The Efficacy of Vitamin D Supplementation in Patients With Alzheimer’s Disease in Preventing Cognitive Decline: A Systematic Review

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Abstract

To evaluate the role of vitamin D supplementation in preventing cognitive decline in patients with Alzheimer’s disease (AD), five databases such as PubMed, PubMed Central (PMC), Medical Literature Analysis and Retrieval System Online (MEDLINE), ScienceDirect, and Google Scholar were searched for articles relevant to the research question with filters such as English and human studies from 2011 to 2022. Two investigators extracted the data and assessed the quality of the study using the predefined criteria. We identified 24 relevant articles after the critical screening. There were five randomized controlled trials (RCTs), two observational studies, two systematic reviews and meta-analyses, one pilot study, and 14 review articles.

Most RCTs showed no significant improvement in vitamin D supplementation except for one study, which reported significant improvement in cognition on taking vitamin D in Alzheimer’s disease but was not taken much into consideration as it had a small sample size (n=210) and was for a shorter duration. Another study evidenced significant improvement in Mini-Mental State Examination (MMSE) score when memantine and vitamin D were taken together compared to when memantine and vitamin D were taken independently. Studies have shown that vitamin D deficiency is associated with an increased risk of developing cognitive impairment. But there is no sufficient evidence indicating vitamin D supplementation can improve cognitive function in Alzheimer’s disease.

Categories: Internal Medicine, Neurology, Preventive Medicine
Keywords: cognitive disorders, dementia, cognitive decline, alzheimer’s disease, vitamin d

Introduction And Background

Among dementia in the elderly, Alzheimer’s disease (AD) is one of the most common types of dementia. AD is a progressive neurodegenerative disorder causing cognitive impairment and memory loss with widespread cortical atrophy. Approximately 10% of persons over 70 years have significant memory loss, with more than 50% of the cause being AD [1]. The prevalence of AD increases with each decade, reaching 20–40% of the population aged more than 85 years. AD is a multifactorial disorder due to a combination of age-related brain changes and genetic, environmental, lifestyle, vascular, and dietary risk factors. The pathogenesis of AD is thought mainly due to the accumulation of amyloid beta (Aβ) 42 and tau protein in the form of neuritic plaques and neurofibrillary tangles, respectively. AD management is mostly symptomatic, and there is no curative or preventive treatment.

The effect of vitamin D on calcium and bone metabolism is well-known, but its effect on many chronic illnesses involving neurocognitive decline was recently noticed. Vitamin D acts through vitamin D receptor (VDR), a nuclear hormone receptor, which is present in neuronal and glial cells in almost all regions of the central nervous system (CNS). The areas essential for cognition are mainly expressed in the hippocampus, amygdala, hypothalamus, cortex, and subcortex [2].

Vitamin D helps in neuroprotection by regulating nerve growth and neurotrophic factors such as nerve growth factor, decreasing L-type calcium channel expression, and regulating the toxicity of reactive oxygen species and nitric oxide synthase [3–6]. Furthermore, vitamin D showed a lower accumulation of Aβ 42 by enhancing its phagocytosis and amplifying brain-to-blood amyloid beta efflux transport at the blood-brain barrier (BBB), leading to fewer amyloid plaques [7–9]. Some studies showed an association between vitamin D receptor (VDR) gene polymorphisms and cognitive decline, AD [10,11]. Vitamin D deficiency has been linked with increasing hypertension, hyperlipidemia, myocardial Infarction (MI), and stroke, which are also risk factors for AD [12]. Vitamin D deficiency is more prevalent as age increases due to a decrease in cutaneous synthesis and decreased absorption of vitamin D. It is evident that low vitamin D concentration in older adults has shown an association with reduced cognitive performance and is more prevalent in those with AD [13,14]. This systematic review will study the efficacy of supplementing vitamin D on cognition in patients with early Alzheimer’s disease.
**Review**

**Methods**

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and principles were used to write this systematic review and report the results [15]. PRISMA flowchart is shown in Figure 1 [15].

