017). Morbidity and mortality are other areas where depression is also a significant factor, not only because of its suicidal nature but because of its close association with other chronic medical conditions such as cardiovascular disease, diabetes mellitus, hypertension, and cerebrovascular disorders (Kessler et al., 2006). In addition to clinical outcomes, depression has significant economic and social effects, such as low productivity, high levels of absenteeism, poor interpersonal functioning, and high healthcare costs (Kessler et al., 2006; Whiteford et al., 2013).

Over the recent years, more and more focus has been given to how nutritional and endocrine factors contribute to the pathophysiology of depressive disorders. Vitamin D3 is one of them, and it has become a possible modifiable biological factor that is involved in mood regulation. Previously known as a hormone involved in the regulation of calcium in the body and bone metabolism, vitamin D is currently being perceived as a neurosteroid hormone that has extensive implications on brain development, neurotransmission, neuroplasticity and neuroprotection. (Eyles et al., 2013). Vitamin D receptors (VDRs) and the 1- α -hydroxylase enzyme are found in large quantities in mood regulation brain areas such as the prefrontal cortex, cingulate cortex, hippocampus and the amygdala. (Garcion et al., 2002).

Various biological processes have been suggested to provide the linkage between the Vitamin D deficiency and depressive symptoms. It is assumed that vitamin D can modulate the synthesis of serotonin by balancing tryptophan hydroxylase, which will impact monoaminergic neurotransmission. (Patrick & Ames, 2014). Also, Vitamin D has immunomodulatory and anti-inflammatory properties, which could be of particular importance in light of the mounting evidence that depressive pathogenesis involves inflammatory mechanisms. (Dowlati et al., 2010; Song & Wang, 2011). Moreover, vitamin D has shown neuroprotective activity against oxidative stress, neurogenesis, and inhibiting neuronal damage by glucocorticoids. (Kesby et al., 2013).

Vitamin D deficiency is extremely widespread across the world and especially in low- and medium-income countries, such as India, because of such factors as insufficient sun exposure, dark pigmentation of the skin, poor nutritional aspects, and sociocultural factors. (Gupta, 2014; Harinarayan et al., 2004). Even though a lot of sunlight reaches the earth, it has been documented that the increasing cases of hypovitaminosis D are prevalent among the Indian population, both in urban and rural settings. Since depression and Vitamin D deficiency are very common in India, the possible connection between them may have a significant clinical and public health value.

Despite the growing body of international literature which is in favour of the association of low serum Vitamin D levels with depressive symptoms, few studies on Indian clinical populations exist. The majority of the literature has been done in Western or East Asian populations, and their results cannot be directly generalised because of the dissimilarities in genetic factors, environmental factors, dietary

factors, and cultural factors. Thus, hospital-based research in the Indian population is clearly in need of identifying the comorbidity of Vitamin D deficiency among patients with depressive disorder and whether it is related to the severity of depressive symptomatology.

The present study was conducted to bridge this knowledge gap by examining the comorbidity of Vitamin D3 deficiency among patients diagnosed with depressive disorder and by exploring the relationship between serum 25-hydroxy Vitamin D levels and the severity of depressive symptoms. By studying a clinically diagnosed population and employing standardized assessment tools, the study seeks to generate clinically relevant evidence that may help guide screening practices and support the use of adjunctive treatment strategies in routine psychiatric care.

2. LITERATURE REVIEW

Numerous epidemiological and clinical studies have explored the association between Vitamin D status and depressive disorders, with accumulating evidence suggesting an inverse relationship between serum Vitamin D levels and the severity of depressive symptoms. Earlier population-based studies have indicated a potential role of Vitamin D deficiency in the development of mood disorders, particularly among elderly populations.

A landmark nine-year cohort study conducted by May et al., 2010. In Utah, USA, involving 7,358 individuals aged 50 years and older with cardiovascular disease, demonstrated that lower serum Vitamin D levels were significantly associated with an increased risk of developing depression. These findings underscore the relevance of Vitamin D deficiency in medically ill populations and suggest a link between cardiovascular risk, Vitamin D status, and depressive outcomes. Similarly, Stewart & Hirani, 2010 examined older adults aged 65 years and above in England and reported a strong association between depressive symptoms and Vitamin D deficiency, particularly when serum 25hydroxyvitamin D levels were below 10 ng/mL.

The study by Milaneschi et al., 2010, was a population-based cohort study, carried out in Tuscany, Italy, among 423 men and 531 women aged 65 years and older, and was undertaken over a duration of six years. The authors discovered that the participants who had serum levels of 25(OH)D below 50 nmol/L were more likely to develop signs of depression, and that the association was stronger in women compared to men. These results demonstrated possible sex-specific influences of the correlation between Vitamin D deficiency and depression. Similar findings were recorded by the Chan et al., 2011 In their study of 939 older Chinese men who reported a cohort of 4 years of follow-up, serum 25(OH)D levels appeared to have an inverse relationship with depression.

