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Relationship of low serum 25 (OH) Vitamin D and dementia – A cross-sectional observational study from a neurology teaching hospital in East India: Relationship of low serum 25 (OH) Vitamin D and dementia in East India

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ABSTRACT

Background: In view of the rapidly growing number of aged population with dementia in India, widespread hypovitaminosis D in the elderly individual, high frequency of dementia of unknown etiology, many studies showing a definite role of Vitamin D in dementia as well as some of the literature showing inconsistent results and reverse causality of hypovitaminosis D in dementia, we planned to investigate the relation between low vitamin D and risk of dementia. **Aims and Objective:** The aim of the current study was to find out any relationship of Vitamin D with dementia. **Materials and Methods:** This cross-sectional observational study was performed at a neurology-teaching hospital, Kolkata, India. Ethical clearance was obtained from the hospital ethics committee. A total of fifty adults completed interviews on a semi-structured questionnaire. In addition, general medical and neurological examination and detailed cognitive assessment, including MMSE, were carried out after taking written consent. All individuals with dementia, and age-gender-matched healthy volunteers provided blood samples for routine and relevant biochemical examination, including the estimation of serum 25(OH) Vitamin D by Chemiluminescence Immuno Assay (CLIA). In addition, appropriate statistical methods were applied to analyse the results. **Results:** Overall, ninety percent of participants had low serum 25(OH)Vitamin D, defined as 25(OH)D < 20mg/ml. Hypovitaminosis D was associated with early and late-stage dementia and was statistically significant. Only five individuals were found to have sufficient 25 (OH) Vitamin D. **Conclusion:** The mean vitamin D level of demented patients was significantly lower compared to the control population. Our observations provide an association between Vitamin D deficiency and dementia and provides a background of longitudinal prospective study in future to show cause and effect relationship between dementia and hypovitaminosis D.

Key words: Dementia/major neurocognitive disorder; 25 (OH) Vitamin D; Mini-Mental State Examination; Cross-sectional study

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INTRODUCTION

Dementia is a common public health problem. The number of people with dementia worldwide is estimated to be 131.5 million by 2050.[1] According to the dementia in India 2020 report, an estimated 5.3 million Indians aged more than 60 years had dementia in 2020, and this number is projected to exceed 14 million by 2050.[2]

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This growing number of people with dementia places an enormous burden on society's health-care system. The increasing life span in Indians and the high burden of vascular risk factors, such as diabetes mellitus, hypertension, obesity, smoking, dyslipidemia in society, and possibly genetic factors, are contributing reasons for the growing number of individuals with dementia in India. However, the prevalence of dementia varies in different regions of India.[3] This variation is related to the studies' adoption of varying methodology, screening tools, defining criteria of dementia, multiethnicity, and multicultural and environmental factors.

The term dementia has been replaced by the term "Major Neurocognitive Disorder" according to the diagnostic and statistical manual of mental disorder V (DSM-V) criteria and encompasses the following.[4] There is presence of significant cognitive decline from a previous level of performance in one or more cognitive domains: Learning and memory, language, executive dysfunction, complex attention, perceptual-motor, and social cognition. The cognitive deficits are sufficient to interfere with independence in everyday activities. These neurodeficits do not occur in the context of delirium and are not better explained by another mental disorder.

Aging is an important risk factor for all causes of dementia. Although dementia mainly affects older people, it is not an inevitable consequence of aging. Dementia results from various diseases and insults that primarily or secondarily affect the brain. It is presently the seventh leading cause of death among all conditions and is one of the major causes of disability and dependency among elderly individuals worldwide. Dementia has physical, psychological, social, and economic impacts not only for themselves but also for their caregivers, family, and society.

Alzheimer's disease (AD) affects 5–10% of people older than 65 years and 50% of those aged 85 years.[5] Non-modifiable risk factors for dementia include female sex, Black race, Hispanic ethnicity, and genetic factors such as the apolipoprotein E gene.[6,7] Modifiable risk factors for all-cause dementia include hypertension, diabetes mellitus, diet, and limited cognitive, physical, and social activities.[8,9]

Pathologically, "mixed dementia" is the most common form of dementia found in 46% of persons with clinically diagnosed AD and most commonly consists of AD neurodegeneration and cerebrovascular disease.[9]

The prevalence of potentially reversible dementias has been reported at 18% in patients under 65 years but only 5% in those over 65 years.[10] These include hypothyroidism, Vitamin B12 deficiency, chronic subdural hematoma, NPH, and infections such as herpes virus, tuberculosis, HIV, toxoplasmosis, cryptococcus, cytomegalovirus, syphilis, Borrelia, and cysticercosis. In addition, the relative frequency of "Dementia of Unknown Etiology" increases with age and is nearly 50% in nonagenarians.[11]

