ISSN: 2577-2996

PROGRESS IN MEDICAL SCIENCES, 2024
VOL 8, NO. 1, PAGE 1 – 5
DOI: doi.org/10.47363/PMS/2024(8)195

RESEARCH ARTICLE

Open Access

Vitamin D for Neuroprotection and for Alzheimer's Disease Prevention and Treatment

Joana Coelho*, Carolina Pratas and Daniel Ferreira

USF 7 Castelos, ACES Loures Odivelas, Portugal

ABSTRACT

Alzheimer's disease (AD) is characterized by progressive loss of memory and cognition. The pathophysiology of AD involves the accelerated ageing of neurons altering neuronal metabolism and stability.

Vitamin D promotes brain health, prevents amyloid accumulation and promotes amyloid clearance, a protein that accumulates in the brain of persons with AD.

Vitamin D deficiency is defined as a 25(OH)D level of less than 50 nmol/L and is highly prevalent and is associated with brain changes and dementia.

To evaluate the efficacy of vitamin D for the prevention and treatment of cognitive defects and Alzheimer's dementia was done a search of articles on the PubMed platform, published between 2013 and 2023 with the term's "prevention", "neuroprotection", "dementia" e "vitamin D". Of the 15 selected articles, 12 met the inclusion criteria, being 6 review articles, 3 clinical trials and 3 prospective studies.

The analyzed articles show that vitamin D levels are significantly low in individuals with Alzheimer's and cognitive impairment, and was found an association between low vitamin D levels and diminished **cognitive** function.

Despite such evidence, the causal association cannot be sufficiently answered. More studies have to be done to explore the effects of vitamin D on neurocognition and determinate the exact dose that can prevent and/or treat cognitive decline and dementia.

Taken together, this suggests that vitamin D may be a new paradigm for prevention and treatment of dementia, but hypovitaminosis D can't be used as a diagnostic or prognostic biomarker of cognitive decline and/ or AD due to insufficient evidence.

ARTICLE HISTORY

Received December 18, 2023
Accepted December 26, 2023
Published January 16, 2024

KEYWORDS: Prevention, Neuroprotection, Dementia, Vitamin D

Introduction

Alzheimer's Disease

Alzheimer's disease (AD), the major cause of dementia worldwide in the ageing population, is clinically characterized by progressive loss of memory and cognition and deficits in other cognitive functions leading to complete incapacity and death within 3–9 years of diagnosis. The pathophysiology of AD involves the accelerated ageing of neurons leading to alteration in neuronal metabolism and stability. Initial symptoms include short-term memory loss, and as the disease advances, other symptoms, such as problems with language, disorientation, and mood swings, would ensue [1,2].

The pathophysiology of AD involves the accelerated aging of neurons leading to alteration in neuronal metabolismo and stability. A link between premature aging, diet, and nutrition is proposed with nutrigenomic research uncovering possible mechanisms such as epigenetic modifications that demonstrate the interaction between genes and environment disturbances and imbalances occurring in a variety of mechanisms (figure 1) [3].

Pathological hallmarks of AD include histopathological changes induced by the extracellular deposition of amyloid β peptides forming senile plaques (SP) and intracellular neurofibrillary tangle (NFT) of hyperphosphorylated tau proteins in the brain [3].

Contact: Joana Coelho, USF 7 Castelos, ACES Loures Odivelas, Portugal.