Other evidence of this relationship was given by Lee et al., 2011 The European Male Ageing Study, in which 3,369 men aged 49 to 71 years were studied. The depression level was included through the Beck Depression Inventory-II, and Vitamin D was checked through the radioimmunoassay. The authors concluded that the depressive symptom scores would be strongly related to lower serum 25(OH)D levels, even with the potential confounders included.

Beyond epidemiological studies, experimental and mechanistic research has strengthened the biological plausibility of this association. Prüfer et al., 1999 also exhibited a broad VDR immunoreactivity in the emotional-controlling areas of the brain, whereas Garcion et al., 2002 focused on Vitamin D in the neuroimmune interactions. This association is also supported by inflammatory models of depression, which have indicated that high concentrations of pro-inflammatory cytokines are consistently found in depressive disorders, and Vitamin D will regulate the inflammatory reaction. (Dowlati et al., 2010; Song & Wang, 2011).

A strong correlation between depression and low Vitamin D levels has also been reported in metaanalyses and systematic reviews, but the causality is controversial. (Anglin et al., 2013; Ju et al., 2013). There are some interventional studies indicating that Vitamin D supplements can enhance depressive symptoms, especially when people are deficient at baseline, but the results have been inconsistent. (Spedding, 2014; Vellekkatt & Menon, 2019).

Although this is an accumulating body of evidence, there is a paucity of Indian research investigating the Vitamin D-depression relationship, especially in populations in hospitals in psychiatric units. As there is a high incidence of Vitamin D deficiency in India (Gupta, 2014; Harinarayan et al., 2004) Given the numerous cases of depressive disorders in the Indian population, it is also important to conduct further research to explain this correlation in the Indian sociocultural and clinical environment.

The current research will add to the previous literature and discuss the comorbidity of Vitamin D3 deficiency in depressed patients and the correlation of depression symptoms with levels of Vitamin D3 in an Indian tertiary care facility, thus providing a rich source of region-specific clinical data.

3. METHODOLOGY

3.1 Study Design

The current research was a cross-sectional, observational, hospital-based study that attempted to measure Vitamin D3 deficiency comorbidity in patients with a diagnosis of depressive disorder, as well as to explore the relationship between Vitamin D3 deficiency and the severity of depressive symptomatology. The cross-sectional design was selected because it was necessary to determine the relation between the serum Vitamin D3 levels and depressive symptoms at a single point in time in a clinical population.

3.2 Study Setting

The research was done in the Department of Psychiatry at ESIC Medical College and Hospital, Alwar, Rajasthan. It is a teaching hospital and a tertiary care referral centre serving a broader population of consumers across Rajasthan, Haryana, and the National Capital Region of Delhi. The environment was the hospital-based setting, which offered access to an access to a clinically diagnosed sample, which was that of patients with depressive disorder.

3.3 Study Population

The population of the study included adult patients who were admitted to the Psychiatry Outpatient Department of ESIC Medical College and Hospital, Alwar and were diagnosed with depressive disorder. The study population was recruited through the outpatient services sequentially within the time frame, and the patients who met the eligibility criteria and gave informed consent were used in the study.

3.4 Sample Size

A total of 300 patients diagnosed with depressive disorder were initially planned to be recruited for the study using a purposive sampling approach. The sample size was determined using a correlationbased calculation, assuming a correlation coefficient of 0.30, a 5% level of significance, and 80% study power, which indicated a minimum required sample size of 54 participants. The decision to plan for a larger sample size was made to improve the precision of the estimates and strengthen the overall reliability of the statistical analysis.

3.5 Inclusion and Exclusion Criteria

The study included patients aged between 18 and 60 years who were diagnosed with depressive disorder in accordance with the International Classification of Diseases–10 Diagnostic Criteria for Research (ICD-10 DCR) and who provided written informed consent to participate in the study. The study excluded patients who had either failed to give informed consent in writing or were unwilling to do so.

3.6 Study Procedure

Following approval from the Institutional Ethics Committee, patients who met the inclusion and exclusion criteria were enrolled in the study after obtaining written informed consent. Sociodemographic and clinical information was collected using a semi-structured proforma. Each participant underwent a detailed clinical evaluation, and the severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale. Subsequently, blood samples were collected for the estimation of serum Vitamin D3 levels, and the relationship between Vitamin D3 status and the severity of depressive symptoms was analyzed.