**Search Strategy**

The major research literature databases and search engines such as Medical Literature Analysis and Retrieval System Online (MEDLINE), PubMed, PubMed Central (PMC), ScienceDirect, and Google Scholar were used to search appropriate keywords and Medical Subject Headings (MeSH) thesaurus and find relevant articles to the topic.

The ultimate MeSH strategy used for PubMed, PMC, and MEDLINE is as follows: (“Vitamin D/therapeutic use” [Majr] OR “Vitamin D/therapy” [Majr]) AND (“Alzheimer Disease/drug therapy” [Majr] OR “Alzheimer Disease/prevention and control” [Majr]) AND (“Cognitive Dysfunction/drug therapy” [Majr] OR “Cognitive Dysfunction/prevention and control” [Majr]). The keywords used for search in ScienceDirect and Google Scholar were vitamin D, Alzheimer’s disease, and cognitive decline. These keywords were combined in several ways using the Boolean operators “AND,” “OR,” and “NOT” to locate relevant articles.

**Inclusion and Exclusion Criteria**
We included articles published in English, focusing on the adult and geriatric population (≥40 years) and relevant to our research question. We excluded articles focusing on the population (<40 years), pregnant females, and unpublished or gray literature. A detailed description of inclusion and exclusion criteria is written in Table 1.

| Inclusion Criteria                      | Exclusion Criteria                           |
|-----------------------------------------|---------------------------------------------|
| 1. Papers relevant to the question      | 1. Paper irrelevant to the question          |
| 2. Papers published in the English language | 2. Papers published in languages other than English |
| 3. Papers including adult (≥40 years) and geriatric population | 3. Papers including the population (<40 years) |
| 4. Papers with only full texts         | 4. Papers that are not full texts            |
| 5. Published papers                     | 5. Papers of gray literature and unpublished articles |

**TABLE 1: A detailed description of the inclusion and exclusion criteria**

Analysis of Study Quality/Bias

Using standardized quality assessment tools, we critically evaluated selected studies, out of which 24 studies qualified as medium or high quality and were included in the review. The following tools were used for quality assessment: (a) Assessment of Multiple Systematic Reviews (AMSTAR) tool for systematic reviews and meta-analyses, (b) Newcastle-Ottawa scale for observational studies, (c) Scale for the Assessment of Narrative Review Articles (SANRA) checklist, and (d) randomized controlled trails (RCTs); Cochrane risk-of-bias assessment tool was used.

Data Extraction

Two investigators independently retrieved data and reviewed the eligible studies. The investigators would discuss the data for its relevance and design to eligibility criteria to reach an accord in case of disagreements. A third investigator was consulted for objectivity when the decision could not be made.

Results

In our initial search of MEDLINE, PubMed, and PubMed Central (PMC) databases, a total of 1164 articles were identified. Out of them, 418 articles were discarded after applying relevant filters per our eligibility criteria (human studies and English papers), and duplicates were removed. Then, the remaining articles (n=746) were screened based on titles, abstracts, full text, and detailed inclusion-exclusion criteria. We were left with 49 articles about our research question after the vigorous screening. Three articles were added by searching the relevant keywords to our topic in ScienceDirect and Google Scholar directly. A total of 24 studies were included for a thorough quality/bias assessment using standardized quality assessment tools and were included in this systematic review.