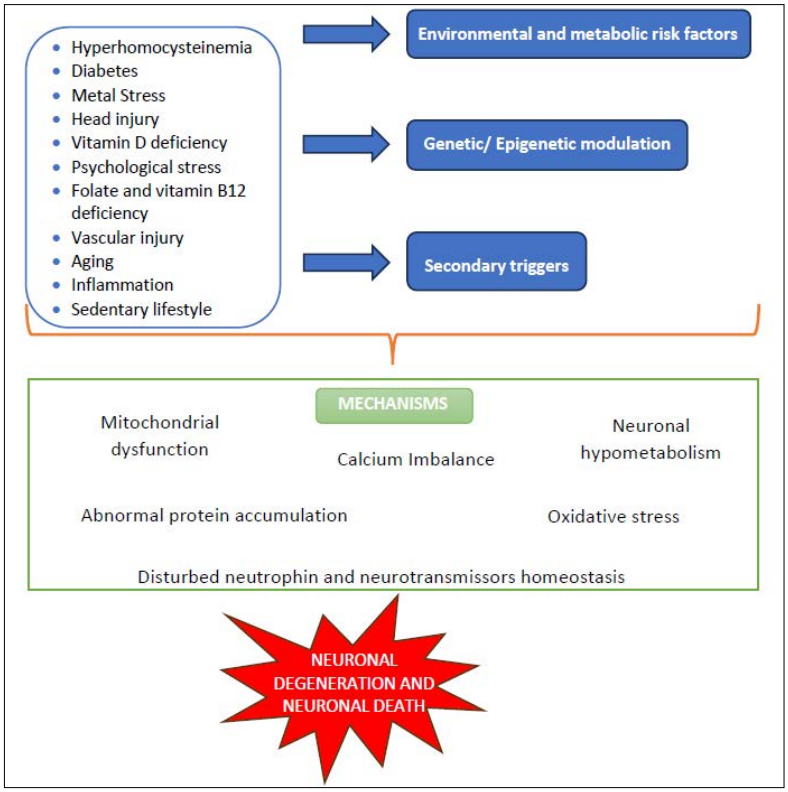

Figure 1: Risk factors and pathogenic mechanisms involved in the etiopathogenesis of sporadic Alzheimer's disease (AD) (adapted from 1).

Mechanism of Action and Functions of vitamin D

Vitamin D exists in nature in two major forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Cholecalciferol is mainly produced in animal skin from 7-dehydrocholesterol (7-DHC) while ergocalciferol is synthesized in plants and fungi from ergosterol (E) by ultraviolet rays (UVR) irradiation. For humans, most vitamin D is produced in the skin by the irradiation of UVR and only 20% of vitamin D is ingested diet Most vitamin D enters the blood circulation and binds to vitamin D binding protein (VDBP) or chylomicron to be transported to tissues and organs where it exerts its function [4].

Vitamin D can reach the brain by crossing the blood-brain barrier (BBB) through passive diffusion. 'e active form, 1,25(OH)D, binds to the vitamin D receptor (VDR) and influences gene expression. Vitamin D exerts its action via VDR present in neurons, glial cells of the hippocampus, orbitofrontal-cortex, cingulate, amygdala, and thalamus [5].

Vitamin D is a neurosteroid hormone that has anti-inflammatory, antioxidant, and neuroprotective properties. It increases neurotrophic factors such as nerve growth factor which further promotes brain health. Moreover, it is also helpful in the prevention of amyloid accumulation and promotes amyloid clearance, a protein that accumulates in the brain of persons with AD (figure 2) [5].

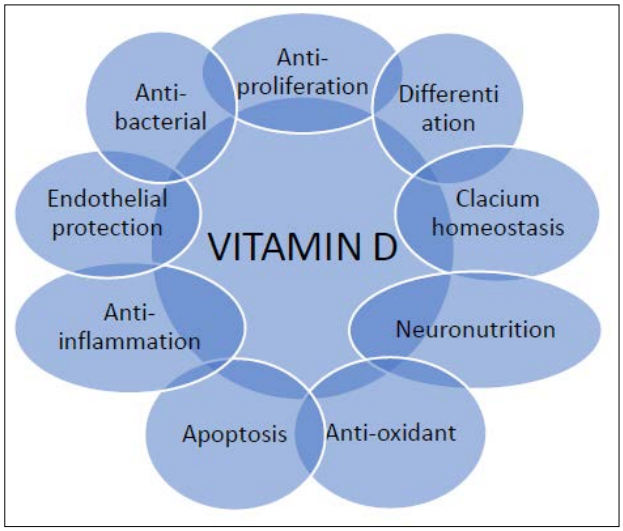

Figure 2: Vitamin D Functions (Adapted from 2).

Vitamin D and Neuroprotection

1,25-Dihydroxyvitamin D [1,25(OH)2D] plays a pivotal role in neuronal differentiation and maturation via control of the synthesis of neurotrophic agents such as nerve growth factor (NGF), that is important for the growth, maintenance, and survival of certain target neurons and also has been implicated in maintaining and regulating the normal functioning of the septohippocampal pathway, which is involved in learning and memory. It has been noted that mature NGF levels are substantially decreased in the forebrain of aged animals and patients with AD. Calcitriol and vitamin D analogs were enhance NGF induction and the genetic expression of numerous neurotransmitters in the brain, including acetylcholine, dopamine, serotonin, and β-aminobutyric acid is regulated by 1,25(OH)D which is notably in the hippocampus [1].

