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Association of Cognition and Depression with Serum 25-Hydroxyvitamin D in Alzheimer's Disease

Abhishek Kumar[1,*], K S Anand[2], Mina Chandra[3],Jyoti Garg[4]
[1]Senior Resident, [2] Professor, [4] Associate Professor in Dept. of Neurology, [3] Associate Professor in Dept. of Psychiatry
**Corresponding Author: Dr Abhishek Kumar*

Abstract: ***Background:*** *Aim of the study was to investigate the association of cognition and depression with serum 25-Hydroxyvitamin D in Alzheimer's disease*
Material and Method*. A total 44 Alzheimer disease (AD) patients diagnosed by NINCDS-ADRDA criteria were recruited fulfilling inclusion and exclusion criteria. The 25-Hydroxyvitamin D levels were determined using Chemi-luminescent immunoassay (CLIA) method. Patients were divided into 2 subgroups: normal vitamin D (serum 25-hydroxyvitamin D ≥20 ng/mL) and deficient (serum 25-hydroxyvitamin D <20 ng/mL). Cognition was assessed by MMSE and CDR scale. Depressive symptoms were assessed using Cornell Scale for Depression in Dementia (CSDD). A total score of 12 or higher was considered to be indicative of clinical depression associated with dementia (DAD).*
Result: *The mean age was 63.14±8.43 years. The mean serum 25-OH Vitamin D was 19.21±14.37 ng/ml and vitamin D deficiency was encountered in 69.77% of AD patients. The mean MMSE and CDR scores were compared between vitamin D deficient (25-OH Vitamin D<20ng /ml) and AD patients who were Vitamin D sufficient (25-OH Vitamin D ≥20ng/ml). There was no statistical significant difference between MMSE scores (16.41±5.6 vs 16.46 ±4.52,p=0.489) and CDR scores (2.03±0.72vs 1.85±0.8). The mean 25-OH Vitamin D was found significantly low in AD patients with depressive symptoms (16.06±14.39 vs 24.98±14.36). Patients with Vitamin D deficiency had significantly higher Cornell scores (11.47±6.03vs 7.15±5.21).*
Conclusion: *Present study showed 2/3 patients with had deficiency of 25-OH Vitamin D. AD with depression showed significantly low vitamin D levels compared to those patients with AD without depression. There was no association between low serum 25-OH vitamin D and cognition*
Key words: *Alzheimer disease,25-Hydroxyvitamin D,MMSE , CDR,Cornell Scale ,Depression*

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I. Introduction

Alzheimer's disease (AD) is the most common form of dementia in the aging population. Currently 37 million people around the globe have dementia and the number is expected to double every 20 years [1, 2]. AD and AD related dementias (ADRD) are a global health problem[3]. AD is clinically characterized by progressive deficits of memory and other cognitive functions leading to complete incapacity and death within 3–9 years of diagnosis [4]. Pathological hallmarks of AD include histopathological changes induced by the extracellular deposition of amyloid β peptides forming senile plaques (SP) and intracellular neurofibrillary tangle (NFT) of hyperphosphorylated tau proteins in the brain [5].

In recent years, the associations between vitamin D and AD or dementia have attracted growing interests .[6-8.] First, accumulating studies indicate that vitamin D deficiency is prevalent in AD and dementia patients [9-10] and a meta-analysis study supported that AD patients possess lower level of 25-hydroxyvitamin D [25(OH)D] compared with age-matched healthy controls [11]. Second, low 25(OH) D level may be a potential risk factor of developing AD and dementia as supported by recent studies [12-13]. However, there is a lack of a comprehensive evaluation on whether vitamin D deficiency correlates with high risk of AD and dementia development, which has important implications for the prevention of these disorders. Several studies have inconsistently reported that lower levels of serum 25(OH) D are significantly associated with depression [14].

In the present study, we evaluated whether circulating 25(OH) D levels are associated with cognitive impairment and depressive symptom in AD.

II. Material And Method:

On approval from ethical committee in our cross sectional study 44 cases were recruited during the year Nov 2014 to April 2016 in neurology department at PGIMER, DR RML Hospital, and New Delhi.