Vitamin D is a neurosteroid with neuroprotective and vasculoprotective effects in the central nervous system.[12] In recent years, evidence has linked a lack of Vitamin D not only to its known calcium and bone metabolism but also to neurocognitive decline.[13] In addition, Vitamin D receptors are present in brain regions responsible for memory development, cognitive functions, and plaque clearance.[14,15]

About 90% of Vitamin D is produced in the epidermis from 7-dehydrocholesterol as a reaction to sunlight (Solar Ultraviolet B Radiation; 290–315 nm).[16] With advancing age, the capacity of the skin to produce Vitamin D3 decreases, irrespective of the season, and the degradation of its active form increases.[17] Factors that limit the cutaneous production of Vitamin D3 include higher latitude, covering of skin, lack of outdoor activities, sunscreen use, old age, female sex, and darker skin pigmentation.[18]

In India, widely consumed food items such as dairy products are rarely fortified with Vitamin D. Indian socioreligious and cultural practices do not facilitate adequate sun exposure, thereby negating the potential benefits of plentiful sunshine. The above factors have given rise to the high prevalence of subclinical hypovitaminosis D in urban and rural settings across all socioeconomic and geographic strata.

Vitamin D deficiency prevails in epidemic proportions all over the Indian subcontinent, with a prevalence of 70–100% in the general population.[19]

The aging population is increasing exponentially in India. India has a high prevalence of hypovitaminosis D, irrespective of age, gender, race, and geography. The longitudinal and cross-sectional studies and their meta-analysis exhibit an association of low Vitamin D with cognitive impairment and AD. Moreover, the interventional studies showed mixed results on Vitamin D supplementation's role in preventing and treating cognitive impairment and dementia. All these factors prompted us to investigate the relation of dementia and low Vitamin D in our patients.

The study is important because correction of Vitamin D deficiency may have immense potential for preventing cognitive impairment and dementia because of the high prevalence of dementia and the easy, inexpensive, and safe way of Vitamin D supplementation. Our aim is to estimate

the level of serum 25 (OH) Vitamin D in subjects with dementia/major neurocognitive disorder, to measure the prevalence of hypovitaminosis D among patients with dementia, and to find out any relationship between serum 25 (OH) Vitamin D and cognitive function in our study population.

MATERIALS AND METHODS

This is a cross-sectional observational study to examine the relationship between cognitive function and serum 25 (OH) Vitamin D in a hospital-based Indian population. This study was carried out at the neurology superspecialty teaching hospital in East India. The Institutional Ethics Committee approved the study, and all the participants and their close relatives gave their written informed consent.

A total of 50 patients diagnosed with dementia/major neurocognitive disorder attending the hospital's neurology outpatient and inpatient departments were included in this study over 18 months (1st January 2018 to 30th June 2019). Age- and gender-matched controls were selected from among the patients' healthy relatives.

Inclusion criteria

Patients with predominantly degenerative dementia / major neurocognitive disorder (as per DSM-V criteria)

Exclusion criteria

1) Patients who are already taking Vitamin D supplements.
2) Patients of dementia with chronic kidney disease, advanced liver disease and other systemic illnesses.
3) Patients on antiretroviral drugs, psychoactive drugs, antirejection drugs, anticonvulsants, diuretics, or glucocorticoids.
4) Patients of dementia with malabsorption disorders (e.g. short bowel syndrome, celiac disease, cystic fibrosis, inflammatory bowel disease, gastric bypass surgery)
5) Patients with Pseudodementia (depression, mania, schizophrenia, dissociative disorder)

The diagnosis of dementia was made using DSM-V criteria based on Mini-Mental State Examination (MMSE) and another relevant cognitive function testing. A standard MMSE cut score of ≤23 was taken to define dementia, yielding a sensitivity of 0.58 and specificity of 0.98 in detecting probable and possible AD across ethnicity.

