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Research Article

Relationship between Vitamin D Status, Neurocognitive Function, and Depressive Symptom Severity in Patients with Major Depressive Disorder

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ABSTRACT
Background: Major depressive disorder is frequently accompanied by cognitive difficulties that may impair daily functioning and treatment outcomes. The role of vitamin D in brain function, mood regulation and the performance of the neurocognitive function has been more and more investigated. The purpose of this study was to determine whether there was a correlation between depression severity, vitamin D status and neurocognitive function in patients with major depression.
Methods: This cross-sectional analytical study was conducted at Khalifa Gul Nawaz Teaching Hospital, Bannu from January 2025 to June 2025. The subjects were selected by non-probability consecutive sampling technique, total of 78 patients with major depressive disorder were selected. Serum 25-hydroxyvitamin D (25(OH)D) was quantified, and vitamin D deficiency, insufficiency, or sufficiency was defined. The Montreal Cognitive Assessment (MoCA) was used to measure neurocognitive function and the Patient Health Questionnaire-9 (PHQ-9) was used to measure the severity of depressive symptoms. IBM SPSS Statistics version 25.0 was used for data analysis. The group comparisons were performed by using group correlation, chi-square testing and a p value <0.05 was accepted as statistically significant.
Results: The mean serum vitamin D level was 21.7 ± 9.4 ng/mL. Vitamin D deficiency was present in 35 (44.9%) participants, insufficiency in 25 (32.1%), and sufficient levels in 18 (23.1%). The mean MoCA score increased significantly across deficient, insufficient, and sufficient vitamin D groups (20.8 ± 3.9, 23.5 ± 3.4, and 26.2 ± 3.1, respectively; $p < 0.001$). Mean PHQ-9 scores showed the opposite pattern (18.4 ± 4.7, 15.0 ± 4.2, and 11.8 ± 4.0, respectively; $p < 0.001$). Cognitive impairment was significantly more frequent among vitamin D-deficient patients (71.4%) than among those with insufficient (48.0%) or sufficient (27.8%) vitamin D levels ($p = 0.005$). Serum vitamin D was positively correlated with MoCA score ($r = 0.52$, $p < 0.001$) and inversely correlated with PHQ-9 score ($r = −0.47$, $p < 0.001$).
Conclusion: Lower vitamin D levels were significantly associated with poorer neurocognitive performance and greater depressive symptom severity among patients with major depressive disorder. Assessment of vitamin D status may provide useful supplementary information in the evaluation of patients with MDD, although larger longitudinal and interventional studies are required to determine causality.
Keywords: Major depressive disorder, vitamin D, neurocognitive function, MoCA, depressive symptoms, PHQ-9.

INTRODUCTION

Major depressive disorder (MDD) is a frequent psychiatric disorder that involves a persistent low mood, loss of interest or pleasure, sleep and appetite disturbances, decreased concentration, diminished energy, and impairment in functioning. Patients with MDD often have complaints of attention, memory, executive functioning and information processing deficits as well as emotional symptoms. These neurocognitive impairments can continue even after depressive symptoms resolve and can negatively impact academic, work, social and daily functioning. Therefore, potentially modifiable biological factors associated with both depressive symptoms and cognitive dysfunction may be useful for better overall assessment and management of patients with MDD (1-3).

Vitamin D is a fat soluble vitamin where there is well established evidence of its role in calcium homeostasis and bone metabolism, but in

recent years, there has been a growing interest in its possible role in brain function and mental health. In the CNS, vitamin D receptors and vitamin D-metabolizing enzymes are found in several regions that are involved in mood regulation, memory and cognition. These pathways could help vitamin D affect brain plasticity, the production of neurotransmitters, neurotrophic activity, the regulation of the immune system, and inflammatory responses. Therefore there has been an interest in whether low levels of vitamin D are a potential biological mechanism for depression and cognitive dysfunction (4, 5).