Sample size calculation: Taking Prevalence of Vitamin D deficiency could be 57.5 %(Wilkin et al 2006) and Type α error could be 10% and power of study as 90%. The recommended size of sample could be 43**.**

Study selection: 43 Patient of Alzheimer disease (AD) will be recruited in my study after fulfilling inclusion and exclusion criteria. Study will be conducted on these patients presenting to us in either outpatient or in patient department of neurology, PGIMER, Dr. RML Hospital, New Delhi. These patients will be diagnosed by using criteria of National Institute of Neurologic and communicative Disorders and stroke and Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA). Written informed consent shall be taken from all the patients before inclusion in the study .All the patient with history of psychosis, alcohol or substance dependence other than nicotine, recent major stress (death in family, surgery), using calcium or vitamin D supplements were excluded from the study.

Clinical and Cognitive Assessments: The clinical evaluation included obtaining past medical, social, and family history from a reliable informant, usually a spouse or adult child. Information regarding possible cognitive change in comparison with previously obtained levels of function that was sufficient to interfere with accustomed activities was obtained by a clinician from semi structured interviews with the informant and separately with the participant.The interview with both the participant and informant were useful in assigning the CDR. The MMSE is an 11-item tool that assesses memory, orientation, attention, and visual-spatial function. The MMSE has a maximum score of 30, with a higher score indicating better performance. Each participant was assigned a CDR, which determined the presence or absence of dementia and, when present, rates its severity. Using the complete clinical evaluation, the clinician used the CDR to rate cognitive performance in each of 6 categories: memory, orientation, judgment and problem solving, community affairs, home management and hobbies, and personal care. A CDR of 0 indicated no dementia; a CDR of 0.5 indicated very mild dementia; and CDRs of 1, 2, and 3 indicated mild, moderate, and severe dementia, respectively. Patient with AD were categorized into mild (CDR score=1) and moderaate (CDR score=2)and severe group(CDR SCORE=3). Participants' depressive symptoms were assessed using Cornell Scale for Depression in Dementia (CSDD). A total score of 12 or higher is indicative of possible clinical depression. Laboratory and radiological investigations like complete blood count, serum 25-Hydroxyvitamin D level, serum vitamin B12 level, and thyroid function test, metabolic parameter (KFT, LFT, serum electrolyte), ELISA for HIV and CT/MRI Brain(whenever applicable) to rule out secondary dementia will be done.

Vitamin D Assessment: Serum was collected at the time of the clinical assessment. The 25-hydroxyvitamin D levels were determined using Chemi-luminescent immunoassay (CLIA) method.
Subjects were divided into 2 subgroups: normal vitamin D (serum 25-hydroxyvitamin D ≥20 ng/mL) and deficient (serum 25-hydroxyvitamin D <20 ng/mL). Vitamin D deficiency is defined as less than 20 ng/mL based on the laboratory reference range for the 25-hydroxyvitamin D assay utilized in this study.Cognition in those with normal vitamin D (serum 25- hydroxyvitamin D ≥20 ng/mL) compared to those with a deficient (serum 25-hydroxyvitamin D <20 ng/ml)

Statistical Methods: The quantitative variables are expressed as mean±SD and compared using unpaired t-test between groups. Qualitative variables are expressed as frequencies/percentages and compared using Chi-square/Fisher's exact test. Pearson's correlation coefficient is used to assess linear relationship between quantitative variables. A p-value <0.05 is considered statistically significant. SPSS version 16.0 software is used for statistical analysis.

III. Result

Patient characteristic:

A total of 43 subjects of Alzheimer's disease (AD) were recruited in the study. The mean age was 67.14±8.43 years. Most of the subjects (51.16%) belonged to 60-70 years of age group. Of these 65% of subjects were male. Present study revealed that most of the AD subjects were in mild (27.91%) and moderate (46.51%) stage (Table1). In the present study prevalence of DM and HTN was 13.95% and 30.23% respectively (Table1). The mean level of 25-OH vitamin D in the study group was 19.21±14.37 and vitamin D deficiency was encountered in 69.77% of AD subjects (Table-1). For cognition measures, MMSE score and CDR scores were used. The mean MMSE score was 16.43 ±5.23 points, the mean CDR Score was1.98±0.74 and mean Cornell Scale score was 10.16±6.07 (Table-1).

