

Hypothesis

Does Vitamin D Reduce the Risk of Dementia?

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Abstract. The understanding of the role of vitamin D in maintaining optimal health has advanced sharply in the past two decades. There is mounting evidence for beneficial roles for vitamin D in reducing the risk of bone diseases and fractures, many types of cancer, bacterial and viral infections, autoimmune diseases, and cardiovascular diseases. Recently, several reports have also been published regarding the role of vitamin D in neuroprotection. This article develops the hypothesis that vitamin D can reduce the risk of developing dementia, presenting the evidence from observational and laboratory studies. The observational evidence includes that low serum 25-hydroxyvitamin D [25(OH)D] has been associated with increased risk for cardiovascular diseases, diabetes mellitus, depression, dental caries, osteoporosis, and periodontal disease, all of which are either considered risk factors for dementia or have preceded incidence of dementia. The laboratory evidence includes several findings on the role of vitamin D in neuroprotection and reducing inflammation. Although this evidence is supportive, there do not appear to be observational studies of incidence of dementia with respect to prediagnostic serum 25(OH)D or vitamin D supplementation. Such studies now appear to be warranted.

Keywords: Alzheimer's disease, cardiovascular disease, cathelicidin, periodontal disease, tooth loss, ultraviolet-B, vitamin D, vascular dementia

INTRODUCTION

Dementia includes Alzheimer's disease (AD), vascular dementia (VaD), Lewy Body disease, and frontotemporal dementia [1]. Dementia is a significant disease among older residents of Western developed countries. AD affected approximately 2.4–3.0 million Americans in the early part of this century [2–5]. Because the fraction of those with dementia attributed solely to VaD in Western developed countries is about 0.3 [5], the total number of those with dementia in the United States then was about 3.4–4.3 million. As the number of elderly increases, the number with demen-

tia will increase. The number of those with dementia in developing countries is also increasing [6]. During the past decade, risk of dementia has been increasingly linked to diet [3,7–9], lifestyle [10], and vascular factors and metabolic diseases including diabetes mellitus, heart disease, and hypertension [11–16], as well as depression [17] and tooth loss [18,19].

There are differences in risks for AD and VaD. AD is linked to oxidative stress [20] and characterized by neurofibrillary tangles and amyloid- β plaques [21]. VaD is caused by single or multiple infarcts or other microvascular insults [1], although the pathology of VaD is complex [22]. The distinction between AD and VaD is somewhat blurred in that although AD is characterized by amyloid- β plaques and neurofibrillary tangles, vascular factors such as infarcts [21] and hypoperfusion [23] are also involved. Moreover, as many as 45% of those with dementia may have mixed dementia, or a

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combination of AD and VaD [24]. Interestingly, the AD amyloid hypothesis, now more than 20 years old [25] – although validated in proof-of-concept studies in pre-clinical animal models, and some are being tested in the clinic – have not been translated to therapeutic use to date [26,27].

During the past decade, the understanding of the roles of vitamin D for optimal health in reducing the risk of chronic and infectious diseases has advanced considerably. Originally, vitamin D was found to prevent rickets [28]; however, there is now strong evidence that vitamin D reduces the risk of many types of cancer [29], bacterial infections [30,31], and autoimmune diseases such as multiple sclerosis [32]. There is also observational evidence that vitamin D reduces the risk of dental caries [33], periodontal disease [34,35], hypertension [36,37], type 2 diabetes mellitus [38,39], viral infections [40], cardiovascular disease [41,42], coronary heart disease [43,44], and congestive heart failure [45]. There are also several good reviews on the health benefits of vitamin D [46–48].

Recently, two studies discussed the role of vitamin D in maintaining brain function. One examined evidence linking vitamin D deficiency to brain function/dysfunction [49]; the other explored the role of vitamin D in preventing neurocognitive dysfunction [50]. Taken together, many of these reports lay the groundwork for the hypothesis that vitamin D can reduce the risk of dementia.

