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Vitamin D

Is vitamin D important for preserving cognition? A positive correlation of serum 25-hydroxyvitamin D concentration with cognitive function

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Abstract

This study investigates the association of vitamin D status with cognitive function and discusses potential mechanisms for such an effect. The relationship of vitamin B12 with cognition was also assessed. A retrospective review of older adults presenting to a university-affiliated clinic providing consultative assessments for memory problems was performed. Charts of all patients ($n = 80$) presenting for initial visits were reviewed to identify those who had serum 25-hydroxyvitamin D (25(OH)D), vitamin B12, and mini-mental state examination score (MMSE) all obtained on their first visit ($n = 32$). Correlation analyses between MMSE and 25(OH)D and vitamin B12 levels were performed. Serum 25(OH)D concentration and MMSE showed a ($p = 0.006$) positive correlation; no ($p = 0.875$) correlation was observed between serum B12 concentration and MMSE. In conclusion, the positive, significant correlation between serum 25(OH)D concentration and MMSE in these patients suggests a potential role for vitamin D in cognitive function of older adults.

Keywords: Vitamin D; Cognition; Dementia

Vitamin D deficiency has long been known to cause rickets and osteomalacia [1]. More recently, osteoporosis, [2,3] falls [4–6] and fracture [7] have been associated with vitamin D insufficiency. Additionally, epidemiologic observations have associated low vitamin D status with increased risk of non-musculoskeletal diseases such as cancer [8], diabetes [9] and multiple sclerosis [10]. Such non-classical effects of vitamin D are not surprising in that many tissues, including neurons, possess vitamin D receptors [11] and vitamin D gene expression has been demonstrated in neural tissues [12]. Moreover, since both 25-hydroxylase and 1α-hydroxylase are present in the central nervous system [13,14], it is plausible that local production of active vitamin D (1,25-dihydroxyvitamin D) is important for normal cognitive function.

While vitamin B12 deficiency has long been associated with cognitive impairment [15], there has been no evaluation of a potential association of vitamin D inadequacy and impaired cognition in humans. This clinical evaluation begins to explore the possibility of such an association by comparing the mini-mental state examination (MMSE,[1] a commonly utilized clinical tool to evaluate cognitive status) results of elderly patients with their serum 25-hydroxyvitamin D (25(OH)D) concentration at the time of cognitive testing. A possible correlation between their vitamin B12 level and MMSE score was also assessed to help explain a positive correlation, should one exist.

Methods

Patients

In this retrospective chart review, the clinic records of all patients presenting to a monthly community-based, university-affiliated consultative clinic (in existence July 2002 through May 2005) were reviewed. All

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[1] *Abbreviations used:* 25(OH)D, 25-hydroxyvitamin D; MMSE, mini-mental state examination score; VDR, vitamin D receptor; GDNF, glial cell line derived neurotropic factor; NT3, neurotrophin 3; iNOS, inducible nitric oxide synthetase.

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patients had been referred for the assessment of memory loss or behavioral problems related to cognitive impairment. In addition to memory testing, the patients received a general geriatric assessment by one physician (RP), resulting in acquisition of clinical chemistries to ascertain nutritional status. Only data from patients with measurements of serum 25(OH)D and vitamin B12 concentration obtained on the same day as MMSE testing were included in this report.

25(OH)D and vitamin B12 testing

Blood samples for 25(OH)D and vitamin B12 were acquired within six hours of cognitive testing. Serum 25(OH)D and B12 concentrations were determined in routine clinical manner. Specifically, 25(OH)D was measured at an accredited regional laboratory using the DiaSorin (Stillwater, MN) RIA method. The vitamin B12 determinations were performed using chemiluminescence methodology on a Beckman Coulter (Fullerton, CA) Access® system at the hospital supporting the clinic.

Mini-mental state examination (MMSE)

The MMSE [16] was administered by a psychologist or trained technician for all patients included in this analysis. This test was done before the clinical chemistry assessments; thus, the vitamin B12 and 25(OH)D levels were not known at the time of cognitive testing.

Ethical consideration

This study was reviewed and determined to be exempt from requirements for informed consent by the University of Wisconsin Health Sciences Human Subjects Committee.

Statistical analysis

Serum concentrations of 25(OH)D and B12 were correlated with MMSE values by linear regression using Statview software (Abacus Concepts, Cary, NC). Descriptive statistics (e.g., patient demographic data, MMSE, serum vitamin B12 and 25OHD) were also obtained using this software.

Results

Patient demographics

Eighty patients were assessed over the 34-month period at the consultative memory clinic. Forty patients had 25(OH)D and 54 had vitamin B12 concentrations assessed on the day of MMSE testing. Of the 78 patients in whom a MMSE score was obtained, 32 also had both 25(OH)D and vitamin B12 levels assessed on the day of cognitive testing. In this cohort of 32 patients, 25 had a serum 25(OH)D less than 30 ng/ml and one patient had a serum B12 less than 200 pg/ml. The MMSE score (mean 19.2; maximum possible score = 30) indicates that substantial cognitive impairment was common in this population. Descriptive statistics of the patient cohort are presented in Table 1.