3.7 Tools for Data Collection

A semi-structured proforma was used as a tool to gather data pertaining to the sociodemographic characteristics (age, sex) as well as the corresponding clinical information. The degree of depression symptoms severity was assessed with the help of the Hamilton Depression Rating Scale (HDRS), a 17-item scale that should be administered by a clinician. Depression was classified as normal, mild, moderate or severe according to the overall HDRS. The level of Vitamin D3 in serum was determined and classified under sufficiency, insufficiency, deficiency and severe deficiency to conduct an analysis.

3.8 Statistical Analysis

Information was presented in Microsoft Excel and analysed. Sociodemographic and clinical characteristics of the study population were summarised with the help of descriptive statistics. The correlation test by Pearson was used to determine the relationship between the serum level of 25hydroxy Vitamin D and the level of HDRS scores. The p-value that was considered to be statistically significant was taken to be less than 0.05.

3.9 Ethical Considerations

The approval of the Institutional Scientific and Ethics Committee of ESIC Medical College and Hospital, Alwar, was obtained before conducting the study. All the participants were provided with informed consent, which was written before being included in the study. Privacy and anonymity of participants during the research process were ensured, and participation was fully voluntary, with participants having the right to withdraw at any point without any implication on the treatment.

4. RESULTS

4.1 Sociodemographic Characteristics of the Study Population

The study involved 54 patients who had the diagnosis of depressive disorder. The age of respondents was between 16 and 71 years. The sample comprised male and female patients, though the females had a relatively greater representation. The age groups of most of the patients were in the young and middle adult age group, which is the normal age distribution of patients with depressive disorders in an outpatient psychiatric service.

Table 1: Sociodemographic Characteristics of the Study Population (n = 54)

Variable	Frequency
Total participants	54
Gender – Male	26
Gender – Female	28
Age range (years)	16–71

Table 1 shows the simplest sociodemographic characteristics of the participants of the study, such as age range and gender distribution. It gives a demographic profile of the patients diagnosed with depressive disorder and incorporated in the study.

4.2 Serum Vitamin D3 Status

With Vitamin D3 levels in serum analysed, it was found that a big percentage of all patients were poorly stocked in Vitamin D. The most prevalent was vitamin D insufficiency, then deficiency and severe deficiency. The percentage of patients with adequate Vitamin D3 levels was small. In total, Vitamin D3 insufficiency and deficiency were the largest population of the study, and it is possible to state that hypovitaminosis D is highly comorbid in patients with a depressive disorder.

Table 2: Distribution of Serum Vitamin D3 Status Among Patients

Vitamin D3 Status	Number of Patients (n)	Percentage (%)
Sufficiency	10	18.5
Insufficiency	34	63.0
Deficiency	3	5.6
Severe deficiency	7	13.0
Total	54	100

Table 2 presents the distribution of the study participants under various categories of serum Vitamin D3 status, which are sufficiency, insufficiency, deficiency and severe deficiency. It shows the rate of patients having poor Vitamin D3 levels.