Aging brain and also Alzheimer's disease show calcium dysregulation, [6]. The L-type voltage sensitive Ca2+ channel, one of the most important proteins in calcium metabolism, aging, and neurodegeneration is regulated by vitamin D, which regulates intraneuronal calcium homoeostasis via the regulation of these channels, including those targeted by Aβ [7].

There is a potente immune-modulatory and anti-inflammatory action of vitamin D has long been, which leads to the fact that age-related inflammatory changes in the hippocampus may be reversed by vitamin D [8].

Nevertheless, it is worth mentioning that vitamin D also regulates the APP and amyloid beta metabolic aspects, having the ability to attenuate amyloid β plaques accumulation by stimulating phagocytosis of the Aβ peptide and enhancing brain-to-blood Aβ efflux across BBB, resulting in decreased number of amyloid plaques [9].

Vitamin D was also shown to exhibit neuroprotective properties against glutamate toxicity. through the upregulation of VDR expression and antioxidant effects. Various reports show that vitamin D exerts its protecting effects against free radicals generated by reactive species of oxygen and nitric oxide, inhibits the synthesis of inducible nitric oxide synthase, and regulates the activity of the gamma glutamyl transpeptidase [76–. 1,25(OH)2D also protects from cerebral endotelial dysfunction by its inhibitory effects on ROS production and NF-βB activation [10].

Hypovitaminosis D and Alzheimer's Disease

About 1 billion individuals worldwide are estimated to have hypovitaminosis D. Typically, vitamin D deficiency is defined as a 25(OH)D level of less than 50 nmol/L, with severe deficiency defined as less than 25 nmol/L and insufficiency between 50 and 75 nmol/L. Hypovitaminosis D is highly prevalent in adults, especially in those with age above 65 years old and is associated with brain changes and dementia [11,12].

Hypovitaminosis D increases the risk of cognitive decline and dementia in older adults and may alter the clinical presentation as a consequence of related comorbidities and influences cognition actively through deleterious effects and/or passively by loss of neuroprotection [11,12].

Nearly one in two older adults aged 65 years and above and 70–90% of adults with cognitive difficulties have hypovitaminosis D [13].

Recent studies have identified that low serum concentrations of vitamin D can substantially increase the risk of AD [14].

Materials and Methods

The aim of this work is to evaluate the efficacy of vitamin D for the prevention and treatment of cognitive defects and Alzheimer's dementia.

Search of articles on the PubMed platform, published between 2013 and 2023 with the terms "prevention" "neuroprotection", "dementia" e "vitamin D".

Of the 15 selected articles, 12 met the inclusion criteria, being 6 review articles, 3 clinical trials and 3 prospective studies.

Results

There is a sum-up of the results of the articles analysis in the table 1.

Table 1: sum-up of the results of the articles analysis

Articles conclusions	
[12]	• Cellular studies: Vitamin D has multiple functions throughout the central nervous system and could be implicated in the prevention and treatment of disorders such as dementia and AD. • Cross-sectional and case-control studies: Confirm that vitamin D concentrations are lower in individuals with cognitive impairment and dementia although reverse causality remains a possibility. • Longitudinal studies: Some find an association between low vitamin D concentrations and an increased risk of cognitive decline, all-cause dementia, and AD; some did not find that association; There is lack of consensus over the exact dosage of vitamin D to be used and optimal age of treatment initiation of individuals at risk remains unidentified.
[11]	• Hypovitaminosis D (and/or the inefficient utilization of vitamin D) can be considered an aetiological/risk factor for cognitive decline and for dementia in general. • Vitamin D concentration in older adults is associated with subsequent cognitive change and, in particular, that hypovitaminosis D predicts incident occurrence of cognitive decline and dementia • Concentration of serum 25OHD cannot be used as a biomarker of ADRDs, because hypovitaminosis D is too common in older adults and that it is not sufficiently specific to be an efficient biomarker of ADRDs, or to be useful for the screening or diagnosis of ADRDs or for evaluating the response or tolerance to medical treatment. • It is impossible at present to determine whether vitamin D status is a prognostic marker for ADRDs, as no studies have yet examined the risk of cognitive decline according to vitamin D status in patients with ADRDs and it is unclear whether patients with hypovitaminosis D progress more quickly to a more severe stage of dementia than patients with higher vitamin D levels. • Alterations in the vitamin D/ VDR axis might explain, at least in part, the diversity of symptoms and clinical characteristics observed in ADRDs, because hypovitaminosis D has been associated with numerous diseases such as hypertension, type 2 diabetes, vascular disease and osteoporosis, as well as the propensity to fall, that might increase the risk of dementias. • Vitamin D supplements should be part of the care management of older adults with cognitive disorders/ADRDs, because the studies have shown cognitive improvements, mainly of executive functions, after vitamin D supplementation,

