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REVIEW ARTICLE

Vitamin D and neurocognitive disorder due to Alzheimer's disease: A review of the literature

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BACKGROUND: According to the Alzheimer's Disease 2014 Facts and Figures report,[1] an estimated 5 million older Americans are living with Alzheimer's disease (AD). AD is the sixth leading cause of death in the United States and the only 1 among the top 10 that cannot be prevented, cured, or even slowed. Predictably, AD puts an enormous cost burden on the U.S. health care system, with costs expected to soar to $1.2 trillion in 2050. Many individuals with minor cognitive impairment do not seek treatment and/or delay treatment until perceptible deficits indicative of moderate stage of disease are present. Several new drugs for AD are under development based on etiological disease theories, but their long-term impact on cognition and/or function is unclear. One potential treatment is to address low serum 25-hydroxy vitamin D (25[OH]D).

METHODS: We performed a literature review on the topic of low vitamin D levels and cognition in geriatric patients.

RESULTS: Recent studies have associated low vitamin D levels with cognitive complaints, impairment, and AD in geriatric patients; however, there is a dearth of prospective studies on the topic.

CONCLUSIONS: Available data suggest that more research is needed to promote a better understanding of vitamin D levels and incident AD.

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INTRODUCTION

According to the Alzheimer's Disease 2014 Facts and Figures report,[1] 1 in 9 people age ≥65—an estimated 5 million Americans—are living with Alzheimer's disease (AD). Classified in DSM-5 as "neurocognitive disorder due to Alzheimer's disease," AD is the sixth leading cause of death in

the United States and the only 1 among the top 10 that cannot be prevented, cured, or slowed. Predictably, AD puts an enormous cost burden on the already strained U.S. health care system. The direct costs of caring for those with AD or other dementias in the United States are estimated to be $214 billion in 2014, of which 70% are costs to Medicare and Medicaid. With the rising tide of older adults, and absent disease-modifying treatments, total direct costs are expected to soar to $1.2 trillion in 2050 (in 2014 dollars). Caregiver burden also is high, and climbing with the growth of the senior population. It is estimated that >15 million Americans provided unpaid care for persons with AD and other dementias in 2013, which is valued at $220.2 billion.[1]

Current treatments for AD include the acetylcholinesterase inhibitors, which help compensate for AD-associated decreases in brain cholinergic activity. Memantine, a noncompetitive, low-affinity, voltage-dependent modulator of glutamatergic *N*-methyl-D-aspartate receptors, also is available and is indicated for treatment of moderate to severe AD.[2] These drugs can provide short-term plateauing of symptoms in some patients and could offer important psychological and social benefits to patients and caregivers.[2] Nonetheless, they do not reverse the illness in a substantial or clinically relevant fashion. Complicating treatment is the stigma that historically has associated AD with "dementia"[3] and the fact that many individuals with minor cognitive impairment do not seek treatment. Therefore, by the time an individual has perceptible deficits, he or she may already be in the moderate stage of the disease.

Several new drugs are under development based on a variety of etiological theories of AD. Many have focused on the removal of amyloid β-peptide aggregates, which form the characteristic plaques seen in the brains of AD patients.[4] Although experimental therapeutics have been shown to clear amyloid β from the brain, it remains to be seen what long-term impact such clearance might have on cognition and/or function. Current thinking is that these agents should be used to treat patients at the earliest sign of impairment, in hopes that this approach will mitigate and perhaps even halt disease progression.[5] Given the length of trials that are underway and the necessary regulatory steps, new treatments are several years away at best.[6]

One potential addition to the physician's treatment armamentarium for neurocognitive disorder due to AD is to address low serum 25-hydroxy vitamin D (25[OH]D), hereinafter referred to as "low D." The physiologically active form of vitamin D is a fat-soluble steroid hormone that has been shown to play a role in a number of age-associated diseases.[7] Although several studies in recent years have associated low D with cognitive complaints and impairment in geriatric patients,[8-10] there is a dearth of prospective studies on the topic. This paper provides a brief review of some key literature to date, and will conclude with a call to action for research that can promote a better understanding of vitamin D levels and incident AD in geriatric patients.