Vitamin D deficiency is found throughout the world and can happen when people do not spend enough time in the sun, do not eat foods that contain vitamin D, do not do much outdoor activity, are obese, have chronic illness or other lifestyle and environmental factors. Many of these factors also occur often with people suffering from depressive disorders. Patients suffering from more severe depression may invest less time in out-of-door activity, have poor nutritional intake and be less physically active, thereby becoming vulnerable to vitamin D deficiency. This is a complex interplay between vitamin D deficiency and depression, and vice versa, where depression itself may increase the risk of low vitamin D status, and depressive and cognitive symptoms may be related to vitamin D deficiency (6, 7).

Neurocognitive functioning is now recognized as an important component of MDD. Poor attention, learning, memory and processing speed can lead to poor treatment adherence and to incomplete functional recovery. Severity of depression symptoms, which can be influenced by the severity of cognitive test, can also have a negative effect on performance on cognitive test. Therefore, the assessment of vitamin D levels together with the assessment of neurocognitive function and depressive symptom severity may be a more comprehensive assessment of biological and clinical factors of MDD (8, 9).

Although previous research has individually examined vitamin D deficiency, depression, and cognitive impairment, their combined relationship among patients with established major depressive disorder requires further investigation (10, 11). There remains a need to determine whether variations in serum vitamin D levels are associated with measurable differences in cognitive performance and depressive symptom burden. Therefore, the present study was conducted to assess the relationship between vitamin D status, neurocognitive function, and depressive symptom severity among patients with major depressive disorder.

METHODOLOGY

This cross-sectional analytical study was conducted at Khalifa Gul Nawaz Teaching Hospital, Bannu from January 2025 to June 2025**.** The study was designed to evaluate the relationship between serum vitamin D status, neurocognitive performance, and the severity of depressive symptoms among patients diagnosed with major depressive disorder. A total of 78 patients fulfilling the predefined eligibility criteria were enrolled during the study period. Ethical approval was obtained from the relevant institutional ethics review committee before initiation of data collection, and written informed consent was obtained from each participant after explaining the purpose and procedures of the study.

Eligible patients included adults (18 years or older) with a clinical diagnosis of major depressive disorder (MDD) who had a confirmed diagnosis based on standard clinical diagnostic criteria. The sample size was 78 and sampling was done through non-probability consecutive sampling method. Patients with severe medical illness that affects cognitive function, chronic renal / hepatic disease, psychosis, bipolar disorder, major neurological disorders, or a history of substance dependence were excluded. People with conditions that significantly affect vitamin D metabolism (vitamin D excess or vitamin D deficiency) and those who were taking high doses of vitamin D replacement were also excluded to minimize confounding.

A structured data collection form was used to collect demographic and clinical data after enrollment. The variables were age, sex, body mass index, marital status, residence, number of previous depressive episodes, treatment with antidepressant drugs, and pertinent medical history. BMI was calculated as weight (in kilograms) divided by the square of the height (in meters). A medical history and medical records were obtained to confirm the diagnosis of MDD and to determine if something in the medical or clinical history may have an impact on cognitive function or vitamin D levels.

A venous blood sample was collected from each participant under aseptic conditions for measurement of serum 25-hydroxyvitamin D [25(OH)D], which was used as the biochemical indicator of vitamin D status. The vitamin D

level in the serum was measured in ng/mL and classified into three groups: deficient, insufficient, and sufficient, based on the established laboratory reference levels. The samples were all processed and analyzed in the hospital laboratory with the available standard biochemical assay system with routine quality-control procedure.

The Montreal Cognitive Assessment (MoCA) was used to assess neurocognitive function. The overall MoCA score was completed for each patient and lower scores were associated with worse cognitive functioning. Cognitive impairment was defined as follows: based on the recommended cut-off for the instrument; and appropriate educational adjustment where necessary. The Patient Health Questionnaire-9 (PHQ-9) was used to measure the severity of depressive symptoms. All the PHQ-9 items were summed to create a total score and the subjects were classified into the standard severity categories of mild to severe depressive symptoms.