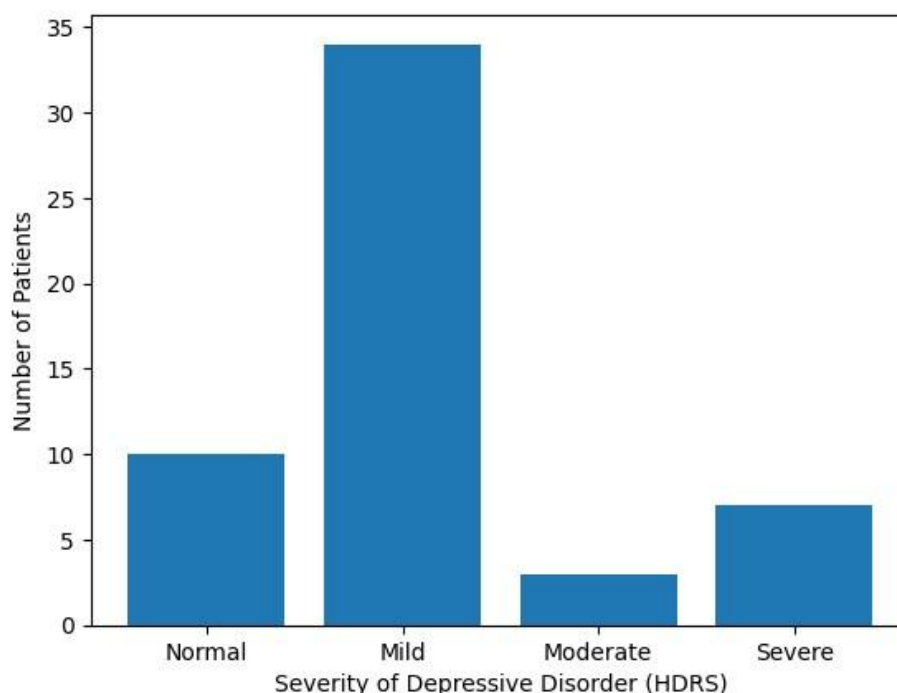


Figure 1: Distribution of Serum Vitamin D3 Status Among Patients

The patients are distributed in various categories of serum Vitamin D3, as graphically illustrated in Figure 1. It is a graphical representation of the relative amount of sufficient, insufficient, deficient, and severely deficient members of the study population.

4.3 Severity of Depressive Disorder

According to the Hamilton Depression Rating Scale, most patients were observed to be experiencing minor depressive symptoms. There was a lower percentage of patients who had moderate depression, and a few cases were of severe depression. There was even heterogeneity in the severity of the symptoms in the study population, with some patients being classified as possessing normal or minimal depressive symptoms.

Table 3: Severity of Depressive Disorder Based on HDRS

Depression Severity	Number of Patients (n)	Percentage (%)
Normal	10	18.5
Mild	34	63.0
Moderate	3	5.6
Severe	7	13.0
Total	54	100

Table 3 represents the distribution of the patients based on the severity of the depressive symptoms using the Hamilton Depression Rating Scale. HDRS scores are used to classify patients as normal, mild, moderate and severe depression.

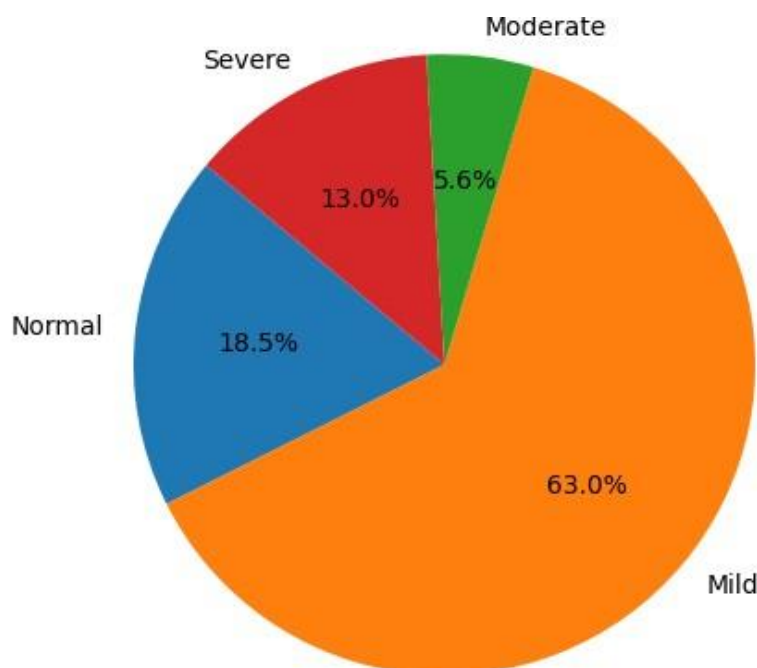


Figure 2: Severity of Depressive Disorder Among Study Participants

Figure 2 presents the distribution of patients based on the categorisation of patients with depressive symptoms into three groups according to HDRS. It gives a graphical representation of the frequency of normal, mild, moderate, and severe forms of depression.

4.4 Distribution of Vitamin D3 Status Across Depression Severity

A strong pattern existed between the status of Vitamin D3 and the severity of depression. The normal depression group had mostly patients with adequate amounts of Vitamin D3. Mild depression was most often related to people with Vitamin D deficiency. The most significant instances of Vitamin D deficiency were found in the patients with moderate depression, and severe Vitamin D deficiency was only linked to severe depression in the sample of the research.

Table 4: Association Between Vitamin D3 Status and Severity of Depression

Vitamin D3 Status	Normal	Mild	Moderate	Severe
Sufficiency	10	0	0	0
Insufficiency	0	34	0	0
Deficiency	0	0	3	0
Severe deficiency	0	0	0	7

The cross-tabulation of Vitamin D3 status in serum and depressive disorder severity is shown in Table 4. It shows how various categories of Vitamin D3 are spread among different levels of severity of the depressive symptoms.