[1]	• Multitargeted neuroprotective action of vitamin D makes it a lucrative candidate for the prevention as well as treatment strategy in AD and ADRDs. • Hypovitaminosis D and the inefficient utilization of vitamin D increase the risk of cognitive decline/ADRDs in older adults and may alter the clinical presentation of the disease, particularly as a sequel of accompanying morbidities. • However, at present, hypovitaminosis D should not be used as a diagnostic or a prognostic biomarker of cognitive decline/ADRDs due to lack of specificity and insufficient evidence. • The experts recommended measurement of serum 25(OH)D because of the high prevalence of hypovitaminosis D in this population and supplementation, if necessary.
	• Further, animal-based studies and drug trials need to be conducted to determine the threshold concentration of vitamin D to prevent neurodegeneration, so that the correct dose of supplementation could be determined.
[2]	• Vitamin D exhibits its functions through binding to its nuclear receptor VDR, membrane receptor 1,25 D3-MARRS, or interfering with molecules in signaling pathways that are associated with the pathogenesis of neurodegenerative diseases, such as AD, PD, MS, and VaD. Still, more experiments on cell and animal models are required for further insight into molecular mechanisms of vitamin D to attenuate cognitive and motor dysfunctions caused by neurodegenerative diseases. • In addition, some of the clinical studies that we concluded in this review demonstrated positive effects of vitamin D supplementation on neurodegenerative diseases while the rest displayed no significant influence. • The contradictory results can probably be attributed to diverse doses and durations of vitamin D treatment. • Therefore, intricately designed, large multicenter clinical trials need to be conducted to investigate and analyze the potency of vitamin D in influencing the clinical symptoms of patients with neurodegenerative disorders whether as clinical nutrition or as a therapy
[15]	• Overall, this study does not support the protective Effect of vitamin D status on cognitive decline or dementia. • A significant positive association with incident dementia and AD was found among women which seems more pronounced in the very old, but these results were not replicated in the analysis on cognitive decline. • Despite the non-conclusive results of this study, further research is needed to clarify this relation, particularly in women.
[16]	• Vitamin D deficient individuals appear to have a modest reduction of memory function without structural brain atrophy. • As vitamin D deficiency is highly prevalent and effective therapies for cognitive dysfunction and dementia are lacking, future studies should explore if vitamin D supplementation can improve cognitive function.
[17]	• These data suggest that memantine combined with vitamin D stops axonal degeneration induced by AB-peptide and glutamate. • Beyond its possible utility for slowing down disease progression in patients who already have AD symptoms, there is hope that the combination of memantine with vitamin D can be applied to prevent the onset of AD.
[18]	• At current state vitamin D can hardly be considered a therapeutic agent with an established efficient dose in AD. • Authors of studies suggest that vitamin D is important in AD prophylaxis in elderly patients with age-related reduction of serum calcidiol levels.
[19]	• Low plasma vitamin D levels have often been associated with cognitive decline, particularly in elderly populations. • For vitamin D, there is a high level of evidence of association between low vitamin D levels and diminished cognitive function, particularly in the elderly, however causality cannot be confirmed from the available evidence.
[20]	• Women (age range 55–67yrs) with vitamin D levels above 25nmol/L maintained better executive functioning in late-life, in particular, improved mental flexibility and psychomotor speed. And trend for less decline on the TMT-B and the CVLT-II delayed recall over the 10-year follow-up.
[21]	• We found that the use of memantine was associated with improved cognitive performance after 6 months of treatment only in the event of vitamin D deficiency at M6. • This pilot study raises the hypothesis that memantine might prevent the cognitive decline that accompanies the onset of vitamin D deficiency.
[22]	• Our data strongly suggest the existence of a regulatory intracrine/autocrine feedback loop in pericytes balancing the inflammatory potential of TNF-α and Interferon-γ. • A paracrine role for the 1,25D produced by pericytes in the NVU during inflammation can also be considered. • In conclusion, our results point to brain pericytes and 1,25D as two active players in the regulation of neuroinflammation. • They provide additional evidence fora role of vitamin D metabolites in the prevention and the therapy of neurodegenerative/neuropsychiatric diseases through the modulation of neuroinflammation. • They also strengthened the interest of targeting brain pericytes for controlling brain disorders such as AD.