Table 1: Baseline characteristics of AD Patients

Characteristics	
Age,years,mean ± SD	67.14±8.43
Male,n(%)	28(65.12)
Hypertension,n(%)	13(30.23)
Diabetes mellitus,n(%)	6(13.95)
Serum 25-OH vitamin D level (ng/dl),mean±SD	19.21±14.37
Vitamin D deficiency(<20 ng/dl), n (%)	30(69.77)
Staging of AD(CDR)	
Mild AD	12(27.91)
Moderate AD	20(46.51)
Severe AD	11(25.58)
MMSE Score,mean±SD	16.43±5.23
CDR score,mean±SD	1.98±0.74
Cornell Scale score,mean±SD	10.16±6.07

Analysis was performed between vitamin D-deficient groups [25-OH Vitamin D<20 ng/ml] and vitamin-D-sufficient group [25-OH Vitamin D>20ng/ml]) and MMSE Scores, CDR Grading and Cornell Scores. There was no statistical significant difference between MMSE scores (16.41±5.6 vs. 16.46 ±4.52, p=0.489) and CDR scores (2.03±0.72vs 1.85±0.8, p=0.226). There was slight significant difference between the two groups on Cornell scale (11.47±6.03 vs. 7.15±5.21,p=0.015) vide Table-1, Figure-1, 2, 3.

Table 2: Comparison of cognitive & depression scale between 25-OH Vitamin D deficient and sufficient group

	Mean	±SD	Mean	± SD	P value
MMSE score	16.41	±5.6	16.46	±4.52	0.489
CDR score	2.03	±0.72	1.85	±0.8	0.226
CORNELL score	11.47	±6.03	7.15	±5.21	0.015

Figure-1: Comparison of MMSE Score between 25-OH Vitamin D deficient and sufficient group

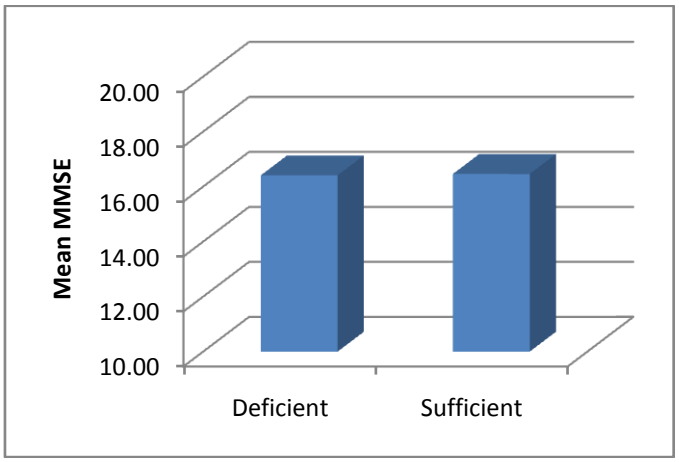


Figure-2: Comparison of CDR Score between 25-OH Vitamin D deficient and sufficient group

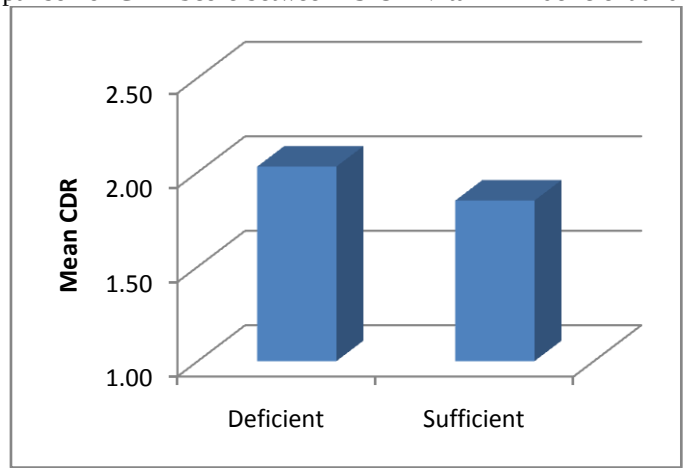
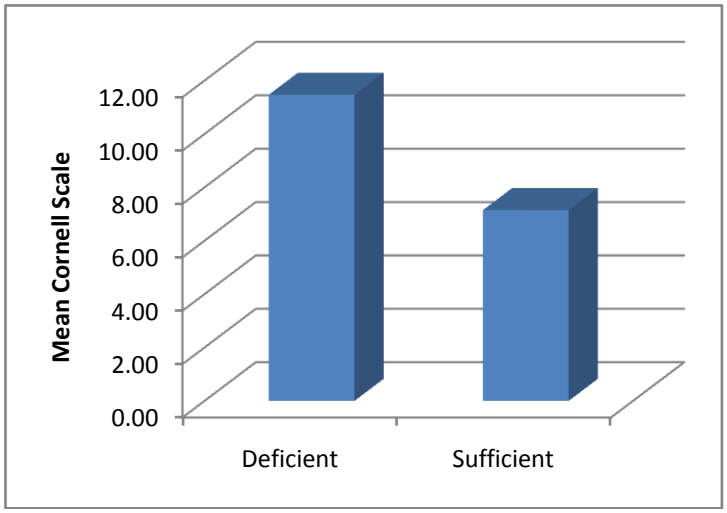