Vitamin D is produced by ultraviolet-B (UVB) (280–315 nm) irradiance's photolyzing 7-dehydrocholesterol (provitamin D₃) in the epidermis to previtamin D₃. Previtamin D₃ undergoes a thermally-induced isomerization to vitamin D₃ that takes 2–3 days to reach completion [51]. In the liver, vitamin D₃ is given a hydroxyl radical and becomes 25-hydroxyvitamin D₃ [25(OH)D₃], the most common circulating metabolite of vitamin D. In the kidney and other organs, it is given a second hydroxyl radical and becomes 1,25-dihydroxyvitamin D [1,25(OH)₂D₃], the hormonal, or “active,” form of vitamin D₃ [52]. Also, 1,25(OH)₂D₃ induces production of human cathelicidin, LL-37, which has both antimicrobial and antiendotoxic effects [31].

This review marshals evidence for the hypothesis that low vitamin D is a risk factor for dementia either directly or indirectly through affecting risk factors for dementia.

RESULTS

Epidemiological findings regarding the noncalcemic benefits of vitamin D

Vitamin D has been found to be important in reducing the risk of many types of chronic and infectious diseases. Important for this study are diseases related to risk of dementia, such as vascular diseases, heart diseases, and dental diseases. Findings from the literature with respect to serum 25(OH)D, calcitriol, or hours of sunshine are presented in Table 1. The results are mostly from 2004–2008, an indication of how recent the findings are. All results are significant, with many of them highly significant. There may be null results, but such reports were not sought.

All these studies are strictly observational; there are as yet no randomized, controlled trials (RCTs) for any of these diseases. However, in most cases, mechanisms to explain the findings are known. Zittermann [45] reviewed the mechanisms whereby 1,25(OH)₂D reduces the risk of coronary heart disease. The effects include 1) protection against the deleterious effects of matrix metalloproteinases, inflammatory cytokines, and advanced glycation end products, as well as 2) beneficial effects on synthesis of matrix Gla protein, osteopontin, interleukin (IL) 10, and type IV collagen, both of which reduce the risk of vascular calcification. For hypertension, vitamin D regulates the renin–angiotensin system [55]. For diabetes, it is thought that vitamin D regulates plasma calcium levels, which regulate insulin synthesis and secretion, through a direct action on pancreatic β -cell function [56]. For dental caries and periodontal disease, the hypothesized mechanism is reduced risk of bacterial infection through production of human cathelicidin, LL-37 [31].

Risk factors for dementia

To determine the benefits of vitamin D in reducing the risk of dementia, one must know the risk factors. Dementia may involve several mechanisms, including oxidative stress [20], inflammation [57], small infarcts [23], advanced glycation end products [58–60], transition metal and aluminum ions from diet leading to oxidative stress [3,57,61], nitric oxide production [62], reduced neurogenesis in the adult brain [63], and embolism [64]. These mechanisms should be well known to the dementia research community and so will not be discussed further here.

Table 1
Vitamin D dose-disease response relations for metabolic and related diseases

| Disease and outcome | Results with respect to serum 25(OH)D level | Reference |
|---------------------------------------|---|-----------|
| Coronary heart disease, incidence | RR, 2.09 (95% CI, 1.24–3.54; $p_{\text{trend}} = 0.02$) <10 ng/mL vs. >30 ng/mL | [43] |
| Coronary heart disease, death | HR = 2.17 (95% CI, 1.58–2.99) <10 ng/mL; = 1.40 (1.03–1.91), >10 ng/mL but <20 ng/mL | [44] |
| Cardiovascular disease, incidence | HR = 1.80 (95% CI, 1.05–3.08) < 10 ng/mL vs. >15 ng/mL | [41] |
| Stroke, death | OR = 0.67 (0.46 to 0.97; $p = 0.032$) per Z value | [42] |
| Hypertensive disease, incidence | RR = 3.18 (95% CI, 1.39–7.29), < 15 ng/mL vs. >30 ng/mL | [36] |
| Peripheral artery disease, prevalence | PR = 1.35 (95% CI, 1.15–1.59) for each 10 ng/mL lower | [53] |
| Diabetes mellitus, prevalence | OR = 0.25 (95% CI, 0.11–0.60) for non-Hispanic whites for ≥ 32.4 ng/mL vs. ≤ 17.6 ng/mL | [54] |
| Diabetes mellitus, incidence | OR = 0.28 (95% CI, 0.10–0.81) for males, for >30 ng/mL vs. <10 ng/mL | [39] |
| Congestive heart failure, death | 0.51 (95% CI, 0.33–0.77) calcitriol >73 pmol/L vs. <43 pmol/L | [45] |
| Dental caries | PR = 0.60 for >3000 hours of sunshine/yr vs. <2200 hours for boys aged 12–14 yrs | [33] |
| Periodontal disease | AL = 0.39 mm (95% CI, 0.17–0.60 mm) for men >50 yrs for >34.2 ng/mL vs. <16.1 ng/mL | [34] |

Note: AL, attachment loss; CI, confidence interval; HR, hazard ratio; OR, odds ratio; PR, prevalence ratio; RR, risk ratio.