Of the 24 included studies, there were two observational studies, five randomized controlled trials (RCTs), one pilot study, and two meta-analyses, and the remaining were review articles. A total of 9592 participants were included in these studies. The summary characteristics of articles included in the study are in Table 2.
| Year | Authors | Study Design | Objective | Intervention | Comparison | Results or Findings |
|------|----------|--------------|-----------|-------------|------------|--------------------|
| 2011 | [17]     | Review article | To determine if vitamin D serum levels were associated with Alzheimer's disease patients from the Cilento area | Vitamin D deficiency in patients from the Cilento region is independent of Alzheimer's disease | Not available (N/A) | 25 |
| 2012 | [18]     | Review article | The role of vitamin D in the progression of Alzheimer's disease and its potential as a therapeutic agent | To assess the association of vitamin D deficiency with Alzheimer's disease and cognitive impairment | Not available (N/A) | - |
| 2013 | [19]     | Review article | The association of vitamin D deficiency with the risk of dementia and Alzheimer's disease | To determine if vitamin D can be used as a biomarker for diagnosis and to predict cognitive impairment | Not available (N/A) | Not available (N/A) |
| 2014 | [20]     | Prospective cohort study | The association of low serum vitamin D levels with increased frequency of dementia and Alzheimer's disease | To assess the association of low serum vitamin D levels with increased frequency of dementia and Alzheimer's disease | Not available (N/A) | Not available (N/A) |
| 2015 | [21]     | Review article | The role of vitamin D in the neurological functions | Vitamin D and cognitive impairment and dementia | Not available (N/A) | Not available (N/A) |
| 2016 | [22]     | Review article | The effect of vitamin D on cognitive function | To assess the association of low serum vitamin D levels with increased frequency of dementia and Alzheimer's disease | Not available (N/A) | Not available (N/A) |
| 2017 | [23]     | Review article | The association of vitamin D deficiency with cognitive impairment and dementia | To determine if vitamin D can be used as a biomarker for diagnosis and to predict cognitive impairment | Not available (N/A) | Not available (N/A) |
| 2018 | [24]     | Review article | The effects of vitamin D on the nervous system | To determine if vitamin D can be used as a biomarker for diagnosis and to predict cognitive impairment | Not available (N/A) | Not available (N/A) |
| 2019 | [25]     | Randomized controlled trial (RCT) | The effects of vitamin D and calcium on cognition in elderly females | To determine if vitamin D and calcium can improve cognitive function in elderly females | Not available (N/A) | 4143 |
| 2020 | [26]     | Randomized controlled trial (RCT) | The effects of vitamin D on cognitive function | To determine if vitamin D can be used as a biomarker for diagnosis and to predict cognitive impairment | Not available (N/A) | 210 |
| 2021 | [27]     | Randomized controlled trial (RCT) | Memantine and vitamin D | Treatment with memantine plus vitamin D showed improvement in Mini-Mental State Examination score compared to memantine (or) vitamin D alone | Not available (N/A) | 43 |
| 2022 | [28]     | Review article | Vitamin D deficiency is seen most common in older people but unable to indicate optimal vitamin D levels to improve cognition in healthy elderly | Based on the conference by the Nutrition Society | Not available (N/A) | Not available (N/A) |
| 2023 | [29]     | Review article | The effects of giving vitamin D and placebo (starch granules) | To determine if vitamin D can be used as a biomarker for diagnosis and to predict cognitive impairment | Not available (N/A) | Not available (N/A) |
| 2024 | [30]     | Randomized controlled trial (RCT) | The effects of vitamin D on cognitive function | To determine if vitamin D can be used as a biomarker for diagnosis and to predict cognitive impairment | Not available (N/A) | Not available (N/A) |
| 2025 | [31]     | Systematic review meta-analysis | The association of vitamin D levels and cognition in adults | To determine if vitamin D can be used as a biomarker for diagnosis and to predict cognitive impairment | Not available (N/A) | Not available (N/A) |
TABLE 2: Summary characteristics of studies included in the analysis of the role of vitamin D deficiency and its supplementation in cognition and Alzheimer’s disease

Discussion

Pathogenesis of Alzheimer’s Disease

Alzheimer disease (AD) is characterized by progressive memory and cognitive impairment, which deteriorates to complete disability and death within three to nine years of diagnosis [39]. The pathological hallmark of AD includes the deposition of amyloid beta peptides outside the cells forming senile plaques (SP) and intracellular hyperphosphorylated tau proteins in the brain [40].

AD is multifactorial due to the complex interaction between genetic, aging process, environmental, and lifestyle factors that leads to neuronal degeneration. Environmental and lifestyle factors escalate the risk of developing AD through cerebrovascular damage [41]. Major interrelated networks leading to neuronal and synaptic degeneration in AD were amyloid beta accumulation, hyperphosphorylation of tau protein, metal dysregulation, oxidative stress, mitochondrial dysregulation, and inflammatory reaction [27]. Amyloid beta protein is formed following the consecutive hydrolysis of amyloid precursor protein (APP) [42]. In AD, amyloid beta (Aβ40) and amyloid beta (Aβ42) are major types of amyloid beta peptides. Among them, Aβ42 is more prevalent in neuritic plaques and has a higher predisposition to aggregate and form the characteristic toxic amyloid fibrils [27]. Regardless of the evidence, it is still unclear how amyloid deposition and “tauopathy” contribute to the complexity and heterogeneity of AD.