The MMSE is a quick and easy measure that assesses seven areas of cognitive function. It has good test-retest reliability and acceptable sensitivity and specificity to detect mild-to-moderate dementia.[20] MMSE had a sensitivity of 87%, specificity of 92%, and positive predictive value of 69% at a cutoff point of 23/30 for the detection of dementia.[21]

Table 1: Vitamin D status and its distribution in the study population

Vitamin D state	Number (total=50)	Percentage
Deficient	24	48
Insufficient	21	42
Sufficient	5	10

Table 2: BMI levels according to the gender of the individual

BMI	Normal	Overweight	Obese	Total
Male	3	3	28	34
Female	5	7	4	16
Total	8	10	32	50

BMI: Body mass index

Table 3: The distribution of Vitamin D status and BMI states: (P<0.01)

Vitamin D state	Normal BMI=18.5–24.9	Overweight BMI=25–29.9	Obese BMI>30	Total
Deficient	0	2	22	24
Insufficient	7	5	9	21
Sufficient	1	3	1	5
Total	8	10	32	50

BMI: Body mass index

A trained psychologist administered a battery of neuropsychological tests to assess cognitive function. Patients with pseudodementia (depression, mania, schizophrenia, and dissociative disorder), individuals with a history of psychoactive drugs, and those who had been taking Vitamin D and calcium supplements in the past 6 months were excluded from the study.

Data collection included sociodemographic information, lifestyle, medical complaints, treatment history, medication use, alcohol and tobacco use, addiction, high-risk behavior, anthropometric data, general and detailed neurological examination, and MMSE as relevant cognitive function testing, and blood sampling.

Citrated blood samples were drawn after an overnight fast and rested for half an hour. Then, the samples were centrifuged and stored at minus seventy degree centigrade until analyzed. Serum 25 (OH) Vitamin D was quantitatively estimated using a chemiluminescence-based immunoassay.[22]

The results of estimated 25 (OH) Vitamin D were categorized as deficiency (<12 ng/ml), insufficiency (12–20 ng/ml), sufficiency (<20 ng/ml), and toxic (>100 ng/ml).[23] Appropriate statistical methods were applied to analyze the results.

RESULTS

Fifty patients diagnosed with dementia (major neurocognitive disorder) were included in this study. The mean age of the study population was 57.78±14.48 years (age range 18–79 years). Thirty-three (66%) were male, while 17 (34%) were female.

The mean Vitamin D level of the study population was 13.86±5.06 ng/ml (normal>20 ng/ml). According to the state of Vitamin D deficiency (<12 ng/ml), insufficiency (12–20 ng/ml), and sufficiency (>20 ng/ml), the distribution was written in Table 1.

The average Vitamin D levels in the control population were 19.51±8.58 ng/ml. There was a statistically significant difference in the Vitamin D levels between the cases and controls (P≤0.01).

The mean Vit. D level was 12.15 ng/ml among males and 17.49 ng/ml among females, with a statistically significant difference (P<0.01) (Table 2).

The body mass index (BMI) classification of the study population was as follows (Table 3):

- Normal (BMI=18.5–24.9)=8 (16%)
- Overweight (BMI=25–29.9)=10 (20%)
- Obese (BMI >30)=32 (64%).

It was observed that a greater number of males were obese (BMI>30) compared to females. The difference in BMI between both genders was statistically significant (P<0.01).

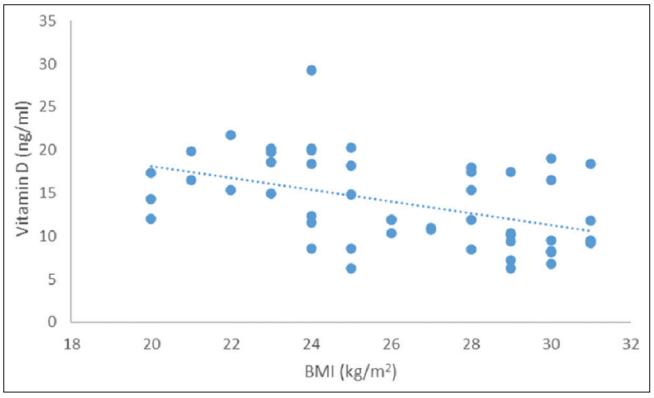

Figure 1: Correlation between Vitamin D levels and body mass index. Pearson's correlation coefficient=−0.452, P<0.001

The correlation between Vitamin D levels and BMI was also found to be significant (Pearson' correlation coefficient=−0.452, P<0.001) (Figure 1).

The distribution of Vitamin D levels among the age groups of the patients is mentioned in Table 4 (P=0.320). The Figure 2 shows the insignificant correlation between the age and vitamin D. Whereas, the Figure 3 shows the insignificant correlation between the age and MMSE.

The mean MMSE score of the patients was 17±4.54. The age-wise distribution of MMSE scores is shown in Table 5.

The relationship between Vitamin D levels and MMSE state is shown in Table 6.