Characterization and importance of vitamin D

Vitamin D refers to ≥1 members of a group of steroid molecules. Vitamin D3, or cholecalciferol, is the natural form that the body synthesizes from sunlight. It also is available in a limited number of foods. The flesh of fatty fish (eg, salmon, tuna, and mackerel) and fish liver oils are among the best natural sources, while lesser amounts are found in eggs, cheese, and fortified foods such as milk and cereals.[7] Vitamin D2, or ergocalciferol, is synthesized by irradiating plants and fungi. Neither calciferol has significant biological activity and must be metabolized within the body to the hormonally active form known as 1,25-dihydroxycholecalciferol, also known as calcitriol.[11] This transformation occurs in 2 steps: first within the liver and then within the kidney to yield the biologically active form.[8]

Vitamin D3 is more efficacious than D2 at raising serum 25(OH)D and generally is thought to be superior to D2 in terms of health benefits.[12] Foods may be fortified with either D2 or D3, but there is a trend away from the D2 form. The major biological function of vitamin D is to maintain normal blood levels of calcium and phosphorous. Its role in skeletal health is well-established. Deficiency is commonly defined as <50 nmol/L, although other cut-off points are used. Increasing consensus is that serum 25(OH)D levels should be 75 nmol/L for optimal health.[8] Despite this fact, U.S. population-based data from the 2000 to 2004 National Health and Nutrition Examination Survey (NHANES), a nationally representative cross-sectional study of the U.S. population, showed that approximately 25% of men and one-third of women had serum levels <50 nmol/L.[8]

Low D has been associated with several diseases, including cancer, heart disease, type 2 diabetes mellitus, stroke, and multiple sclerosis.[13-16] More recently, low D has been associated with increased odds of cognitive

dysfunction and AD in geriatric patients.[8] This association may be informed, at least in part, by recent research showing the presence of amyloid β, which characterizes AD and triggers neurodegeneration by dramatically suppressing vitamin D receptor expression. Administration of D3 to this model of amyloid β-associated neurodegeneration was shown to protect neurons by preventing cytotoxicity and apoptosis.[17] Other research has shown that the addition of vitamin D3 stimulates amyloid β clearance[18] and protects against glucocorticoid-induced apoptosis in hippocampal cells.[19] Although the clinical relevance of these findings is unknown, they strengthen the case for vitamin D as a neuroprotective agent that may play an important role in age-related neurodegeneration and cognitive decline. The following section will examine the mounting evidence in support of this assertion.

Associating low D with cognitive problems in geriatric patients

In a large, population-based study, Llewellyn et al[9] conducted a retrospective analysis of data from the NHANES III survey, to determine whether low D was associated with increased odds of cognitive impairment in geriatric patients (N = 3,325; age ≥65). Data obtained from NHANES III for analysis purposes included serum 25(OH)D concentrations and results from a series of 6 neuropsychological tests that measured orientation, immediate and delayed verbal memory, and attention. Standardized scores from each of the tests were summed to arrive at a global cognitive score for each individual, and cognitive impairment was defined as the lowest 10% of the distribution.

Using logistic regression models, the researchers divided the levels of serum 25(OH)D into clinically relevant groups to aid interpretation. Severely deficient was defined as <25 nmol/L, deficient as 25 to 49 nmol/L, insufficient as 50 to 74 nmol/L, and sufficient as ≥75 nmol/L. Only 37.5% of the sample was found to have sufficient levels of 25(OH)D; the remainder was considered insufficient (39%), deficient (21.8%), or severely deficient (1.8%). Those participants without sufficient levels of 25(OH)D were at increased risk of cognitive impairment, an association that remained significant after adjusting for a number of potential confounders. In the fully adjusted model, in fact, the severely deficient were approximately 4 times more likely to be cognitively impaired than the participants with sufficient D (odds ratios of 0.86, 1.52, and 3.94, respectively, for insufficient, deficient, and severely deficient groups).

Although the Llewellyn et al[9] analysis of composite cognitive data establishes a clear association between vitamin D deficiency and increased odds of overall cognitive impairment, it also showed that participants who were 25(OH)D insufficient were less likely to have impaired memory than those who were sufficient. This association was seen in another analysis of NHANES III data by McGrath et al,[20] who reported that older U.S. adults with the highest levels of serum 25(OH)D were more likely to be impaired on a single recall task designed to measure memory. In a cross-sectional investigation of elders receiving home health services in Boston, Buell et al[21] grouped elders (N = 1,080; age 65 to 99) by serum 25(OH)D levels as follows: deficient <10 ng/mL or <25 nmol/L; insufficient <20 ng/mL or <50 nmol/L; sufficient 20 to 30 ng/mL or 50 to 75 nmol/L; and optimal >30 ng/mL or ≥75 nmol/L. Insufficient or deficient levels of 25(OH)D were present in >47% and 18% of the participants, respectively. Moreover, circulating 25(OH)D was strongly associated with measures of complex cognitive tasks, such as planning, problem solving, or sequencing, as well as attention-processing speed. However, as in the Llewellyn et al[9] and McGrath et al[20] studies, memory was associated with sufficient D, a finding that underscores the need for more study, particularly with respect to the role of vitamin D in memory.