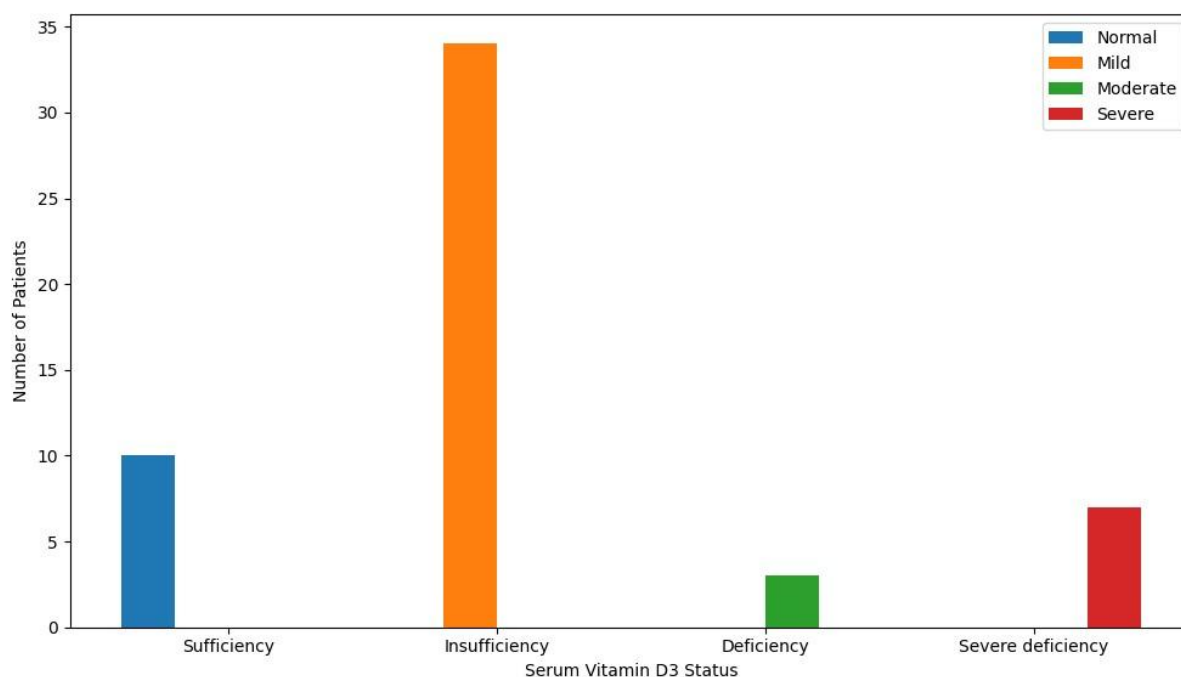


Figure 3: Relationship Between Vitamin D3 Status and Severity of Depression

Figure 3 shows how serum Vitamin D3 status is related to the severity of depressive disorder. It visually demonstrates the realisation of the degree of varying severity of depressive symptoms in different categories of Vitamin D3 status.

4.5 Correlation Between Vitamin D3 Levels and Depressive Symptom Severity

The levels of serum Vitamin D3 showed an inverse correlation with the severity of depressive symptoms. Reduced levels of Vitamin D3 were linked to increased severity of depression, and increased levels of Vitamin D3 were linked to low or no symptoms of depression. This result indicates

that there is a negative correlation between the Vitamin D3 status and depressive symptomatology in patients with depressive disorder.

5. DISCUSSION

The present cross-sectional, hospital-based study was conducted to examine the comorbidity of Vitamin D3 deficiency among patients with depressive disorder and to explore its relationship with the severity of depressive symptoms. The findings indicate a high prevalence of suboptimal serum Vitamin D3 levels in this population, with Vitamin D deficiency emerging as the most commonly observed category. In addition, an inverse association was identified between serum Vitamin D3 levels and the severity of depressive symptoms, such that lower Vitamin D3 levels were associated with more severe depression. These findings suggest that Vitamin D3 deficiency may represent an important biological correlate of depressive symptom severity in clinical populations.

The high rate of Vitamin D insufficiency and deficiency in patients with depressive disorder is observed in line with emerging information about increased susceptibility of people with psychiatric illnesses to hypovitaminosis D, which could be attributed to reduced outdoor activities, poor nutritional intake, sedentary lifestyles, and psychomotor retardation that is usually experienced by patients with depressive disorder. (Bertone-Johnson, 2009). Also, the depressive illness in itself might be contributing to the worsening of the habits that minimise exposure to the sun, which consequently leaves one at a higher risk of deficiency.

The association observed in the present study between lower Vitamin D3 levels and greater severity of depressive symptoms is consistent with findings from several cross-sectional and clinical studies conducted in psychiatric populations. According to (Hoogendijk et al., 2008) The serum Vitamin D levels of patients with major depressive disorder were significantly lower than those of non-depressed controls, and the deficiencies in patients with severe depression were more severe. Likewise, Jorde et al., 2008 showed that there is a strong negative correlation between the levels of serum 25hydroxyvitamin D and depressive symptoms scores, which confirms the idea that Vitamin D status can determine mood regulation.