Vitamin D Metabolism

Vitamin D is a prohormone. Ergocalciferol (vitamin D2) is found mostly in food, whereas cholecalciferol (vitamin D3) is synthesized from 7-dehydrocholesterol in the human skin by the photochemical reaction of ultraviolet B rays [43]. Ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) forms must undergo two enzymatic hydroxylation reactions to become biologically active. The first hydroxylation of vitamin D occurs in the liver by 25-hydroxylase enzyme forming 25-hydroxy vitamin D (25-(OH)D) or calcidiol [44]. The second hydroxylation of 25-hydroxy vitamin D occurs in the kidney by one -hydroxylase and converts it to 1,25-dihydroxy vitamin D (1,25(OH)2D) or calcitriol [44]. Calcitriol plays an important role in the differentiation and maturation of neurons by regulating the synthesis of neurotrophic agents such as nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) neurotrophin-3 [3]. These nerve growth factors are also required to maintain and regulate the septohippocampal pathway’s normal functioning, involved in learning and memory. Vitamin D also regulates the genetic expression of various neurotransmitters in the brain, particularly in the hippocampus [48].
Few studies states that intraneuronal calcium homeostasis is regulated by vitamin D through an L-type voltage-sensitive calcium channel (LVSCC) along those targeted by $\alpha_6$ [4]. Gezen-Ak et al. show that the silencing of VDR causes a rapid increase in L-type voltage-sensitive calcium channel alpha (α)-IC (LVSCC-AIC) expression, indicating that chronic deficiency of vitamin D renders the neurons in the brain vulnerable to neurodegeneration [49]. Therefore, treatment with vitamin D leads to the downregulation of LVSCC expression and channel density in the plasma membrane of the hippocampal neurons, which protects the neurons from calcium excitotoxicity [4].

The suppression of proinflammatory cytokines in the brain may be the mechanism of action of vitamin D for neuroprotection and increase brain-to-blood Aβ efflux across the blood-brain barrier (BBB), resulting in a decreased number of amyloid plaques [27]. Vitamin D has shown protective action against acute glutamate exposure in cultured rat's cortical neurons through the upregulation of VDR expression and antioxidant effects [5].

**Vitamin D Relation With Neurocognition and Alzheimer's Disease**

Llewellyn et al. found that low vitamin D levels were associated with an increased risk of losing points on the Mini-Mental State Examination (MMSE) in the elderly over six years [38]. A meta-analysis by Balion et al. compared mean MMSE scores with levels of 25-hydroxy vitamin D (25(OH)D), where a higher-average MMSE score was observed in those participants with higher 25(OH)D concentrations [21]. Chai et al. found a significant positive association between vitamin D deficiency and dementia and AD risk and that the association is proportionate to the level of vitamin D deficiency [28]. In 2014, Littlejohns et al. conducted a prospective study over 5.6 years that reported an increased risk association between vitamin D deficiency and AD [30]. Another recent cross-sectional study by Pizza et al. reported no significant association between vitamin D deficiency and AD. But this study was performed on a small group of patients [24].

AD was predisposed to vitamin D deficiency due to feeding difficulties along with less intake of food rich in vitamin D and inadequate sun exposure. Long-term prospective studies have demonstrated a temporal link between vitamin D deficiency and cognitive disorders. Older people with lower vitamin D levels were more likely to experience executive dysfunction and general cognitive decline than those with normal or higher vitamin D levels [58].

Neurons ineffectively use vitamin D due to changes in the receptors VDR and 1,25 membrane-associated rapid response steroid-binding (1,25-MARRS), genes involved in its action, and vitamin D metabolism resulting in neurodegenerative changes. The association between AD and polymorphisms of VDR and megalin strongly supports this notion and, therefore, explains the neurotoxic effects of VDR and 1,25-MARRS suppression [27].