A study by Seamans et al[22] demonstrated that 25(OH)D deficiency, defined as <30 nmol/L, is relatively low among healthy, older Europeans (n = 387, age 55 to 87 years), but that insufficiency, defined as <50 nmol/L, is widespread. In addition, serum 25(OH)D concentrations of >80 nmol/L, considered optimal, were associated with significantly fewer errors in tests of spatial working memory, an executive function, particularly among women. This finding is in line with findings from the Buell et al[21] study. Taken together, the findings suggest that suboptimal vitamin D may impede executive functioning ability in geriatric patients.

Annweiler et al[10] have conducted extensive work in examining associations between low D and cognition. In one population-based study,[10] they examined non-drug dietary intake of vitamin D in 5,596 community-dwelling older women (mean age 80.5) who were participants in the Epidémiologie de l'Ostéoporose (EPIDOS) study in France. They found a significant association between low D intake (defined as <35 μ/week, or 400 IU/year)

and scores on the Pfeiffer Short Portable Mental State Questionnaire (SPMSQ), a measure of global cognitive performance, even after adjusting for sun exposure, education, chronic diseases, disability, and use of psychoactive drugs. In a separate, cross-sectional study, Annweiler et al[23] completed another analysis of 752 women from the EPIDOS study, and found a significant correlation between serum 25(OH)D deficiency (defined as <10 ng/mL or <25 nmol/L) and low SPMSQ scores. Notably, neither study specifically evaluated memory in the context of the SPMSQ scores. Finally, to examine the association between vitamin D status and mild cognitive impairment (MCI), they examined community dwellers without dementia but with subjective memory complaints (n = 95; mean age 71.1 years), divided them into groups according to diagnostic classification (MCI or cognitively healthy), and compared their levels of serum 25(OH)D. As expected, low 25(OH)D concentrations were associated with MCI in this group after controlling for multiple confounders.[24]

Low D as a cause of cognitive decline

Thus far, the evidence presented for a link between vitamin D and cognition in geriatric patients has been associational rather than causal. To date, there have only been 2 known pre-post studies on vitamin D supplementation and cognition in geriatric patients. The first, by Przybelski et al,[25] evaluated the safety and efficacy of high-dose oral vitamin D2 (ergocalciferol 50,000 IU, 3 times weekly for 4 weeks), administered in an unblinded manner to 25 nursing home residents (mean age 86.2) with low vitamin D status (ie, serum 25[OH]D ≤25 ng/mL, or 62.4 nmol/L). Participants with higher levels of vitamin D constituted a comparison group of 38 (mean age 87.4) who did not receive supplementation. It is notable that, at baseline, 27 (43%) of all study participants were receiving oral calcium and 29 (46%) were receiving oral vitamin D supplements. Of these patients, 85% (23 of 27) and 86% (25 of 29) were in the comparison group. In the treated group, mean total 25(OH)D concentrations increased from 17.3 ng/mL (~43.2 nmol/L) to 63.8 ng/mL (~159.2 nmol/L), although 25(OH) D3 concentrations declined. Przybelski et al[25] note that the decrease in 25(OH)D3 concentration (from 15.4 ng/mL or ~38.4 nmol/L to 9.1 ng/mL or 22.7 nmol/L) in the treatment group is consistent with earlier reports in which vitamin D2 administration leads to a reduction of 25(OH)D3. The mechanism of this reduction may be due to competition for available 25-hydroxylase activity; however, in-vivo regulation of vitamin D 25-hydroxylase in humans is not entirely understood. Both total 25(OH)D and 25(OH)D3 remained stable at approximately 87 nmol/L in the comparison group. Cognitive testing was performed on treated participants at baseline and following 4 weeks of supplementation, using the clock-drawing and semantic fluency tests. The researchers found no differences between the vitamin D2-treated and comparison groups on either measure. By comparison, Annweiler et al[26] conducted a longer pre-post study of vitamin D3 supplementation in 44 geriatric outpatients visiting a memory clinic; they did find cognitive improvement in treated participants, compared with controls. There was no difference between the treated and control groups at baseline in terms of cognitive scores and serum 25(OH)D concentration. Serum 25(OH)D levels in the D3-treated group increased from 42 nmol/L at baseline to 75 nmol/L at 16-month follow-up, but decreased in the control group over the course of the study (from 63 nmol/L at baseline to 48 nmol/L). Treated participants also had higher final scores on the Mini-Mental Status Examination (MMSE) and the Cognitive Assessment Battery. In particular, treated participants showed improvements in the Frontal Assessment Battery, a measure of executive function. The fact that these results conflict with those of Przybelski et al[25] could be caused by several factors, including different populations studied (nursing home vs memory clinic patients), study duration, form of supplementation (D3 as opposed to D2), and/or different underlying pathologies and cognitive measures used.