Relationship of 25(OH)D and B12 with MMSE

Serum 25(OH)D concentration and MMSE score showed a significant ($p = 0.006$) positive correlation (Fig. 1a). In contrast, no correlation ($p = 0.875$) was observed between serum B12 concentration and MMSE score (Fig. 1b).

Table 1
Patient data (32 patients)

Parameter	Mean (SEM)	Range
Age (years)	79.5 (1.6)	61–92
MMSE (# of 30)	19.2 (1.0)	9–30
25(OH)D (ng/ml)	21.6 (1.6)	7–44
Vitamin B12 (pg/ml)	530.5 (52.7)	167–1275

All data obtained at initial clinic visit.

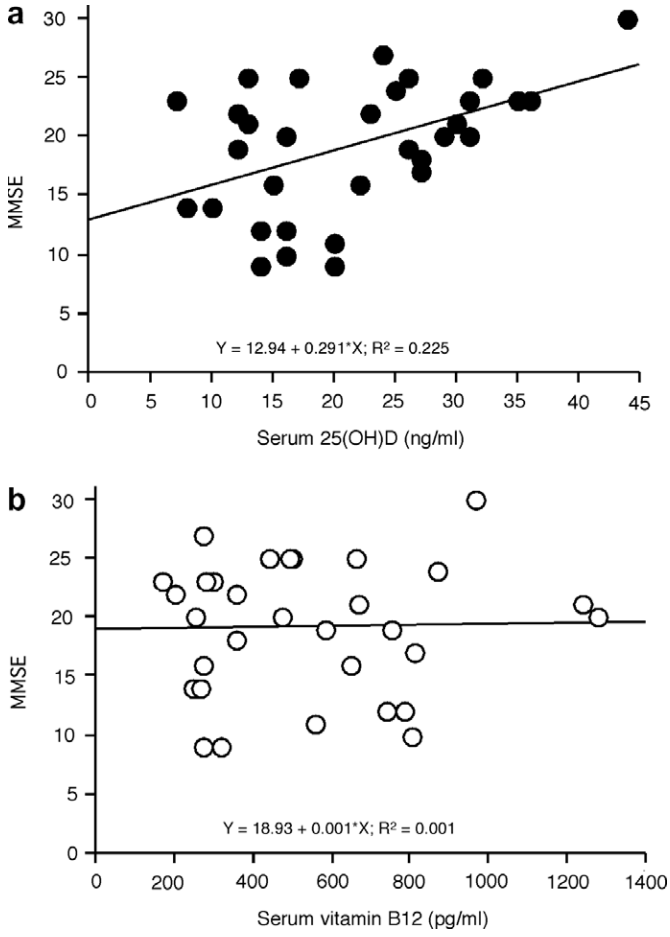

Fig. 1. (a and b) Relationship of Serum 25-hydroxyvitamin D [25(OH)D] and Vitamin B12 With mini-mental status exam (MMSE) Score. In this patient population, serum 25(OH)D is positively correlated ($p = 0.006$) with MMSE score (1a). However, serum B12 is unrelated ($p = .875$) to MMSE score (1b).

Discussion

This clinical observational report demonstrates a positive correlation between circulating 25(OH)D concentration and the MMSE test results of older adults presenting for memory assessment at a university-associated, community-based consultative clinic. Additionally, no similar correlation between serum B12 level and MMSE score is observed. Since all but one patient had adequate total vitamin B12 levels (≥200 pg/ml) [17], overall poor nutrition seems unlikely to be responsible for either the low 25(OH)D levels or reduced MMSE scores present in this

cohort of patients. Therefore, the positive, significant correlation between 25(OH)D concentration and MMSE score suggests the possibility that vitamin D may play a specific role in cognitive function of older adults.

Measurement of circulating 25(OH)D concentration is recognized as the best functional measure of vitamin D status [18]. Though the precise definition of vitamin D inadequacy remains controversial, it is increasingly accepted that a serum 25(OH)D concentration below 30 ng/ml is suboptimal [19]. Using this definition, most (78%) of the patients in this study had vitamin D inadequacy. This is consistent with multiple studies demonstrating a high prevalence of vitamin D insufficiency in older adults [20–22]. Given this widespread inadequacy, any potential impact on cognitive performance may have major importance.