**The Role of Vitamin D in AD Treatment**

The purpose of drug treatment in AD is to improve cognitive ability and slow the progression of symptoms. Four drugs are currently approved by the Food and Drug Administration (FDA) for treating cognitive symptoms of AD. They are anticholinesterase agents (galantamine, rivastigmine, and donepezil) and memantine (act by preventing excitatory neuronal damage) [50].

Several strategies were proposed to halt the disease progression, such as decreasing the synthesis of $\alpha_6$ by $\beta$-secretases or $\beta$-secretases inhibition, increasing the amyloid beta clearance by active or passive immunization from the brain or promoting it’s enzymatic degradation and the activation of nonamyloidogenic processing of amyloid precursor protein (APP) through $\beta$-secretase action modulation, preventing the aggregation and fibrillization of $\alpha_6$, inhibiting tau phosphorylation and antibodies against $\alpha_6$, and reducing inflammation or oxidative stress or excitotoxicity [50]. But still, they are in the trial period, or some trials have shown non-promising results.

There is no adequate treatment for AD, despite different treatment strategies. As we have discussed above, vitamin D interacts through different mechanisms in preventing AD and cognitive decline, indicating that vitamin D can be a multitargeted therapeutic option. Randomized controlled trials (RCTs) are required to know the actual vitamin D effectiveness in improving cognitive function, but there are few current RCT studies. In older females, increased vitamin D dietary consumption was linked to a decreased chance of developing AD, according to Annweiler et al.’s seven-year follow-up research [56]. The first of these experiments, the AD-IDEA trial, which examined the efficacy of vitamin D in Alzheimer’s disease and related dementia (ADRD) patients, was a randomized, placebo-controlled study [37].

An RCT study by Rossm et al. reported no significant difference in dementia even on vitamin D and calcium supplementation [32]. Another study by Jia et al. concluded that using vitamin D daily for 12 months improved cognitive function in AD patients [33]. Rossm et al.’s study was given importance as it had a larger sample size and longer follow-up period compared to Jia et al.’s study.

A six-month study trial by Annweiler et al. reported that combined vitamin D and memantine could improve
cognitive function, as evidenced by an improved MMSE score. Still, these studies had limited populations and duration [54]. In 2020, an RCT by Bischoff-Ferrari et al. evaluated the impact of vitamin D supplements on the Montreal Cognitive Assessment (MoCA) in a three-year follow-up and concluded that vitamin D has no impact on cognitive function improvement [55].

Additionally, even though blood 25-hydroxy vitamin D concentrations are linked to these function-specific domains of cognition, none of this research evaluated executive or episodic memory as outcome measures [12]. The present argument against vitamin D supplementation is from a few numbers of clinical trials. So, to know the effectiveness of vitamin D supplements against placebo better in patients with AD, additional well-conducted RCTs are essentially needed at this time.

Limitations
The limitations of this study are having a smaller number of RCTs to examine the effectiveness of vitamin D alone in AD. The main issues of the existing RCTs were their small sample size, the lack of agreement over the dose, and age at which vitamin D supplements are to be given to prevent cognitive impairment. Therefore, there is a need for large double-blind, randomized controlled trials to assess the benefits of vitamin D supplementation in preventing and treating cognitive impairment.

Conclusions
Many studies evidenced various functions of vitamin D throughout the central nervous system and the association of its deficiency with an increased risk of cognitive decline in older adults. There is a high risk of developing vitamin D deficiency in older people mainly due to decreased dietary intake and the cutaneous synthesis of vitamin D, thus suggesting its supplementation in the prevention and treatment of cognitive disorders and AD. But only a few randomized controlled trials (RCTs) indicate significant vitamin D improvement (cholecalciferol, vitamin D3). Some RCTs reported no significant improvement. However, there is no clear evidence that vitamin D supplementation can prevent AD onset and halt its progression. Given the inclusive scientific studies, it is too early to recommend a specific vitamin intake that delays or slows down cognitive decline. Hence, long-term, randomized, placebo-controlled trials need to assess the potential benefits of vitamin D addition in treating AD and dementia patients.

Additional Information
Disclosures
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