Table 2
Mechanisms whereby vitamin D metabolites protect the brain

| Factor | Mechanism | Reference |
|-------------------------------------|--|-----------|
| Vasculoprotection | | [45] |
| Advanced glycation end products | 1,25(OH) ₂ D blunts the impact on endothelial cells. | [65] |
| Neuronal protection | Ca ²⁺ regulation, stimulation of neurotrophin release, interaction with reactive oxygen and nitrogen species, and neuroimmunomodulatory effects of calcitriol | [66,67] |
| | Facilitates detoxification through inhibiting synthesis of inducible nitric oxide synthase and increased glutathione levels. | [68–70] |
| | Enhances neurotrophin synthesis. | [71] |
| | Enhances antioxidant pathways. | [68] |
| | Upregulates neurotrophin factors. | [72] |
| Neuron growth factor (NGF) | Induces production of NGF. | [73] |
| Neuronal calcium regulation | Protects against excess calcium entry into the brain. | [74] |
| Reduces inflammatory factors | Downregulates proinflammatory cytokines such as serum tumor necrosis factor α , IL-1, and IL-6. | [45,75] |
| | Reduces biomarkers of inflammation such as C-reactive protein. | [76] |
| | Attenuates neuroinflammatory age-related changes. | [77] |
| Thrombosis | Reduces risk of thrombosis. | [78] |
| Transition metal ion concentrations | By increasing calcium absorption, may decrease transition metal (copper, iron, zinc) ion levels. | [79] |

The roles of vitamin D in reducing the risk of these mechanisms are presented in Table 2. It appears that vitamin D metabolites, especially 1,25(OH)₂D₃, can counter many of the mechanisms linked to risk of dementia.

Other preexisting diseases

People often have more than one vitamin D-sensitive disease throughout their lives. There are many vitamin D-sensitive diseases, and low serum 25(OH)D levels can predispose people to several of them. Thus, examining correlations between diseases can be used as an indication of shared risk-modifying factors. For exam-

ple, those being treated for rheumatoid arthritis generally have a reduced risk of developing AD [80], possibly because they are using nonsteroidal anti-inflammatory drugs.

Osteoporosis: Osteoporosis and hip fractures are associated with reduced vitamin D and calcium over a period of many years [46]. A study of 46 Japanese with AD found that they had significantly reduced bone mass density and serum 25(OH)D levels [81]. The same researchers later found that those with reduced bone mass density had a higher rate of hip fracture [82]. However, because AD is probably a risk factor for falling, increased risk of hip fracture cannot be considered an independent risk factor.

Depression: Those with AD often have depressive symptoms [17,83–85]. Several studies have investigated the temporal relation between depressive symptoms and development of AD. A study of 2220 participants in the Cardiovascular Health Study Cognition Study with high cognitive function at baseline found that depressive symptoms at baseline were associated with increased risk of mild cognitive impairment (10.0%, 13.3%, and 19.7% for those with no, low, and moderate or high depressive symptoms, respectively). Vascular factors did not significantly affect these results [86]. Cognitive impairment is often a precursor to dementia [87]. A study in Rotterdam of 503 persons, 134 of whom reported a history of depression, concluded the following: “History of depression, and particularly an early onset, but not presence of depressive symptoms increased the risk for Alzheimer disease. This risk was not mediated by smaller hippocampal or amygdalar volumes.” [17] A study of 526 people without dementia at baseline concluded the following: “The prospective relation between depressive symptoms and AD is not explained by a history of vascular risk factors and stroke, suggesting that other mechanisms may account for this association.” [85].