Figure-3: Comparison of Cornell Score between 25-OH Vitamin D deficient and sufficient group

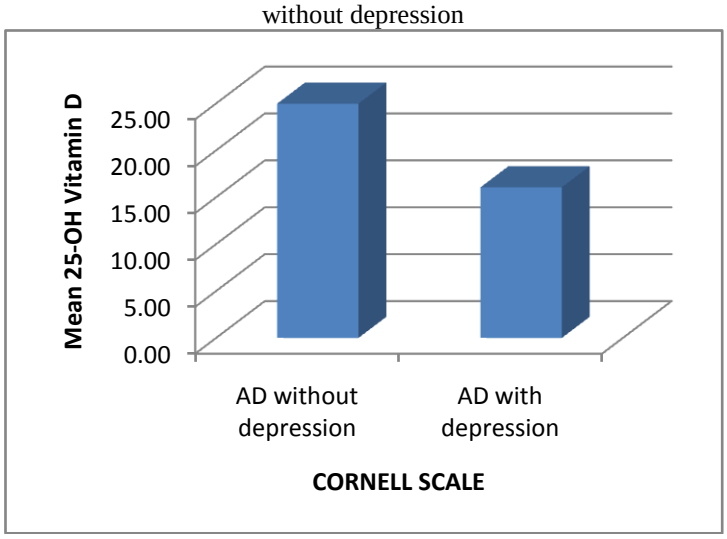


Comparison of mean 25-OH Vitamin D between two groups of patients with AD having depression (n=21) and AD patients without depression showed a significant difference between groups (p-value<0.05).Table 2, Fig 4

Table 2: comparison of mean 25-OH Vitamin D between two groups of patients with AD having depression and without depression

CORNELL SCALE	25-OH VITAMIN D (ng/ml)		p-value
	Mean	±SD	
AD without depression	24.98	14.36	0.001
AD with depression	16.06	14.39	

Fig 4: comparison of mean 25-OH Vitamin D between two groups of patients with AD having depression and without depression



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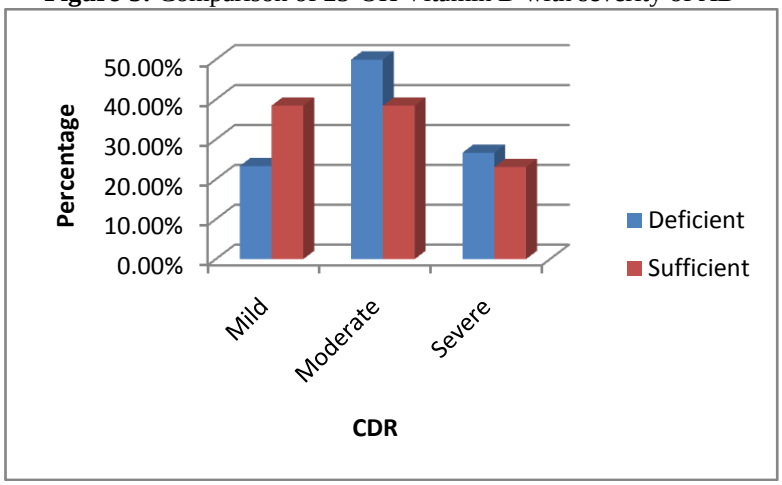
Comparison of 25-OH vitamin D with respect to CDR rating: After comparing mean CDR between Vitamin D deficient and sufficient group, no statistically significant difference between these two groups was observed. (2.03±72vs1.85±0.8, p=0.226). Table 3, Fig 5