This relationship is further confirmed by the categorical form of distribution, where patients who had adequate levels of Vitamin D3 in their bodies were mostly related to low or no symptoms of depression, and severe Vitamin D deficiency was realised in those patients who had a severe depressive condition. These results and the hypothesis of Vitamin D deficiency as a contributing factor to the pathophysiology or worsening of the depressive manifestations are supported, even though the study lacks causality because of its cross-sectional nature. Some of the suggested mechanisms are the dysfunction of monoamine neurotransmitters, high inflammatory processes, the dysfunction of the hypothalamic-pituitary-adrenal axis, and poor neuroplasticity. (Belzeaux et al., 2015).

Interventional research also sheds more light on the clinical implications of this relationship. Improved depressive symptoms have been described in randomised controlled trials with Vitamin D supplementation, especially in people who were deficient at baseline. (Khoraminy et al., 2013). Despite the inconsistency in the findings of supplementation trials, the possibility of Vitamin D as an adjunctive treatment in depression has been receiving growing support, particularly due to its low cost and good safety profile. (Shaffer et al., 2014).

Although these findings are encouraging, one should remember that the current study has certain shortcomings. First, owing to the nature of the study design, the research design is cross-sectional, which does not allow for inferring causality, and it is not clear whether Vitamin D deficiency is a cause of depression or vice versa. Second, the research was done on one tertiary care facility, and the sample size used was relatively small, and hence may not be applicable in a wider community setting. Third, the possible confounding variables, including dietary consumption, sunlight exposure, and level of physical activity, body mass index, season fluctuation, and the use of Vitamin D supplementation, were not assessed and controlled systematically. Also, the fact that categorical classification of

Vitamin D status and depression severity has been used instead of using continuous variables may not be as precise as correlation analysis.

To address the limitations in future research, longitudinal and interventional research designs should be used. Potential cohort studies would be useful in illuminating the temporal association of Vitamin D deficiency and the development or worsening of depressive symptoms. Controlled randomised studies on the impact of Vitamin D supplementation on depressive outcomes, especially in Vitamin D-deficient persons, are necessary to define causation and therapeutic efficacy. Moreover, more multicentric research with an elaborate evaluation of lifestyle, nutritional, and biological confounders would improve the strength of results as well as their generalizability.

Finally, the current research suggests that Vitamin D3 deficiency is highly comorbid in depressive disorder patients and is indirectly correlated with the level of depressive symptoms. The findings highlight the need to take into consideration the Vitamin D status when a depressive disorder is being evaluated comprehensively. Regular diagnosis and treatment of Vitamin D deficiency can be a lowcost but effective complementary intervention to the overall management of depression, especially where resources are scarce.

6. CONCLUSION

The current cross-sectional in-patient study not only indicates that there is a great deal of comorbidity in Vitamin D3 deficiency among patients with diagnosed cases of depressive disorder, but also shows that there is an inverse relationship between the levels of serum Vitamin D3 and the severity of depressive symptoms. The results have shown that most patients with depressive disorder had poor Vitamin D3 concentrations, and Vitamin D deficiency was the most common category. Moreover, the severity of depressive symptoms was observed to increase, and the levels of Vitamin D3 fell significantly, indicating that there is a clinically significant relationship between Vitamin D status and the degree of depression. The results are especially applicable in the Indian case, where depressive disorders and Vitamin D deficiency were both extremely common despite the high levels of sunlight availability. The findings align with the emerging data that lend credence to the possibility of Vitamin D as a biological determinant that may have a role in mood control and (depression) symptom expression. Even though the lack of causality may arise because of the cross-sectional design, the noted association highlights the value of including nutritional and metabolic variables in the overall evaluation of depressive disorders. Clinically, it may be useful to perform regular screening of Vitamin D deficiency in patients with depressive symptoms, particularly in patients with moderate to severe cases of depression. Treatment of Vitamin D deficiency would be a cheap, easy, and uncomplicated supplementary measure to the conventional pharmacological and psychological therapy, especially where resources are meagre. Nevertheless, the results are to be understood in the context of several limitations, such as the single-centre study, a rather limited sample size, and failure to control the possible confounding factors (sunlight exposure, dietary consumption, and physical activity). The research topics that should be considered by future researchers include larger multicentric longitudinal studies and randomised controlled trials to help understand the cause-and-effect relationship and determine the therapeutic value of Vitamin D supplementation in depressive disorders. Finally, this research adds significant clinical evidence relating Vitamin D3 deficiency to the severity of depressive symptoms, which proves that combined and holistic strategies are imperative in the treatment of depressive disorders.