The collected data was entered and analysed in IBM SPSS Statistics 25.0. Mean and standard deviation were used to present continuous variables (where appropriate) and frequencies and percentages were used to present categorical variables. One-way analysis of variance (ANOVA) was used to evaluate differences in mean cognitive and depressive symptom scores between the vitamin D categories, and categorical associations were evaluated using the chi-square test or Fisher's exact test, as appropriate. Pearson correlation coefficient was used to assess the relationship between serum vitamin D level, MoCA score and PHQ-9 score if the assumption of normality was met. A p-value <0.05 was considered statistically significant.

RESULTS

The overall number of patients in the study was 78 patients diagnosed with major depressive disorder (MDD). Participants had a mean age of 41.6 ± 11.2 years ranging from 20-65 years of age. Among the participants, 45 (57.7%) were females and 33 (42.3%) were males. The mean body mass index was 26.8 ± 4.1 kg/m². The majority were suffering from depressive symptoms for over a year, and 46 (59.0%) were being treated for depression at time of assessment.

Table 1. Demographic and clinical characteristics of the study participants (n = 78)

Variable	Frequency/Mean	Percentage/SD
Age, years	41.6	±11.2
Male	33	42.3%
Female	45	57.7%
BMI, kg/m²	26.8	±4.1
Married	51	65.4%
Unmarried	27	34.6%
Urban residence	47	60.3%
Rural residence	31	39.7%
Duration of MDD, years	3.8	±2.6
Receiving antidepressant treatment	46	59.0%
Previous depressive episode(s)	32	41.0%

The average serum 25-HV-D (25-hydroxyvitamin D) level was 21.7 ± 9.4 ng/mL. In 35 (44.9%) participant's vitamin D deficiency was observed and in 25 (32.1%) vitamin D was insufficient and in 18 (23.1%) it was sufficiently present. The mean Montreal Cognitive Assessment (MoCA) score was 22.9 ± 4.2 and 42 (53.8%) individuals had scores that indicated cognitive impairment. The average score for the depressive symptom (based on the PHQ-9) was 15.8 ± 5.4.

Table 2. Vitamin D status, neurocognitive findings, and depressive symptom severity

Variable	Frequency/Mean	Percentage/SD
Serum 25(OH)D, ng/mL	21.7	±9.4
Vitamin D deficient	35	44.9%
Vitamin D insufficient	25	32.1%
Vitamin D sufficient	18	23.1%
MoCA score	22.9	±4.2

Cognitive impairment	42	53.8%
No cognitive impairment	36	46.2%
PHQ-9 score	15.8	±5.4
Mild depressive symptoms	14	17.9%
Moderate depressive symptoms	25	32.1%
Moderately severe symptoms	23	29.5%
Severe depressive symptoms	16	20.5%

There was a progressive improvement in cognitive performance as vitamin D status increased. Patients with vitamin D deficiency had the lowest mean MoCA score (20.8 ± 3.9) followed by the group with vitamin D insufficiency (23.5 ± 3.4) and sufficient vitamin D levels (26.2 ± 3.1). The mean MoCA scores were statistically different across the groups of vitamin D ($p < 0.001$). Likewise, there was a decrease in the severity of depressive symptoms with an increase in vitamin D status. The mean PHQ-9 scores were highest in the vitamin D deficient group (18.4 ± 4.7), and were followed by the insufficient group (15.0 ± 4.2) and the vitamin D sufficient group (11.8 ± 4.0). This difference also was statistically significant ($p < 0.001$).

Table 3. Neurocognitive and depressive symptom scores according to vitamin D status

Vitamin D status	n	MoCA score, mean ± SD	PHQ-9 score, mean ± SD
Deficient	35	20.8 ± 3.9	18.4 ± 4.7
Insufficient	25	23.5 ± 3.4	15.0 ± 4.2
Sufficient	18	26.2 ± 3.1	11.8 ± 4.0
p-value		**<0.001**	**<0.001**

A large proportion of patients with vitamin D deficiency had cognitive impairment. Of the 35 vitamin D deficient participants, 25 (71.4%) had cognitive impairment, while 12 (48.0%) of vitamin D insufficient and 5 (27.8%) of vitamin D sufficient had cognitive impairment. The correlation between vitamin D level category and cognitive impairment was statistically significant ($p = 0.005$).