Table 3: Comparison of 25-OH Vitamin D with severity of AD

CDR	Vitamin D deficient (<20 ng/ml)		Vitamin D Sufficient (>20ng/ml)		p-value
	n	%	n	%	
Mild AD	7	23.33%	5	38.46%	0.155
Moderate AD	15	50.00%	5	38.46%	0.243
Severe AD	8	26.67%	3	23.08%	0.402
Total	**30**	**100%**	**13**	**100%**	

Figure-5: Comparison of 25-OH Vitamin D with severity of AD



IV. Discussion

Vitamin D deficiency is widespread in Indian populations and is contributing to burden of disease in this region. It is surprising that in South Asia, 80% of the apparently healthy population is deficient in vitamin D[15].In this study the prevalence of vitamin D deficiency (less than 20 ng/ml) among AD patients was 69.77%. The mean vitamin D level in this study groups was 19.21±14.37 ng/ml. Skin complexion, poor sun exposure, vegetarian food habits and lower intake of vitamin D fortified foods could be attributed to the high prevalence of VDD in India[16].

In this study we found no significant association between cognition with serum 25-OH Vitamin D. For cognition measure we used MMSE and CDR. Analysis bycomparing mean MMSE scores between participants with 25(OH)D concentration <20ng/ml (vitamin-D-insufficient) to those with concentrations ≥20 ng/ml (vitamin-D-sufficient), showed no statistically significant difference (16.41±5.6vs16.46±4.5,p = 0.489).

By using CDR scale we divided all AD patient into mild (CDR=1), moderate (CDR=2), severe (CDR=3).There was no association between serum 25-OH Vitamin D with CDR (i.e. severity of Dementia). Analysis bycomparing mean CDR (severity of Dementia) between participants with vitamin-D-insufficient to those with vitamin-D-sufficient, present study showed no statistically significant difference (2.03±0.72vs1.85±0.8, p=0.226).

Though evidence suggests vitamin D may play a role in cognitive performance [17]; present study showed no statistically significant correlation between cognitive function tests and vitamin D level. This is in agreement with Jordeet al.[18], who didn't find a statistically significant correlation between the performance in several neuropsychological tests and serum levels of vitamin D. Barnard and Colon-Emeric[19] suggested that cognitive function measured by MMSE was not associated with 25 (OH) D levels.Manzo C et al studied the relationship between 25(OH)D and cognitive functions taking into account comorbidities and cognitive functions assessed by MMSE (Mini Mental State Examination), CDT (Clock Drawing Test) and CIRS (Cumulative Illness Rating Scale), in 132 consecutive elderly patients with low levels of 25(OH)D (<10 ng/ml) compatible with the condition of vitamin deficiency. They found no statistically difference among the levels of 25(OH)D and MMSE and CDT scores[20] . In a much larger cross-sectional investigation of NHANES III data, McGrath et al. found no association between 25(OH)D and cognitive function in adolescence (16–19y) and adults (20–59y), but revealed an inverse association between 25(OH)D and a test of learning and memory in older adults (60–90y) [21.] Breitling et al. also did not observe a significant association between low 25(OH)D levels and worse cognitive function at 5-year follow-up; however, this study lacked measures of baseline cognitive function.[22]

In contrast, many of the previous studies reporting significant associations between 25(OH) D levels and cognition and dementia. Przybelski RJ et al found the positive, significant correlation between serum 25(OH) D concentration and MMSE suggests a potential role for vitamin D in cognitive function [23].

In another study conducted by Oudshoorn C et al an association was found between MMSE test scores and serum 25-hydroxyvitamin D(3) levels, with a beta-coefficient of 0.05 (p = 0.01).They found that vitamin-D-sufficient patients had significantly higher MMSE scores as compared to vitamin-D-insufficient ones[24]. Wilkins et al.[25] found that vitamin D deficiency was associated with worse performance on the "Short Blessed Test" (SBT) and higher "Clinical Dementia Rating" (CDR) in the vitamin D-deficient group, and Rondanelli et al.[26], found a significant negative correlation between dietary intake of vitamin D and poor performance on cognitive tests. A meta-analysis by Etgen et al. highlighted an increased risk of cognitive impairment in patients with vitamin D deficiency [27]. Balion et al. compared mean MMSE scores with levels of 25(OH)D, where he showed a higher average MMSE score in those participants with higher 25(OH)D concentrations [28]. In another cross sectional study conducted by Consuelo H et al [29]found that participants with vitamin D deficiency had worse performance on the MMSE and SBT and they had higher CDR scores.