We are aware of no large-scale, prospective randomized studies of the use of vitamin D supplementation to treat memory loss or associated neurodegenerative diseases. However, low vitamin D status has previously been reported in patients with Alzheimer's disease [23,24] and schizophrenia [25]. Moreover, that vitamin D may have effects in neurologic conditions has previously been evaluated in small clinical reports. For example, a pilot, randomized clinical trial found that vitamin D supplementation appeared to reduce the seizure incidence in epileptic patients, possibly by increasing serum calcium [26]. Additionally, treatment of brain tumor patients with the vitamin D analog, 1-α-hydroxycholecalciferol, was thought be associated with complete regression (a redifferentiation effect) of tumor in three of 11 patients (two with glioblastoma and one with astrocytoma) [27].

That vitamin D is important for normal neural function is supported by the presence of vitamin D_3 25-hydroxylase and 25-hydroxyvitamin D_3-1α-hydroxylase in brain tissue [14,28,29]. When combined with the observation that rat microglial cells in culture can produce 1,25-$(OH)_2D_3$ [30], and the finding of 1, 25 $(OH)_2D_3$ in human cerebrospinal fluid [31], it is plausible that the brain can locally produce this active form of vitamin D[11]. The 1,25-$(OH)_2D_3$ is thought to act on the vitamin D receptor (VDR) [32,33] found in the brain and spinal cord [34–36], with VDR gene expression having been observed in neuronal and glial cells [12,37–39]. The gene for the enzyme vitamin $D_3$25-hydroxylase is upregulated in glial cells exposed to 1,25-$(OH)_2D_3$ [13], suggesting that the 1,25-$(OH)_2D_3$ can also be degraded by brain tissue, as would be expected if vitamin D was important for normal brain function.

A beneficial effect of vitamin D for cognition potentially could be mediated through a number of mechanisms. A more direct effect might be by increasing acetylcholine concentration in the brain, as suggested by the finding that 1,25-$(OH)_2D_3$ treatment increases choline acetyltransferase activity in specific rat brain nuclei [40]. Another relatively direct effect could be through increased neurotrophin synthesis,[11] as suggested by findings that 1,25-$(OH)_2D_3$ stimulates synthesis of nerve growth factor [12,38,41,42], glial cell line derived neurotropic factor (GDNF) [43] and neurotrophin 3 (NT3) [44] in various non-clinical studies.

Enhanced neuroprotection by vitamin D, as demonstrated in several models of neurodegeneration, could also contribute to maintaining normal cognitive function. Vitamin D has shown neuroprotection against ischemic insult in a rat model of stroke, and the neuroprotective effect in that study correlated with increased GDNF levels.[45] Additionally, 1,25-$(OH)_2D_3$ has also been shown to attenuate the neurotoxicity of 6-hydroxydopamine exposure in rats [46], suggesting that vitamin D could be valuable in the prevention and/or treatment of neurodegenerative diseases [11]. It is plausible that such neuroprotection could be mediated through a reduction of free radicals in brain tissue. For example, inducible nitric oxide synthetase (iNOS) produces nitric oxide, that, in high concentrations, forms radicals that damage neurons and oligodendrogliocytes [47,48]. As 1,25-$(OH)_2D_3$ inhibits iNOS synthesis[49,50] it could serve to protect the brain from free radical induced damage. Moreover, protection against oxygen-derived free radicals might be conferred through an increase in glutathione levels via an upregulation of γ glutamyl transpeptidase, as seen in the brains of rats treated with 1,25-$(OH)_2D_3$ [51].

Vitamin D-enhanced calcium homeostasis also could protect against neurodegeneration and associated cognitive impairment. Down-regulation of L-type voltage-sensitive Ca^{2+} channels in hippocampal neurons has been observed in the presence of 1,25-$(OH)_2D_3$, correlating with the neuroprotective effect against excitotoxic insults [52]. Induction of neuroprotective calcium binding proteins could promote calcium homeostasis in the brain. This has been observed with the increase in parvalbumin in rat caudate putamen in response to vitamin D treatment.[53] Another vitamin D-associated cytosolic protein, calbindin-D (28k), also has been found to regulate intra-cellular calcium concentrations in neurons, and shows reduced levels in the hippocampal tissue of Alzheimers patients [54].

This retrospective chart review is limited in that it is a clinical observation of patients presenting to a memory assessment clinic. Clearly, an association between low vitamin D status and cognitive impairment does not establish that vitamin D inadequacy causes cognitive deterioration. However, if vitamin D inadequacy does constitute a heretofore-unappreciated contributor to cognitive decline, simple supplementation to assure adequate circulating levels of this vitamin could potentially benefit many patients presenting with memory loss. Furthermore, if vitamin D supplementation is found to be of benefit for Alzheimer disease and/or other neurodegenerative disorders, it raises the possibility that this approach could be an inexpensive, safe modality to be utilized in the prevention of these processes. Additional investigation of this clinical observation, particularly with intervention studies, is clearly warranted.

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Author contributions

Dr. Przybelski participated in the study concept and design, acquisition of data, analysis and interpretation of data, and preparation of manuscript.

Dr. Binkley participated in the study concept and design, analysis and interpretation of data, and preparation of manuscript.

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