Three recent prospective studies suggest that there may be a causal relationship between vitamin D deficiency and cognitive decline. Llewellyn et al[27] examined the association between vitamin D status and cognitive decline among a cohort of 858 geriatric patients (mean age 71.6 to 77.5 years) enrolled in a prospective study conducted in Italy. Tests of cognitive function (MMSE, Trail-Making Tests A and B) were administered at baseline, after 3 years, and after 6 years. Participants who were severely 25(OH)D deficient (<25 nmol/L) at baseline declined by 0.3 MMSE points per year more than participants with sufficient D (≥75 nmol/L). This association remained significant after adjustment for a wide range of potential confounders and even when the analysis was restricted to participants who did not have dementia at baseline. On the other hand, Slinin

et al[28] followed a cohort of 1,604 men from geographically diverse American cities. They found little evidence of independent associations between low D and either baseline cognitive function or incident cognitive decline over several years based on either the Modified Mini-Mental State (3MS), a test of global cognitive function, or the Trails B test. The study showed an association between men in the lowest 25(OH)D quartile and incident cognitive decline by the 3MS. However, the magnitude of the association was attenuated by adjustment for several covariates, and the authors concluded that more large prospective studies are needed. The third prospective study was conducted by Annweiler et al,[29] who examined 40 high-functioning older women (mean age 78.4) from the aforementioned EPIDOS study in an effort to determine whether serum vitamin D at baseline could predict the onset of non-Alzheimer's dementia, using DSM-IV criteria. They found that vitamin D deficiency at baseline (defined as 25[OH]D <10 ng/mL, or <25 nmol/L) was associated with the onset of non-Alzheimer's dementia within 7 years.

Vitamin D and AD

Although a growing amount of research suggests an association and even a causal link between low D and cognitive decline, data specific to AD are few and far between. Annweiler et al[30] conducted a review of 10 carefully selected observational studies (9 case-controls and 1 longitudinal prospective cohort study) to examine the evidence linking low D to AD in adults. All of the studies reviewed examined serum 25(OH)D concentration as a continuous variable but used different methods to determine 25(OH)D concentrations. In each study, 25(OH)D levels among participants with AD were compared with those of cognitively normal controls. The 7 case control studies that were eligible for cross-sectional analysis produced a large effect size, indicating a higher prevalence of AD among participants with serum 25(OH)D <10 ng/mL (<25 nmol/L) compared with those with 25(OH)D >20 ng/mL (>50 nmol/L). The single prospective study failed to support this finding. The same group of researchers followed 498 community dwelling older women for 7 years, and found a highly significant association between their levels of vitamin D dietary intake and risk of AD.[31] Specifically, they found that baseline dietary intake of vitamin D was inversely associated with the onset of AD, and that the 98 women who were consistently in the highest quintile of vitamin D dietary intakes (range 77.72 to 205.54 μg/week; mean 104.38 μg/week) showed more than a 4-fold decreased incidence of AD at the end of the 7-year period. This study is important, because it is the first known study to use a prospective design to associate low D consumption with incident AD.

Another recent 2-phase study by Stein et al[32] used a prospective design to determine whether low D was associated with incident AD. The first phase consisted of a pre-post study in which 13 older patients with mild-to-moderate AD were given vitamin D2, 3,000 IU/d for 8 weeks. Similar to the Przybelski et al[25] findings, the associated increase in serum 25(OH)D was accompanied by a significant (in this case, 6 points) improvement in the group's mean Alzheimer's Disease Assessment Scale (ADAS)-cog score. The second phase consisted of a randomized control study in which 16 participants with AD received physiological doses (1,000 IU/d) of vitamin D2 for 8 weeks, while 16 additional participants received supraphysiological doses (7,000 IU/d) over the same period. The researchers examined their ADAS-cog and Wechsler Memory Scale scores at baseline and after 8 weeks and found no between-group differences regarding the change in scores. This result may have been influenced by the method of supplementation (D2 as opposed to D3), the short duration of follow up, or the fact that patients were grouped together for analysis purposes as opposed to being stratified by level of severity.