Discussion/Conclusion

Most of the analyzed articles show that vitamin D levels are significantly low in individuals with Alzheimer's disease and cognitive impairment compared to healthy adults. They also have shown an association between low vitamin D levels and diminished cognitive function. In addition, some of the clinical studies analyzed demonstrated positive effects of vitamin D supplementation on dementia and cognitive decline while the rest displayed no significant influence. The contradictory results can probably be attributed to different dosages and durations of vitamin D treatment.

Despite such evidence, the causal association cannot be sufficiently answered. Furthermore, large doubleblind, randomized, placebo-controlled trials which should consider the effects of vitamin D on comorbidities and explore the stimulating and/ or protective effects of vitamin D on neurocognition at different stages of life and to determinate the exact dose vitamin D supplements that can prevent and/or treat cognitive and dementia.

Hypovitaminosis D and the inefficient utilization of vitamin D increase the risk of cognitive decline/ADRDs in older adults and may alter the clinical presentation of the disease, particularly as a sequel of accompanying morbidities. So, multitargeted neuroprotective action of vitamin D makes it a lucrative candidate for the prevention as well as treatment strategy in AD.

However, at present, hypovitaminosis D should not be used as a diagnostic or a prognostic biomarker of cognitive decline or dementia due to lack of specificity and insufficient evidence. Despite of that, experts recommended measurement of serum 25(OH)D int people with cognitive decline and dementia because of the high prevalence of hypovitaminosis D in this population and supplementation, if necessary. At this time, further laboratory experiments, prospective studies and large trials are essential to clarify the mechanisms through which vitamin D benefits the brain. In parallel Acute and chronic vitamin D treatment or depletion should also be carried out in order to best interpret neurocognitive and behavioral abnormalities associated with vitamin D deprivation.

Taken together, this body of evidence suggests that vitamin D may be a new paradigm for therapy in the prevention and treatment of dementia. Cumulative evidence indicates that vitamin D can ameliorate neurodegeneration, however, at present, hypovitaminosis D should not be used as a diagnostic or a prognostic biomarker of cognitive decline and/ or AD due to lack of specificity and insufficient evidence. However, at present, vitamin D level should not be used as a diagnostic or prognostic biomarker of Alzheimer's disease due to lack of specificity and insufficient evidence.

Future studies should consider the effects of vitamin D on comorbidities and explore the stimulating and/or protective effects of vitamin D on neurocognition at different stages of life.

References

[1] Banerjee A, Khemka VK, Ganguly A, Roy D, Ganguly U, et al. Vitamin D and Alzheimer's Disease: Neurocognition to Therapeutics. Int J Alzheimers Dis 2015; 2015: 192747.

[2] Wang W, Li Y, Meng X. Vitamin D and neurodegenerative diseases. Heliyon 2023; 9: e12877.

[3] Praticò D. Oxidative stress hypothesis in Alzheimer's disease: a reappraisal. Trends Pharmacol Sci 2008 ;29: 609-15.

[4] D.D. Bikle, Vitamin D metabolism, mechanism of action, and clinical applications, Chem 2014; 21: 319–329.

[5] E. M. Brouwer-Brolsma and L. C. P. G. M. de Groot, "Vitamin D and cognition in older adults," Current Opinion in Clinical Nutrition and Metabolic Care 2015; 18 : 11–16.