REFERENCES

1. Anglin, R. E., Samaan, Z., Walter, S. D., & McDonald, S. D. (2013). Vitamin D deficiency and depression in adults: Systematic review and meta-analysis. *The British Journal of Psychiatry*, 202(2), 100–107. <https://www.cambridge.org/core/journals/the-british-journal->

- ofpsychiatry/article/vitamin-d-deficiency-and-depression-in-adults-systematic-review-andmetaanalysis/F4E7DFBE5A7B99C9E6430AF472286860
2. Belzeaux, R., Boyer, L., Féron, F., Leboyer, M., & Fond, G. (2015). Mood disorders are associated with a more severe hypovitaminosis D than schizophrenia. *Psychiatry Research*, 229(1–2), 613–616. <https://www.sciencedirect.com/science/article/pii/S0165178115002619>
3. Bertone-Johnson, E. R. (2009). Vitamin D and the occurrence of depression: Causal association or circumstantial evidence? *Nutrition Reviews*, 67(8), 481–492. <https://academic.oup.com/nutritionreviews/article-abstract/67/8/481/1839131>
4. Chan, R., Chan, D., Woo, J., Ohlsson, C., Mellström, D., Kwok, T., & Leung, P. (2011). Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. *Journal of Affective Disorders*, 130(1–2), 251–259. <https://www.sciencedirect.com/science/article/pii/S0165032710006439>
5. Depression, W. H. O. (2017). Other common mental disorders: Global health estimates. *Geneva: World Health Organisation*, 24(1).
6. Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, 67(5), 446–457. <https://www.sciencedirect.com/science/article/pii/S0006322309012293>
7. Eyles, D. W., Burne, T. H., & McGrath, J. J. (2013). Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Frontiers in Neuroendocrinology*, 34(1), 47–64. <https://www.sciencedirect.com/science/article/pii/S0091302212000295>
8. Garcion, E., Wion-Barbot, N., Montero-Menei, C. N., Berger, F., & Wion, D. (2002). New clues about vitamin D functions in the nervous system. *Trends in Endocrinology & Metabolism*, 13(3), 100–105. [https://www.cell.com/trends/endocrinology-metabolism/abstract/S10432760\(01\)00547-1](https://www.cell.com/trends/endocrinology-metabolism/abstract/S10432760(01)00547-1)
9. Gupta, A. (2014). Vitamin D deficiency in India: Prevalence, causalities and interventions. *Nutrients*, 6(2), 729–775. <https://www.mdpi.com/2072-6643/6/2/729>
10. Harinarayan, C. V., Ramalakshmi, T., & Venkataprasad, U. (2004). High prevalence of low dietary calcium and low vitamin D status in healthy south Indians. *Asia Pacific Journal of Clinical Nutrition*, 13(4). https://www.researchgate.net/profile/Dr-Prasad-Uv/publication/260246234_High_prevalence_of_low_dietary_calcium_and_low_vitamin_D_status_in_healthy_South_Indians/links/00b7d5304c2e720d5e000000/High-prevalence-of-lowdietary-calcium-and-low-vitamin-D-status-in-healthy-South-Indians.pdf
11. Hoogendijk, W. J., Lips, P., Dik, M. G., Deeg, D. J., Beekman, A. T., & Penninx, B. W. (2008). Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Archives of General Psychiatry*, 65(5), 508–512. <https://jamanetwork.com/journals/jamapsychiatry/article-abstract/482702>
12. Jorde, R., Sneve, M., Figenschau, Y., Svartberg, J., & Waterloo, K. (2008). Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: Randomized double blind trial. *Journal of Internal Medicine*, 264(6), 599–609. <https://doi.org/10.1111/j.13652796.2008.02008.x>
13. Ju, S.-Y., Lee, Y.-J., & Jeong, S.-N. (2013). Serum 25-hydroxyvitamin D levels and the risk of depression: A systematic review and meta-analysis. *The Journal of Nutrition, Health and Aging*, 17(5), 447–455. <https://www.sciencedirect.com/science/article/pii/S1279770723017840>
14. Kesby, J. P., Cui, X., Burne, T. H., & Eyles, D. W. (2013). Altered dopamine ontogeny in the developmentally vitamin D deficient rat and its relevance to schizophrenia. *Frontiers in Cellular Neuroscience*, 7, 111. <https://www.frontiersin.org/journals/cellularneuroscience/articles/10.3389/fncel.2013.00111/full>