Controversy still exists regarding which domains of cognition are influenced more by vitamin D. Buell et al found that low 25(OH)D levels were associated with worse scores in executive functioning, attention, and processing speed, but not in memory in a cohort of older patients receiving home health services.[30] Similarly, analyses from the NHANES III study also concluded that attention was affected, while memory appeared to not be adversely affected by vitamin D deficiency.[31] Prospectively, Slinin et al did not find an association with low vitamin D levels and a decline in executive functioning over time, as measured by TMT-B.[32]Llewellyn et al found an association with cognitive decline over time in global cognitive function, as assessed by the MMSE, and executive function as assessed by TMT-B, but not processing speed, as assessed by TMT-A.[33]

In our study we did not conduct an extensive battery of cognitive tests; thus, we were unable to examine potential associations between 25(OH)D levels and different cognitive domains.

Depression is one of the most frequent non-cognitive symptoms in Alzheimer's disease [34].The prevalence of depressive symptoms and syndromal depression in AD depends on the severity of dementia and on the scales used for their detection[35]. In most studies a prevalence of 20–30% is reported, ranging between 0 and 87% [36]. Our study showed prevalence of 70% in AD patients.

The present study has also investigated association of serum levels of 25(OH) D with depressive symptoms in patients with AD. This study showed partial association between serum 25(OH) D and depressive symptoms as reported by CSDD score above 12. The mean CSDD score are higher in vitamin D insufficient group (11.47±6.03vs7.15±5.21, p=.015).The 25-OH Vitamin D was found significant low in participant with depressive symptoms.

There are many studies indicating associations between the two variables. Milaneschi et al. in a large cohort study on population aged 18–65 years indicated that low levels of 25(OH) D were associated to presence and severity of the depressive disorders .Milaneschi et al. in a population-based cohort study on older persons suggested that hypovitaminosis D is a risk factor for development of depressive symptoms [37] .Jaddou et al. in a national population-based household sample of 4,002 Jordanian participants, aged ≥25 years, demonstrated a significant association between depression and serum 25-OH Vitamin D level.[38]

However there are many study which showed no association between 25(OH) D and depression. Pan et al. in a population-based study on 3262 community residents, aged 50–70, found that depressive symptoms were not associated with 25(OH) D concentrations in middle-aged and elderly Chinese [39]. Zhao et al. in a survey on 3916 participants aged ≥ 20 years could not determine any associations between serum concentrations of 25(OH) D and any rating of depression[40].

The absence of correlation between vitamin D level and the performance in cognitive function tests in spite of high prevalence of vitamin D deficiency in this study could be attributed to the choice of cognitive tests as the cognitive tests chosen in this study, they may not reveal cognitive domains affected in vitamin D deficiency.

Vitamin D insufficiency and deficiency are more prevalent among older individuals[2], as are cognitive impairment and dementia [29]. Therefore if 25(OH)D and cognition are both assessed in older individuals, it is possible that an association seen between 25(OH)D levels and cognition and dementia means that low 25(OH)D is a marker of poor health rather than a causative factor in dementia pathogenesis. This is supported by studies showing that persons who are institutionalized due to poor physical health or dementia have less sun exposure, and therefore these persons are more likely to have lower concentrations of 25(OH) D than their healthier counterparts [18.]

V. Conclusion And Recommendation

In our study we found no association between 25-OH vitamin D and cognition, however there was partially association between 25-OH vitamin D and Depression. Further prospective studies with a long follow-up period and with more elaborate data on cognitive function and cognitive test performance are needed to specify the possible contribution of vitamin D deficiency to the onset and course of cognitive decline and AD.

Quite apart from the consideration that vitamin D metabolites may have specific neuroprotective effects, the need to identify and treat comorbid conditions in AD patients remains unchanged.

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