A strong association was observed between Vitamin D and MMSE states of patients, which proved to be statistically significant (Figure 4). Patient with early dementia was mostly Vitamin D insufficient, while those with late dementia were mostly Vitamin D deficient. Only 5 (10%) of the demented patients were Vitamin D sufficient.

DISCUSSION

Vitamin D deficiency is common among older adults, partly because the skin's ability to synthesize Vitamin D from sunshine decreases with age, as well as low dietary intake of Vitamin D in demented individuals for socioeconomic reasons.

In this study, the mean age of the patients who have dementia was 57.78±14.48 years. In the previous studies analyzing the association of Vitamin D deficiency with dementia, the mean age of the study population varied from 73.6 years to 68.1 years.[24-26] In this regard, our study population was younger compared to other studies. However, this may partly be due to the inclusion of cases of dementia of other etiologies besides degenerative diseases.

In this study, 33 (66%) patients were male, while 17 (34%) were female. In most other studies, female patients outnumbered male patients.[24-26] This may be due to a lack of participation by women with cognitive impairment in our study.

Table 4: Vitamin D levels in different age groups of the study population

Vitamin D state	<50 years, n (%)	50–60 years, n (%)	60–70 years, n (%)	>70 years, n (%)	Total, n (%)
Deficient	13.42 ng/ml	13.82 ng/ml	13.32 ng/ml	15.11 ng/ml	13.86 ng/ml
Insufficient	9 (18)	3 (6)	7 (14)	5 (10)	24 (48)
Sufficient	5 (10)	8 (16)	3 (6)	5 (10)	21 (42)
Total	2 (4)	0 (0)	2 (4)	1 (2)	5 (10)

Table 5: MMSE scores in different age groups. P=0.483

Vitamin D state	Average MMSE	Mild CI	Severe CI	Total
		n (%)	n (%)	n (%)
<50 years	16.56	9 (18)	7 (14)	16 (32)
50–60 years	17	7 (14)	4 (8)	11 (22)
60–70 years	16.08	5 (10)	7 (14)	12 (24)
>70 years	18.64	8 (16)	3 (6)	11 (22)
Total		29	21	50

MMSE: Mini-Mental State Examination

Table 6: Correlation between MMSE states and Vitamin D levels (P<0.01)

Vitamin D state	Deficient	Insufficient	Sufficient	Total
	n (%)	n (%)	n (%)	n (%)
Early dementia	4 (8)	20 (40)	5 (10)	29 (58)
Late dementia	20 (40)	1 (2)	0 (0)	21 (42)
Total	24 (48)	21 (42)	5 (10)	50 (100)

MMSE: Mini-Mental State Examination

We observed a significant negative correlation between obesity (BMI) and Vitamin D deficiency. The possible explanation has been hypothesized in many ways. Low sun exposure due to reduced mobility in obese individuals, higher levels of 1α-hydroxylase in adipose cells resulting in greater local use of 25 (OH) Vitamin D in adipose tissue, greater storage of Vitamin D in adipose tissue, and the possibility of genetic predisposition have been provided for Vitamin D deficiency.[27,28]

Gender differences among obese individuals also influence Vitamin D deficiency state. In our study, male individuals had a greater deficiency and were more obese than females. In a Norwegian study, male obese individuals had higher levels of Vitamin D deficiency than women.[29]

The pattern and distribution of abdominal obesity can influence the association between the male gender and Vitamin D deficiency. For example, in another Egyptian study, men had higher visceral fat obesity indices and lower Vitamin D levels than women.[30]

Our study population's mean Vitamin D level was 13.86±5.00 ng/ml (normal >20 ng/ml). There was a significant difference in the Vitamin D levels between the cases and controls.

In some previous studies, the patients' mean Vitamin D level was lower than ours. For example, Annweiler et al., found a mean Vitamin D level of 14.1±0.5 ng/ml in their study population. Licher et al., and Feart et al., showed mean Vitamin D levels of 9.88 ng/ml and 14.32 ng/ml,

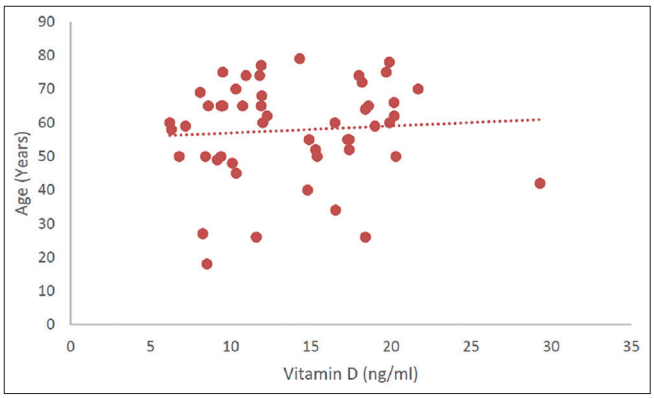

Figure 2: The correlation between age and Vitamin D: Pearson's correlation coefficient=0.072, P=0.620

