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Higher Serum Vitamin D_3 Levels Are Associated with Better Cognitive Test Performance in Patients with Alzheimer's Disease

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Key Words
Vitamin D_3 · Vitamin B_1 · Vitamin B_6 · Vitamin B_{12} · Cognition · Alzheimer's disease · Mini-Mental State Examination

Abstract
Background/Aims: Recent studies suggest that vitamin D metabolites may be important for preserving cognitive function via specific neuroprotective effects. No large studies have examined the association between vitamin D status and cognition. ***Methods:*** In this cross-sectional study, we analyzed the serum 25-hydroxyvitamin D_3 levels and Mini-Mental State Examination (MMSE) test scores of 225 older outpatients who were diagnosed as having probable Alzheimer's disease (AD). In addition to the 25-hydroxyvitamin D_3 levels, we analyzed the serum vitamin B_1, B_6 and B_{12} levels. ***Results:*** An association was found between MMSE test scores and serum 25-hydroxyvitamin D_3 levels, with a β-coefficient of 0.05 ($p = 0.01$). Vitamin-D-sufficient patients had significantly higher MMSE scores as compared to vitamin-D-insufficient ones. No association was found with the other serum vitamin levels. ***Conclusions:*** These data support the idea that a relationship exists between vitamin D status and cognition in patients with probable AD. However, given the cross-sectional design of this study, no causality can be concluded. Further prospective studies are needed to specify the contribution of vitamin D status to the onset and course of cognitive decline and AD.

Introduction

Dementia is associated with a higher rate of comorbidity, poor functional status and increased mortality [1–3]. The emotional and financial burden of dementia and Alzheimer's disease (AD) on society will increase in the next decades [4]. The clinical assessment of dementia in specialized centers, such as memory clinics, has led to earlier diagnosis and has stimulated the search for potential therapeutic agents and preventative strategies [5]. The American Academy of Neurology recommends screening for vitamin B_{12} deficiency and hypothyroidism in patients with dementia [6]. In the Dutch consensus, screening for folate and vitamin B_1, B_6 and B_{12} deficiency is recommended [7].

Recent insights suggest that vitamin D, mostly known for its effects on calcium and bone metabolism, may have neuroprotective functions and could be important for preserving cognitive functions via several different mechanisms [8].

Vitamin D is a secosteroid hormone. The term vitamin D refers to the inert precursors vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). The precursors are either formed in the skin after exposure to sunlight or derived from dietary sources. In the liver, the precursors are converted to 25-hydroxyvitamin D_3 [25-(OH)D_3]. In the kidney, 25-(OH)D_3 is hydroxylated to 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], the most active vitamin D metabolite [9]. The serum 25-(OH)D_3 levels are gener-

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ally used to determine the vitamin D status of an individual. Serum 25-(OH)D_3 levels of >50 nmol/l are generally defined as sufficient, although recent reports suggest that a serum 25-(OH)D_3 level >75 nmol/l may be preferable for optimal health [10].

The vitamin D metabolites exert their effects via the vitamin D receptor (VDR). Recently, it has been shown that neurons also express the VDR, which makes them a potential target tissue for vitamin D metabolites [11]. The VDR is abundantly expressed in regions frequently affected in AD such as the hypothalamus, substantia nigra, cortex and hippocampus. The importance of a sufficient vitamin D status for cognitive functioning in humans is not known. A recent study reported an association between serum 25-(OH)D_3 levels and cognitive functioning in a relatively small cohort of patients referred to a memory clinic [12].

Because of these new insights, we examined the relationship between vitamin D status and cognitive function in a cohort of older patients with probable AD in our memory clinic. We also analyzed the serum levels of vitamin B_1, B_6 and B_{12}, as screening for deficiencies in these vitamins is recommended in the clinical guidelines for the assessment of dementia.

Methods

Patients

We included 962 consecutive patients who were referred to the geriatric outpatient clinic of the Erasmus University Medical Center. The patients were referred for a variety of reasons and underwent a comprehensive geriatric assessment, including history and informant history, medication history, and physical and neurological examination [13]. They were asked to complete the Dutch version of the Mini-Mental State Examination (MMSE), with scores ranging from 0 points (poor cognitive functioning) to 30 points (good cognitive functioning) [14]. A consensus diagnosis of probable AD was obtained for 350 patients by a multidisciplinary memory clinic team including 2 geriatricians, a neurologist, a neuropsychologist and a psychiatrist [15]. Seventy-seven percent also underwent a neuropsychological examination. After exclusion of patients taking any vitamin suppletion at the time of investigation, serum vitamin B_1, B_6, B_{12} and 25-(OH)D_3 levels were available for 225 out of 350 patients.

The study was approved by the medical ethics committee of the Erasmus University Medical Center. Oral informed consent was obtained from the patients and their main caregiver.