To explore whether low vitamin D levels might explain the link between depression and risk of AD, I searched the literature for studies on vitamin D and risk of depression. In a study of 40 with mild AD and 40 nondemented persons, vitamin D deficiency was associated with presence of an active mood disorder (odds ratio, 11.69; 95% confidence interval (CI), 2.04–66.86; $p = 0.022$) [88]. Vitamin D deficiency was also correlated with worse performance on two of four tests of cognitive performance.

In a study of 1282 elderly community residents of The Netherlands, levels of 25(OH)D were 14% lower in 169 persons with minor depression and 14% lower in 26 persons with major depressive disorder than levels in 1087 control individuals ($p < 0.001$). Levels of parathyroid hormone were 5% and 33% higher, respectively ($p = 0.003$) [89]. Exercise out of doors is a good source of vitamin D; however, those with depression are less likely to exercise [90].

Tooth loss: Several studies have correlated tooth loss with development of cognitive impairment [91] and AD [92] or dementia [18,19,93]. In the HARMONY identical twins study in Sweden [18], for the monozygotic co-twin control analysis involving 82 pairs, the odds ratio for development of dementia accounting for comparative exposure within twin pairs was 4.20 (95% CI, 1.58–11.14). One can assume that identical twins

shared not only genetics but also pre-adult life experiences.

In the Nuns’ Study, those with zero to nine teeth had a greatly increased risk of developing dementia [19]. There was a statistically significant correlation between periodontal disease (PD) and tooth loss in this study population, although the authors reported that this finding was insignificant after adjustment for age, education, and APOE (apolipoprotein E) $\epsilon 4$. Kamer et al. [94] reviewed these findings. They proposed several mechanisms to explain these correlations, including elevation of serum inflammatory markers, which included C-reactive protein.

A study of healthy people older than 70 years in Scotland found an inverse correlation between edentulism and cognitive function. However, lower original intelligence predisposed them to edentulism [95]. A study in Sweden among those aged 21–40 years at time of enrollment found those with mild intellectual disability had a higher rate of tooth loss [96].

There are two primary ways that people lose teeth: dental caries and PD, with dental caries being the more important factor below the age of 45–50 years and periodontal disease above that range [97,98]. Both conditions are linked to low vitamin D levels. An ecological study in the 1930s reported an inverse correlation between mean hours of sunlight and presence of dental caries for boys aged 12–14 years living in rural or semirural regions of the United States [33]. There was a nearly linear increase in cavities, going from 2.9 cavities/boy for those living where there was more than 3000 hours of sunshine/year to 4.9 cavities/boy for those living where there was less than 2200 hours of sunshine/year. A similar finding was reported with respect to colon cancer, which led to the development of the UVB–vitamin D–cancer hypothesis [99]. Solar UVB and vitamin D are now well-recognized risk reduction factors for many types of cancer [29].

PD, defined in terms of jaw bone/tooth attachment loss (AL), has also been correlated with vitamin D. In a study of 11,202 subjects aged 20 or more years from NHANES III, compared with men in the highest 25(OH)D quintile, those in the lowest quintile had a mean AL that was 0.39 mm (95% CI, 0.17–0.60 mm) higher; in women, the difference in AL between the lowest and highest quintiles was 0.26 mm (95% CI, 0.09–0.43 mm). In men and women younger than 50 years, there was no significant association between 25(OH)D and AL [34]. In a related study of 6700 never smokers aged 13 to more than 90 years, sites in subjects in the highest 25(OH)D quintile were 20% (95%

CI, 8%–31%) less likely to bleed on gingival probing ($p_{\text{trend}} < 0.001$) [35].

There is little available information on dental conditions in Europe. However, there is a summary of edentulousness in selected European countries [100]. For the six countries of the 17 considered in this study, the percent occurrence for edentulousness ranges from 13% in Italy to 72% in Iceland. The correlation coefficient with respect to latitude is 0.82 ($p = 0.045$). However, diet also plays an important role in dental caries, with sugar an important risk factor. A check of dietary supply values for European countries [101] finds that sugar consumption is also correlated with a correlation coefficient 0.76 ($p = 0.077$). Given the approximations used for both indices, all that can be said is that both diet and solar UVB/vitamin D probably contribute to edentulousness in these six European countries.

The mechanism for vitamin D reducing the risk of dental caries and PD is induction of human cathelicidin, LL-37, by calcitriol [30], which fights the bacterial infections in the mouth. Thus, the several reports of tooth loss with respect to incidence of dementia support the vitamin D-dementia hypothesis.