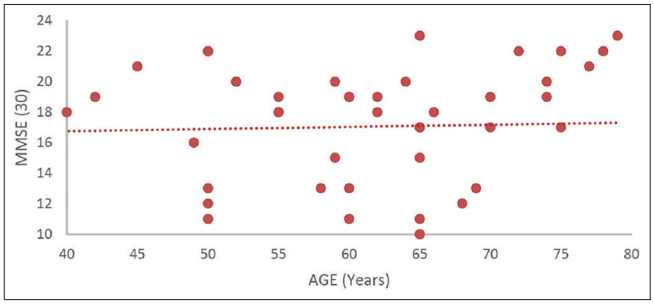

Figure 3: The correlation between age and Mini-Mental State Examination

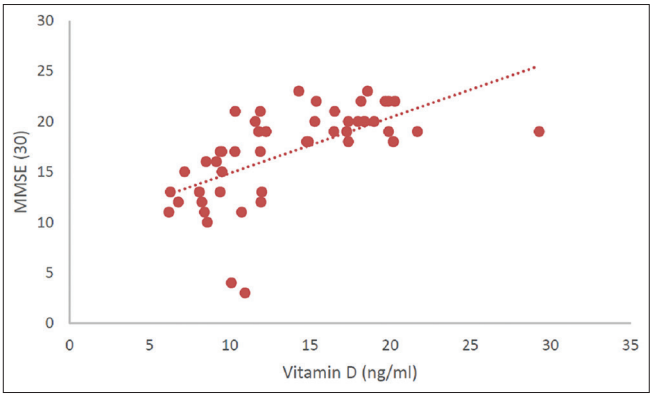

Figure 4: The correlation between Mini-Mental State Examination and Vitamin D: Pearson's correlation coefficient=0.615, P≤0.01

respectively.[31,32] However, in the study by Sakuma et al., on Japanese individuals, the mean Vitamin D level of the patients was 24.6 ng/ml.[26]

Hypovitaminosis D in demented individuals could partly be attributed to the high prevalence of Vitamin D deficiency in the Indian population.[33] On the other hand, some studies have postulated that the reported association between low Vitamin D levels and cognitive impairment can be reverse causation because of limited outdoor activities resulting in lesser sunlight exposure in subjects with dementia.[34]

In our study, 48% (n=24) of the individuals were Vitamin D deficient (Vit. D <12 ng/ml) while 42% (n=21) were Vitamin D insufficient (Vit. D 12–20 ng/ml). In the study by Sakuma et al., they showed that 29.1% of patients were Vitamin D deficient while 43.6% were Vitamin D insufficient.[26] Another study by Llewellyn et al., found that 69.9% of demented subjects had low Vitamin D levels, and the remaining 30.1% had normal Vitamin D levels.[35] Hence compared to other studies, our study documented a greater prevalence of Vitamin D insufficiency and deficiency in Indian patients.

The mean MMSE score of our patients was 17±4.54. It did not vary significantly between male and female individuals and among patients of different age groups. Sakuma et al., noted a mean MMSE score of 25.9±3.7 among the Japanese population.[26] Another study by Oudshoorn et al., showed an average MMSE score of 19.7±6.3 in their subjects.[36] Thus, the mean MMSE score of our study population was comparatively less than that observed in other studies.

Limitations of the study

1. Small sample size in our study
2. We have not accounted for genetic variants of the VDR gene, which is known to influence the blood's circulating 25 (OH) Vitamin D concentration
3. We did a single measurement of 25 (OH) Vitamin D, which has been shown to vary over time within individuals
4. Our study has not addressed the impact of seasonal changes on serum Vitamin D labels
5. Reverse causality cannot be completely excluded.

CONCLUSION

This study provides evidence of deficient and insufficient Vitamin D levels in most demented individuals compared to the control population, and this association is statistically significant. However, the association between Vitamin D deficiency and dementia is only observational. Therefore, double-blinded, placebo-controlled, and randomized trials of Vitamin D supplementation are necessary to establish a cause-effect relationship.

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