Dementia Diagnosis

The diagnosis of dementia was verified according to a standard protocol. Dementia was diagnosed with reference to the American Psychiatric Association's criteria (DSM-IV) [16]. The subdiagnosis of probable AD was based on the criteria of the NINCDS-ADRDA work group [17].

Possible Cofactors

The serum 25-(OH)D_3 level strongly depends on sunlight exposure and therefore data were collected on action radius and mobility as indicators for exposure to sunlight. The action radius was classified as going outside, being housebound or lying in bed >20 h per day. For scoring mobility we used a standardized mobility scale assessing independence in walking, standing, transfers in and out of bed/chair, and wheelchair use. The score for each of these items ranged from 0 points (complete independence) to 3 or 4 points (complete dependence), with a maximum score of 14 points [18]. The total years of education were scored because both cognitive test performance and serum 25-(OH)D_3 level are influenced by educational background [19].

Blood Parameters

Blood samples were collected on the first visit to the outpatient clinic. The serum 25-(OH)D_3 levels were measured using a radioimmunoassay (DiaSorin). The serum vitamin B_1 and B_6 levels were determined by high-performance liquid chromatography according to internal protocols of the clinical laboratory of the Erasmus University Medical Center. The serum vitamin B_{12} levels were measured using a competitive protein-binding assay according to internal protocols of the clinical laboratory of the Erasmus University Medical Center. All assessments were performed at the Erasmus University Medical Center.

Statistical Analysis

The association between serum vitamin levels [25-(OH)D_3, vitamin B_1, B_6 and B_{12}] and MMSE score (dependent variable) was investigated by linear regression. To adjust for possible confounders, the models were adjusted for biologically plausible cofactors. These cofactors were age, gender, total mobility score, action radius, years of education and the vitamin levels not under investigation. They were added to the model one by one as linear covariables. Furthermore, the mean MMSE scores were compared between vitamin-D-insufficient and vitamin-D-replete patients. The cutoff point for defining vitamin D deficiency was set at a serum 25-(OH)D_3 level <50 nmol/l [20]. SPSS version 12.0 was used for statistical analysis (SPSS Inc., Chicago Ill., USA).

Results

The characteristics of the population are shown in table 1. The mean MMSE score was 19.7 ± 6.3 points and the mean serum 25-(OH)D_3 level was 45.4 ± 22.8 nmol/l. In this cohort 141 out of 225 individuals (63%) had a serum 25-(OH)D_3 level <50 nmol/l and 197 out of 225 (88%) had serum 25-(OH)D_3 levels <75 nmol/l. The results of the regression analysis studying the association between serum 25-(OH)D_3 levels and MMSE scores are shown in table 2. A positive association between serum 25-(OH)D_3 levels and MMSE score was observed with a β-coefficient of 0.08 ($p < 0.001$). This finding remained significant after adjustment for possible confounders ($\beta = 0.05$; $p = 0.01$). The mean MMSE score in vitamin-

Table 1. Characteristics of study population (n = 225)

Characteristics	Mean ± SD	Range
Age, years	77.6 ± 7.3	60–94
Female gender	147 (65%)	–
MMSE score, points	19.7 ± 6.3	1–30
Mobility score, points	1.3 ± 2.8	0–14
Education, years	8.8 ± 3.1	3–20
Serum 25-(OH)D_3, nmol/l (normal range: >50)	45.4 ± 22.8	5–106
Serum vitamin B_1, nmol/l (normal range: 70–140)	105.1 ± 26.3	47–167
Serum vitamin B_6, nmol/l (normal range: 46–126)	63.3 ± 44.5	26–151
Serum vitamin B_{12}, pmol/l (normal range: 145–637)	304.5 ± 137.7	60–755

SD = Standard deviation.

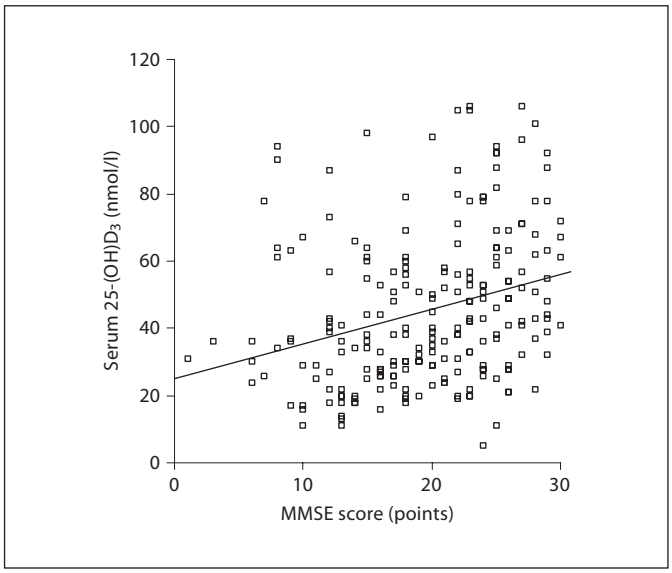

Fig. 1. Scatter plot of the MMSE score versus serum 25-(OH)D_3 level.