Table 4. Association between vitamin D status and cognitive impairment

Vitamin D status	Cognitive impairment n (%)	No cognitive impairment n (%)	p-value
Deficient (n=35)	25 (71.4%)	10 (28.6%)	
Insufficient (n=25)	12 (48.0%)	13 (52.0%)	
Sufficient (n=18)	5 (27.8%)	13 (72.2%)	**0.005**

There was a positive correlation between serum vitamin D level and MoCA score ($r = 0.52$, $p < 0.001$), suggesting that higher serum vitamin D levels were linked to higher MoCA scores. Conversely, there was a significant negative correlation between serum vitamin D and PHQ-9 score ($r = −0.47$, $p < 0.001$), indicating that depressiveness symptom severity is lower with higher vitamin D levels. Depressive symptom severity was also negatively correlated with neurocognitive performance ($r = −0.43$, $p < 0.001$).

Table 5. Correlation between vitamin D, neurocognitive function, and depressive symptom severity

Variables	Correlation coefficient (r)	p-value
Serum vitamin D vs. MoCA score	0.52	<0.001
Serum vitamin D vs. PHQ-9 score	−0.47	<0.001
MoCA score vs. PHQ-9 score	−0.43	<0.001

Overall, the findings demonstrated that lower serum vitamin D levels were associated with poorer neurocognitive performance and greater depressive symptom severity among patients with major depressive disorder. Participants with vitamin D deficiency showed the lowest cognitive scores, the highest depressive

symptom scores, and the greatest frequency of cognitive impairment.

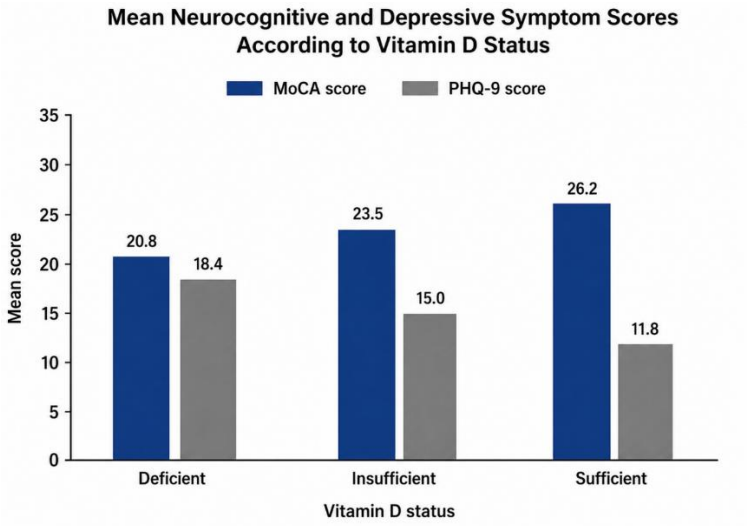

Figure 1. Mean neurocognitive (MoCA) and depressive symptom (PHQ-9) scores according to vitamin D status among patients with major depressive disorder (n = 78).

DISCUSSION

The present study evaluated the relationship between vitamin D status, neurocognitive function, and depressive symptom severity among patients with major depressive disorder. The findings demonstrated that vitamin D deficiency was common in the study population and was associated with poorer cognitive performance and greater severity of depressive symptoms. Patients with deficient vitamin D levels showed the lowest mean MoCA scores and the highest mean PHQ-9 scores, whereas patients with sufficient vitamin D levels demonstrated relatively better cognitive performance and lower depressive symptom scores. These findings suggest that vitamin D status may be an important biological factor associated with both cognitive and affective manifestations of major depressive disorder (12, 13).

