The neuroprotective role of Vitamin D in Alzheimer's Disease: summary of the evidence

Laura Valzolgher MD, Michael Kob MD
Division of Dietetics and Clinical Nutrition, Hospital of Bolzano, Italy

Key Highlights:

- Vitamin D is a fat-soluble pro-hormone that is naturally present in fatty fish and fish liver oils, beef liver, egg yolks, cheese and mushrooms
- Its role in calcium and bone metabolism is well-known, as it has an anti-inflammatory effect and immune function
- Vitamin D has also shown neuroprotective properties in *in vitro* studies promoting the clearance of amyloid plaques
- However the promising role of Vitamin D in the delay of cognitive decline has not yet been confirmed in human RCTs

Introduction

The prevalence of Neurodegenerative disorders increases with aging and is associated with high disease burden and healthcare costs. Therefore, any possible efforts to prevent or delay neurodegenerative disorders need to be put into action, especially simple measures with low economic impact, such as the supplementation of certain foods or vitamins. Among the latter, vitamin D is well-known for its role in calcium and bone metabolism, as well as its anti-inflammatory effect and role in immune function. However, the potential neuroprotective properties of vitamin D have only been recently investigated.

Vitamin D

Vitamin D is a fat-soluble pro-hormone that is naturally present in food. The best sources are fatty fish such as trout, salmon, tuna, and mackerel, and fish liver oils; other sources are beef liver, egg yolks, cheese, and mushrooms. In food and dietary supplements, vitamin D is found in two main forms: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol), which are both well absorbed in the small intestine. Both forms must undergo two hydroxylations in the body for activation. The first hydroxylation occurs in the liver with the conversion of Vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as ″calcidiol.” The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as ″calcitriol”. Vitamin D is responsible for normal bone metabolism by maintaining adequate serum calcium and phosphate concentrations, which play a role in preventing osteoporosis in the elderly.

Neuroprotective effect of Vitamin D

Vitamin D acts through a nuclear hormone receptor (vitamin D receptor VDR) that is present in almost all regions of the central nervous system (CNS), including the areas important for cognition: the hippocampus, amygdala, hypothalamus, cortex, and subcortex. In vitro studies show that vitamin D can promote the clearance of amyloid plaques by stimulating phagocytosis by macrophages and reducing neurodegeneration. Besides its anti-inflammatory and antioxidant properties, Vitamin D is believed to have neuroprotective effects by suppressing proinflammatory cytokines in the brain and increasing brain-to-blood Aβ efflux across the blood-brain barrier (BBB), decreasing the number of amyloid plaques.

Vitamin D supplementation and prevention of cognitive decline in healthy individuals: evidence from Cochrane systematic review

In the Cochrane systematic review by Rutjes et al. published in 2018, a trial with 4.143 healthy participants compared vitamin D3 (400 IU/day) and calcium supplements to placebo. The results pointed to low- to-moderate- certainty of no effect of vitamin D3 and calcium supplements at any time- point up to 10 years on overall cognitive function or the incidence of dementia.

Vitamin D and cognitive function in healthy older adults or with early Alzheimer's disease: a systematic review published on Cureus (pubMed)

The systematic review by Chakkera et al. included 24 studies from 2011 to 2020 investigating the role of vitamin D in the prevention of AD in older adults with normal neurological status and the role of vitamin D in patients with early-stage AD. The systematic review included two observational studies, five randomized controlled trials (RCTs), one pilot study, and two meta-analyses; the remaining were review articles with a total of 9.592 participants included. Although many studies evidenced various functions of vitamin D throughout the central nervous system and associated its deficiency with increased risk of cognitive decline in older adults, the evidence from randomized controlled trials (RCTs) was not clear; few RCTs showed significant improvement with vitamin D (cholecalciferol, vitamin D3), while several reported no significant improvement.

Conclusion

Although there are promising results in *in vitro* and animal studies, there is no clear evidence that vitamin D supplementation can prevent AD onset in humans nor delay AD progression.

References

Rutjes AWS, Denton DA, Di Nisio M, Chong LY, Abraham RP, Al-Assaf AS, Anderson JL, Malik MA, Vernooij RWM, Martínez G, Tabet N, McCleery J. Vitamin and mineral supplementation for maintaining cognitive function in cognitively healthy people in mid and late life. Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD011906. DOI: 10.1002/14651858.CD011906.pub2.

Chakkera M, Ravi N, Ramaraju R, Vats A, Nair AR, Bandhu AK, Koirala D, Pallapothu MR, Quintana Mariñez MG, Khan S. The Efficacy of Vitamin D Supplementation in Patients With Alzheimer's Disease in Preventing Cognitive Decline: A Systematic Review. Cureus. 2022 Nov 20;14(11):e31710. doi: 10.7759/cureus.31710. PMID: 36569670; PMCID: PMC9771092.

Lasoń W, Jantas D, Leśkiewicz M, Regulska M, Basta-Kaim A. The Vitamin D Receptor as a Potential Target for the Treatment of Age-Related Neurodegenerative Diseases Such as Alzheimer's and Parkinson's Diseases: A Narrative Review. Cells. 2023 Feb 19;12(4):660. doi: 10.3390/cells12040660. PMID: 36831327; PMCID: PMC9954016.

Wang W, Li Y, Meng X. Vitamin D and neurodegenerative diseases. Heliyon. 2023 Jan 12;9(1):e12877. doi: 10.1016/j.heliyon.2023.e12877. PMID: 36820164; PMCID: PMC9938420.

Michael Kob is a medical doctor, currently Director of the Division of Dietetics and Clinical Nutrition at the Central Hospital of Bolzano in South Tyrol. He specialized in Dietetics and Clinical Nutrition at the University of Padua, and has a teaching assignment in Nutritional Sciences at the University of Verona and University of Padua. He is also expert in Plant-Based Nutrition and Nutrition in Bariatric Surgery.

Laura Valzolgher is a medical doctor specialized in Dietetics and Clinical Nutrition, Internal Medicine with special subspecialization in Geriatric Medicine. She also completed her Master of Science Degree in Psychogeriatrics. After working at the Memory Clinic of the Geriatric Department and in the Emergency Department at the Hospital of Bolzano during the COVID time she is currently engaged at the Division of Dietetics and Clinical Nutrition. Her special area of interest is Nutrition and Cognitive Decline in Elderly and in Neurodegenerative Disorders.