Table 2. Linear regression β-coefficients describing the association between MMSE score (dependent variable) and serum vitamin levels

AD subgroup (n = 225)	Unadjusted β-coefficient	p value	Adjusted β-coefficient	p value
Serum 25-(OH)D_3	0.08	<0.001	0.05	0.01
Serum vitamin B_1	0.03	0.1	0.02	0.3
Serum vitamin B_6	0.003	0.8	0.005	0.6
Serum vitamin B_{12}	–0.001	0.9	–0.002	0.5

Adjusted: age, sex, mobility score, action radius, total years of education and serum vitamin levels not under investigation.

D-deficient patients [25-(OH)D_3 <50 nmol/l] was 18.5 ± 6.0 points and that in vitamin-D-replete patients was 21.5 ± 6.1 points (p = 0.003). Figure 1 shows a scatter plot of the MMSE score versus serum 25-(OH)D_3 level.

Both in the adjusted and unadjusted models no significant associations were observed between serum vitamin B_1, B_6 and B_{12} levels and MMSE score (table 2).

Discussion

In the present study, performed in a geriatric outpatient population, we tested the hypothesis that the serum 25-(OH)D_3 levels are related to the level of cognitive functioning in patients with probable AD. We found an association between MMSE scores and serum 25-(OH)D_3 levels. No link was observed between MMSE scores and serum vitamin B_1, B_6 or B_{12} levels. This may be due to the fact that the mean serum vitamin B_1, B_6 and B_{12} levels were within the normal range.

The high prevalence of vitamin D deficiency in our patients is in accordance with other reports both from the Netherlands and abroad [21, 22].

Our study is, to the best of our knowledge, the largest to date examining the association between serum 25-(OH)D_3 level and cognition in a cohort of older AD patients. The results are in line with a previous study on the association between serum 25-(OH)D_3 levels and cognitive functioning [12].

Given the cross-sectional design of this study, the association between vitamin D status and MMSE scores can be interpreted in several ways. First, vitamin D deficiency may lead to a gradual decline in cognitive functions. Data, mostly from ex vivo and animal studies, suggest that vitamin D metabolites may have protective effects on neurons or neurotransmitter pathways which could benefit cognition. It has been proposed that vitamin D metabolites exert their protective effects on the central nervous system by stimulating the production of neurotrophins or by inhibiting the production of inducible nitric oxide [8]. A positive effect of 1,25-$(OH)_2D_3$ on the acetylcholine pathway has also been reported [23]. Recent studies suggest that 1,25-$(OH)_2D_3$ may also de-

crease the production of proinflammatory cytokines like tumor necrosis factor α. Tumor necrosis factor α is thought to play a pathogenic role in neurodegenerative disorders, such as AD and Parkinson's disease [24, 25].

Conversely, cognitive decline may cause vitamin D deficiency. It has been shown that AD can lead to malnutrition, which in turn could contribute to the development of vitamin D deficiency [26]. In addition, exposure to sunlight might decrease due to behavioral problems in AD, such as apathy and inertia, leading to more time being spent indoors [27].

A reduction in VDR expression in different layers of the hippocampus in patients with AD has been reported [28]. The hippocampus is the most typical part of the brain involved in AD. The regulators of VDR expression in the central nervous system are still largely unknown. In other cell types such as muscle cells, a decreased expression of the VDR, independent of serum vitamin D level, has been described with aging [29]. However, contradictory results, which question the role of vitamin D metabolites in the preservation of cognitive function, come from a recent animal study that showed muscular and motor impairments, but no impairments in cognition, in VDR knockout mice compared to wild-type mice [30].

Our study has some limitations. First, because of the cross-sectional design, no causality can be concluded. However, it seems worthwhile to gain more insight into the association between vitamin D deficiency and cognitive impairment, as supplementation of vitamin D might be an inexpensive and safe intervention [31].

Second, the MMSE is a crude measure of cognitive functions and fluctuations in cognition could have been missed [32]. However, AD diagnosis in our patients was verified by neuropsychological testing and based on a thorough multidisciplinary diagnostic process.

In view of the high prevalence of vitamin D deficiency in our rather mobile outpatients, our study supports the recommendations for preventative vitamin D supplementation in older people at risk [22].

In conclusion, the results of the present study suggest that an association exists between vitamin D status and cognitive functioning in AD. 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. In the meantime, we should continue to recognize that vitamin D deficiency is prevalent in older persons. 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 [33].

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