15. Kessler, R. C., Akiskal, H. S., Ames, M., Birnbaum, H., Greenberg, P., .A, R. M., Jin, R., Merikangas, K. R., Simon, G. E., & Wang, P. S. (2006). Prevalence and Effects of Mood Disorders on Work Performance in a Nationally Representative Sample of U.S. Workers. *American Journal of Psychiatry*, 163(9), 1561–1568. <https://doi.org/10.1176/ajp.2006.163.9.1561>
16. Khoraminy, N., Tehrani-Doost, M., Jazayeri, S., Hosseini, A., & Djazayeri, A. (2013). Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. *Australian & New Zealand Journal of Psychiatry*, 47(3), 271–275. <https://doi.org/10.1177/0004867412465022>
17. Lee, D. M., Tajar, A., O'Neill, T. W., O'Connor, D. B., Bartfai, G., Boonen, S., Bouillon, R., Casanueva, F. F., Finn, J. D., Forti, G., Giwercman, A., Han, T. S., Huhtaniemi, I. T., Kula, K., Lean, M. E., Punab, M., Silman, A. J., Vanderschueren, D., Wu, F. C., ... the EMAS study group. (2011). Lower vitamin D levels are associated with depression among community-dwelling European men. *Journal of Psychopharmacology*, 25(10), 1320–1328. <https://doi.org/10.1177/0269881110379287>
18. May, H. T., Bair, T. L., Lappé, D. L., Anderson, J. L., Horne, B. D., Carlquist, J. F., & Muhlestein, J. B. (2010). Association of vitamin D levels with incident depression among a general cardiovascular population. *American Heart Journal*, 159(6), 1037–1043. <https://www.sciencedirect.com/science/article/pii/S0002870310002425>
19. Milaneschi, Y., Shardell, M., Corsi, A. M., Vazzana, R., Bandinelli, S., Guralnik, J. M., & Ferrucci, L. (2010). Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. *The Journal of Clinical Endocrinology & Metabolism*, 95(7), 3225–3233. <https://academic.oup.com/jcem/article-abstract/95/7/3225/2596276>
20. Patrick, R. P., & Ames, B. N. (2014). Vitamin D hormone regulates serotonin synthesis. Part 1: Relevance for autism. *The FASEB Journal*, 28(6), 2398–2413. <https://faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fj.13-246546>
21. Prüfer, K., Veenstra, T. D., Jirikowski, G. F., & Kumar, R. (1999). Distribution of 1, 25dihydroxyvitamin D3 receptor immunoreactivity in the rat brain and spinal cord. *Journal of Chemical Neuroanatomy*, 16(2), 135–145. <https://www.sciencedirect.com/science/article/pii/S0891061899000022>
22. Shaffer, J. A., Edmondson, D., Wasson, L. T., Falzon, L., Homma, K., Ezeokoli, N., Li, P., & Davidson, K. W. (2014). Vitamin D supplementation for depressive symptoms: A systematic review and meta-analysis of randomized controlled trials. *Psychosomatic Medicine*, 76(3), 190–196. https://journals.lww.com/psychosomaticmedicine/fulltext/2014/04000/vitamin_d_supplementation_for_depressive_symptoms_9.aspx
23. Song, C., & Wang, H. (2011). Cytokines mediated inflammation and decreased neurogenesis in animal models of depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 35(3), 760–768. <https://www.sciencedirect.com/science/article/pii/S027858461000237X>
24. Spedding, S. (2014). Vitamin D and depression: A systematic review and meta-analysis comparing studies with and without biological flaws. *Nutrients*, 6(4), 1501–1518. <https://www.mdpi.com/2072-6643/6/4/1501>
25. Stewart, R., & Hirani, V. (2010). Relationship between vitamin D levels and depressive symptoms in older residents from a national survey population. *Psychosomatic Medicine*, 72(7), 608–612. https://journals.lww.com/psychosomaticmedicine/FullText/2010/09000/Relationship_Between_Vitamin_D_Levels_and.2.aspx
26. Vellekkatt, F., & Menon, V. (2019). Efficacy of vitamin D supplementation in major depression: A meta-analysis of randomized controlled trials. *Journal of Postgraduate Medicine*, 65(2), 74–80. https://journals.lww.com/jopm/fulltext/2019/65020/efficacy_of_vitamin_d_supplementation_in_major.4.aspx

27. Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., Charlson, F. J., Norman, R. E., Flaxman, A. D., & Johns, N. (2013). Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *The Lancet*, 382(9904), 1575–1586.
[https://www.thelancet.com/journals/lancet/article/PIIS01406736\(13\)61611-6/fulltext?var=greenface](https://www.thelancet.com/journals/lancet/article/PIIS01406736(13)61611-6/fulltext?var=greenface)