Evaluation of the vitamin D-dementia hypothesis

There are established criteria for causality in a biological system as presented by Hill [102] and discussed by others [103,104]. The important criteria include strength of association, consistency of findings, determination of the dose-response relation, an understanding of the mechanisms, and experimental verification. To date, the evidence includes observational studies supporting a beneficial role of vitamin D in reducing the risk of diseases linked to dementia such as vascular and metabolic diseases, as well as an understanding of the role of vitamin D in reducing the risk of several mechanisms that lead to dementia. To my knowledge, there are no prospective studies of risk of dementia with respect to prediagnostic serum 25(OH)D or RCTs of vitamin D supplementation and incidence of dementia. The quickest way to obtain results of such studies may be to use serum 25(OH)D data from other studies or to do an add-on study to past or present vitamin D and calcium supplementation studies such as that done for cancer [105] and seasonal influenza and the common cold [40].

Vitamin D requirements

On the basis of meta-analyses of observational studies of serum 25(OH)D and cancer incidence, as well as RCTs and incidence of cancer and respiratory infections, it appears that the optimal serum 25(OH)D level is at least 40 ng/mL. For each 1000 IU/day, serum 25(OH)D rises by about 10 ng/mL [105]. Thus, for optimal health, people should try to obtain at least 1000–3000 IU of vitamin D per day. Meta-analyses of observational studies on cancer incidence find that it takes about 1500 IU of vitamin D per day to reduce the risk of colorectal cancer by 50% [106] and 3000 IU/day to reduce the risk of breast cancer by 50% [107]. An RCT of vitamin D and calcium found a 35% reduction in all-cancer risk for 1100 IU of vitamin D per day and about 35% for 1500 mg of calcium per day [105]. An RCT found that incidence of colds and influenza was reduced by 90% for those taking 2000 IU/day [40]. It has been estimated that the body can use 3600 IU/day [108]. A study of incidence of multiple sclerosis with respect to prediagnostic serum 25(OH)D for U.S. military personnel found a significant inverse correlation compared with the quartile <25 ng/mL only for the quartile >40 ng/mL [32].

Vitamin D risks

One consideration in changing vitamin D health policy is addressing and minimizing any adverse effects. The primary risk factor associated with vitamin D is extrarenal production of 1,25-dihydroxyvitamin D [1,25(OH)₂D] that gets into the serum and may lead to hypercalcemia by drawing calcium from the bones. For most people, that complication would occur at serum 25(OH)D levels more than 150 ng/mL [109]. For those with granulomatous diseases such as sarcoidosis, the body's innate immune system tries to fight a disease that is in intimate contact with the serum by generating 1,25(OH)₂D [52]. Similar effects can occur for those with rheumatoid arthritis, as well as for about 10%–15% of those with lymphoma. Those likely to suffer adverse effects are probably aware of their condition. They should have serum 25(OH)D, 1,25(OH)₂D, and calcium levels measured if taking vitamin D supplements at levels greater than 400 IU/day.

SUMMARY AND CONCLUSION

There is observational epidemiological evidence that vitamin D reduces the risk of several types of diseases that are risk factors for or can precede dementia. This evidence is supported by identification of mechanisms that vitamin D protects neurocognitive function. The observational evidence may be confounded by lifestyle in that those in better mental and physical condition are more likely to be active out of doors and, therefore, obtain more vitamin D. However, the understanding of the mechanisms is based largely on laboratory studies that are better controlled. However, until RCTs are performed, the hypothesis cannot be considered a fact. It is hoped that RCTs of vitamin D and perhaps calcium supplementation will be performed to evaluate this hypothesis. In the meantime, individuals should consider raising personal serum 25(OH)D levels to 40 ng/mL, and public health officials should review and revise the guidelines on vitamin D supplementation and optimal serum 25(OH)D levels: even if higher 25(OH)D levels do not reduce the risk of dementia, there are many other benefits.

DISCLOSURE

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Note

A recent observational study in England found that serum 25(OH)D was inversely correlated with cognitive impairment status, with an odds ratio of 2.3 (95%: 1.4–3.8) for those with serum 25(OH)D in the first quartile (3–12 ng/mL) versus those in the fourth quartile (26–68 ng/mL) after adjustment for confounding factors [110].

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