A notable finding was the progressive increase in MoCA scores across vitamin D categories. The mean MoCA score of vitamin D deficient patients was 20.8 ± 3.9, while it was 23.5 ± 3.4 for patients with insufficient vitamin D and 26.2 ± 3.1 for those with sufficient vitamin D levels. The statistically significant difference among groups suggests that the groups with lower levels of vitamin D had poorer neurocognitive performance. Vitamin D receptors are expressed across the brain regions which are associated with memory, attention, executive function and emotional regulation. In addition, Vitamin D has neurotrophic activity, is a neuroprotective agent, regulates calcium and influences inflammatory pathways. The deficiency could then result in dysfunctions of different neurons and a decrease in cognitive efficiency, especially in people with psychiatric diseases (13-15).

Vitamin D status also had a definite correlation with the severity of depression symptoms. The mean PHQ-9 score was highest in the vitamin D-deficient group and gradually lower in the vitamin D insufficient and sufficient groups of participants. Additionally, serum vitamin D levels were negatively associated with the PHQ-9 scores, suggesting a tendency for lower levels of vitamin D to be associated with greater depressive symptomology. This association has several biological mechanisms that can be considered, such as the role of vitamin D in the synthesis of serotonin, in the regulation of hypothalamic-pituitary-adrenal axis, in neuroimmune pathways and inflammatory processes. The present cross-sectional design thus does not allow to conclude the direction of the relationship; however, vitamin D deficiency may thus increase vulnerability to depressive symptoms (16, 17).

This relationship of vitamin D levels with cognitive impairment was also clinically significant. Compared to insufficient vitamin D status (48.0%) and sufficient vitamin D status (27.8%), cognitive impairment was noted in 71.4% of vitamin D deficient participants. These findings suggest that cognitive impairments could be more common in depressed patients who have low vitamin D levels. Major Depressive Disorder patients

commonly experience cognitive problems such as attention, memory, processing speed, decision making, and executive function. These deficits can impact the ability to perform in the work situation, in the social realm, to follow treatment, and more generally, recovery. Therefore, vitamin D status assessment could be considered when evaluating a broader clinical assessment of patients with MDD with significant cognitive complaints (18).

The observed relationships were also confirmed with the help of correlation analysis. There was a moderate positive relationship between the serum vitamin D level and MoCA score while there was an inverse association between the serum vitamin D level and PHQ-9 score. Depressive symptom burden was also negatively associated with MoCA scores, indicating that higher scores of depression symptoms were related to poorer cognitive performance. The link between cognition and depression is probably complex, with vitamin D being just one aspect of this relationship. Other factors like age, education, length of disease, drug therapy, quality of sleep, physical activity, diet, social conditions and medical comorbidities may also affect neuropsychological functioning and vitamin D status (19, 20).

The findings of this study have potential clinical implications. Measurement of serum vitamin D could be a potentially modifiable biological risk factor in individuals with MDD, especially those who show signs of cognitive dysfunction or more severe depression. However, the association between vitamin D deficiency and depression and/or cognitive dysfunction is not a standalone justification for supplements and vitamin D deficiency should not be a standalone diagnosis for depression or cognitive dysfunction. The study was restricted to a small number of patients, performed in one centre and was cross-sectional in nature, so that causality or temporal relationships could not be established. The extent to which exposure to sunlight or dietary vitamin D intake, physical activity, seasonality, and specific information about medication use were fully assessed was also not comprehensive. Larger samples and multivariable adjustment are needed in future prospective studies to determine if there is a measurable difference in cognitive performance or severity of depressive symptoms when vitamin D status improves.

CONCLUSION

The study demonstrated a significant relationship between vitamin D status, neurocognitive performance, and depressive symptom severity among patients with major depressive disorder. Lower serum vitamin D levels were associated with poorer MoCA scores, greater frequency of cognitive impairment, and higher PHQ-9 scores. In contrast, patients with sufficient vitamin D levels showed better cognitive performance and lower depressive symptom severity. These findings suggest that assessment of vitamin D status may provide additional clinical information when evaluating patients with major depressive disorder, particularly those with prominent cognitive difficulties. Larger longitudinal and interventional studies are required to determine whether correction of vitamin D deficiency can contribute to improved neurocognitive and depressive outcomes.

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