In conclusion, there is a burgeoning literature that associates low D with neurocognitive problems in geriatric patients. Despite the strides that have been made to better understand the link between vitamin D and cognition, research designed to examine whether vitamin D is preemptive of AD is still in its infancy. As Annweiler and Beauchet[33] assert, "At this stage, only clinical trials testing vitamin D supplements vs placebo can further determine the impact of vitamin D administration on cognition and AD with higher levels of evidence."

Next steps

Future prospective studies on the role of vitamin D in AD-associated neurocognitive disorder should heed the methodological inconsistencies of the studies conducted to date, in an attempt to standardize future research. It is notable that, although thresholds defining low D are similar across studies, methods of 25(OH)D measurement have not been standardized,

although this issue is currently being addressed.[34,35] Radioimmunoassay is the most commonly used assay, but other methods have been used and could contribute to the disparity in findings. It will be necessary for future studies to take this factor into account. Moreover, the effects of serum storage on measurements of 25(OH)D may have had an impact on past study outcomes and should be standardized in future studies. Finally, researchers should consider whether vitamin D supplementation will consist of vitamin D2 or D3, as the studies that have been conducted to date use both and each will produce different results in terms of raising 25(OH)D levels in a study population. Given that vitamin D3 is more efficacious than D2 at raising serum 25(OH)D and generally is thought to be superior to D2 in terms of health benefits,[12] it may be preferable to use vitamin D3 in future trials. Regardless of the form used, assessment of serum 25(OH)D levels is inherently problematic because it reflects endogenous exposure that varies throughout the year.[36] People living in northern or southern latitudes above or below 33°, for example, only receive sufficient radiation during certain months of the year and hours of the day.[8] Future research should take steps to minimize this variance and its potential to influence study results.

The appropriateness of the measures that past studies have used to assess cognitive function also merits further analysis and careful consideration in future prospective studies on the role of vitamin D in neurocognitive disorder due to AD. For example, results of some studies suggest that suboptimal vitamin D may impede executive functioning ability as opposed to memory in geriatric patients.[9,21] Accordingly, measures should be employed to examine, a priori, what aspect of cognitive function will be examined. Research designed to examine frontal lobe deficits such as impaired executive function and processing speed, as opposed to memory, will need measures specific to that end.

Among the studies cited in this review, there are inconsistencies in terms of inclusion/exclusion criteria that may have influenced the findings. The use of concomitant psychotropics or other potentially inappropriate medications among the study population, for example, may have contributed to cognitive decline. This begs the need for pharmacovigilance, both with respect to general pharmacologic treatment of older patients[37] and in the context of studies designed to assess the role of vitamin D on cognition in this population. Other individual factors will also need to be considered in future prospective research. For example, past studies have not consistently adjusted for other age-related disorders that have been associated with low D, such as stroke, diabetes, and hypertension—a factor that should be taken into account as more studies are conducted. Similarly, factors associated with lower vitamin D concentration such as skin pigmentation (a more pigmented skin, for the same sunlight exposure, results in less vitamin D production than whiter skin) and female sex need to be considered.[11] Prospective studies designed to administer supratherapeutic doses of vitamin D will need to monitor for vitamin D toxicity and hypercalcemia, its consequence. Although rare, research has shown that taking vitamin D, 50,000 IU/d, for several months has been shown to cause toxicity. This level is many times higher than the recommended dietary allowance for most adults of 600 IU/d.[38] Finally, studies should be designed to tease out the benefits of vitamin D as opposed to other potential supplements that are thought to be neuroprotective (eg, vitamin B12, thyroid-stimulating hormone, folate).

The relationship between vitamin D and amyloid β also requires further study, particularly given increasing evidence associating the 2. As previously mentioned, amyloid β has been shown to trigger neurodegeneration by dramatically suppressing vitamin D receptor expression.[17] On the other hand, the addition of vitamin D3 has been shown to stimulate amyloid β clearance[18] and protect against neuronal cell death,[19] which begs the question as to its potential role as a neuroprotective agent in AD. Prospective studies that examine the influence of vitamin D supplementation on cognition, and concurrently use positron emission topography to measure amyloid load, may help researchers to understand the relationship between the 2.

In summary, there is a need for more prospective studies that will elucidate the relationship between low D and incident neurocognitive disorder in AD. Such studies stand to help us understand whether vitamin D might serve as either a biomarker or a treatment option in managing this devastating illness. ■

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