[6] D. Gezen-Ak, E. Dursun, and S. Yilmazer, "The effects of vitamin D receptor silencing on the expression of LVSCC-A1C and LVSCC-A1D and the release of NGF in cortical neurons," PLoS ONE 2011; 6: e17553.

[7] E. Dursun, D Gezen-Ak, S Yilmazer, "A novel perspective for Alzheimer's disease: vitamin D receptor suppression by amyloid-β and preventing the amyloid-β induced alterations by vitamin D in cortical neurons," Journal of Alzheimer's Disease 2011; 23: 207–219.

[8] M C Langub, J P Herman, H H Malluche, N J Koszewski, "Evidence of functional vitamin D receptors in rat hippocampus," Neuroscience 2001; 104: 49–56.

[9] M T Mizwicki, D Menegaz, J Zhang, John R Cashman, Milan Fiala, et al. "Genomic and nongenomic signaling induced by 1α,25(OH)2-vitamin D3 promotes the recovery of amyloid-β phagocytosis by Alzheimer's disease macrophages," Journal of Alzheimer's Disease 2012; 29: 51–62.

[10] S Won, I Sayeed, BL Peterson, Wali B, kahn JS, et al. Vitamin D prevents hypoxia/reoxygenation-induced blood-brain barrier disruption via Vitamin D receptor-mediated NF-kB signaling pathways. PLOS ONE 2015; 10: 1-17.

[11] Annweiler C, Dursun E, Féron F, Gezen-Ak D, Kalueff AV, et al. 'Vitamin D and cognition in older adults': updated international recommendations. J Intern Med 2015; 277: 45-57.

[12] Sultan S, Taimuri U, Basnan SA, Ai-Orabi WK, Awadallah A, et al. Low Vitamin D and Its Association with Cognitive Impairment and Dementia. J Aging Res 2020; 2020: 6097820.

[13] Annweiler C, Allali G, Allain P, Bridenbaugh S, Beauchet O, et al. Vitamin D and cognitive performance in adults: a systematic review. Eur J Neurol 2009; 16: 1083-1089.

[14] LH Kuller, TJ Littlejohns, WE Henley, David J Llewellyn, Maya Soni, et al. Vitamin D and the risk of dementia and Alzheimer disease. Neurology 2014; 83: 920-928.

[15] Duchaine CS, Talbot D, Nafti M, Giguère Y, Dodin S, et al. Vitamin D status, cognitive decline and incident dementia: the Canadian Study of Health and Aging. Can J Public Health 2020; 111: 312-321.

[16] Zelzer S, Hofer E, Meinitzer A, Fritz-Petrin E, Simstich S, et al. Association of vitamin D metabolites with cognitive function and brain atrophy in elderly individuals-the Austrian stroke prevention study. Aging (Albany NY) 2021; 13: 94559467.

[17] Annweiler C, Brugg B, Peyrin JM, Bartha R, Beauchet O, et al. Combination of memantine and vitamin D prevents axon degeneration induced by amyloid-beta and glutamate. Neurobiol Aging 2014; 35: 331-335.

[18] Gruber-Bzura BM. Vitamin d in alzheimer's disease - prophylaxis or therapy? Acta Pol Pharm 2016; 73: 1427-1431.

[19] Krause D, Roupas P. Effect of Vitamin Intake on Cognitive Decline in Older Adults: Evaluation of the Evidence. J Nutr Health Aging 2015; 19: 745-53.

[20] Goodwill AM, Campbell S, Simpson S Jr, Bisignano M, Chiang C, et al. Vitamin D status is associated with executive function a decade later: Data from the Women's Healthy Ageing Project. Maturitas 2018; 107: 56-62.

[21] Lemire P, Brangier A, Beaudenon M, Duval GT, Annweiler C. Cognitive changes under memantine according to vitamin D status in Alzheimer patients: An exposed/unexposed cohort pilot study. J Steroid Biochem Mol Biol 2018; 175: 151-156.

[22] Nissos MF, Guttin A, Zenga C, Berger F, Issartel JP, et al. Additional clues for a protective role of vitamin D in neurodegenerative diseases: 1,25-dihydroxyvitamin D3 triggers an anti-inflammatory response in brain pericytes. Alzheimers Dis 2014; 42: 789-99.