EDITORIAL

Magnitude of Vitamin D in Alzheimer's Disease

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ABSTRACT

Keywords

Alzheimer's Dementia, Alzheimer's Sclerosis, Alzheimer's Syndrome, Major Neurocognitive Disorder, Presenile Dementia, Ergocalciferol-D2, Cholecalciferol-D3, Alfacalcidol, Fat-Soluble Vitamin, Ultraviolet (UV) Rays, sunshine vitamin,

The term dementia has been given to an acquired syndrome due to disease or injury of the brain, which involves the declining of cognitive functions progressively resulting in loss of abilities of cognition. Loss of cognitive skills in this condition is severe to the point that the ability to perform daily activities is reduced [1]. Dementia has a subtype known as Alzheimer's disease [(AD), one of the most common dementia types, with 75% of elderly with dementia being affected] in which there is the development of neurofibrillary tangles and neuritic plaques. Globally, about fifty million patients have Alzheimer's disease, which, by the year 2050, is estimated to rise by 3 folds [2]. This condition heavily burdens the global healthcare system, with a staggering cost of over eighty billion dollars per year [3].

There is an abnormal accumulation of phosphorylated tau protein within specific neurons' perikaryal cytoplasm and Amyloid beta [(Aβ) a protein fragment that is a key part of the plaques found in the brains of people with AD] peptide accumulation extracellularly [2]. Amyloidopathy (a condition where amyloid proteins build up in the body, affecting the brain and other organs) is one of the suggestive causes of the development of Alzheimer's disease, and its regulation occurs through several processes. These processes include Aβ degradation, microglial clearance, astrocytic clearance, and Aβ generation. Aβ generation depends on the APP (Amyloid precursor protein) cleavage by enzymes γ-secretase and β-secretase. The levels of Aβ also depend on its degradation by endopeptidases like insulin-degrading enzymes and neprilysin [4,5].

Vitamin D activation in the central nervous system

The conversion of vitamin D into its active form requires the presence of 25-hydroxylase and 1α-hydroxylase. The vitamin D receptor (VDR) and 1α-hydroxylase are found in the human

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brain's glia and neurons [6]. The blood-brain barrier can be crossed by vitamin D, and its metabolites and metabolism can occur within the central nervous system [7]. Vitamin D interacts with the VDR/RXR (retinoic acid receptor) complex and thus plays a role as a transcription factor to promote the expression of various genes [8]. Hence, vitamin D deficiency possibly modulates the central nervous system functions [9].

Vitamin D, immune cells, and inflammation

Vitamin D influences the immune cells and hence mitigates inflammation [10]. This vitamin promotes the differentiation of monocytes to macrophages [11]. IL-10 secretion is promoted while the release of proinflammatory cytokines like tumor necrosis factor-alpha (TNFα), IL-6, cyclooxygenase-2 (COX-2), IL-1,b, and RANKL are reduced in macrophage by vitamin D [12]. Mitogen-activated protein kinase (MAPK) phosphatase (MKP)-1 upregulation and eventual inhibition of lipo-polysaccharide-induced p38 activation by vitamin D results in downregulation of the proinflammatory cytokines [13]. This may also occur by employing inhibition of COX-2 expression [14].

Induction of cluster of differentiation 40 (CD40), F4/80 [(macrophage marker) EGF-like module-containing mucin-like hormone receptor-like 1], DEC205 [(CD205) is one of the major endocytic receptors on dendritic cells] and increasing C-C chemokine receptor type 5 (CCR5) expression by vitamin D can lead to suppression of IL-12 and enhancement of interleukin (IL)-10 production [15-20]. Vitamin D can also directly bind to the IL-10 promoter region and cause upregulation of IL-10 formation and downregulation of Cluster of Differentiation (CD)86 and CD74 [10,21,22]. Vitamin D also inhibits T-helper 1 (Th 1) [(interferon-γ, TNFα, IL-2), Th22 (IL22), Th9 (IL-9), and Th17 (IL17)] proinflammatory cytokines and enhances the secretion of Th2 (IL-3, IL-4, IL-5, IL-10) cytokines that reduce inflammation [23-30]. Another study also reported vitamin D downregulates IFN- γ [by activation of TCRγδ [(T cell receptor (TCR) made up of a γ (gamma) and a δ (delta) chain], T cell] and TNFα [31,32]. Treg (regulatory T cell) differentiation by vitamin D in humans is under debate [33,34].IL-4 production is promoted by vitamin D from invariant natural killer T (NKT) cells [35].

Role of Vitamin D in Cognition

Pérez-López et al. 2011 and Annweiler et al. 2010 reported that vitamin D has a substantial role in maintaining cognition functions. [36,37]. Previous studies have reported the existence of vitamin D receptors in brain areas related to memory and cognition function [37-39]. Vitamin D deficiency may play a part in AD progression since this vitamin is involved in neuroplasticity, neuroprotection, neurotransmission, and neurotrophy [40]. Studies have observed an association between a deficiency of vitamin D and a decline in cognition [41,42]. Relationship between vitamin D deficiency and Alzheimer's disease, with the strongest association between severe deficiency of vitamin D (<10ng/ml) and the disease when compared to those with moderate vitamin D deficiency (10-20 ng/ml) has been found in a meta-analysis done by Chai et al. 2019. Their meta-analysis was done on 4 cross-sectional and 12 prospective cohort studies [43]. An inverse association between AD and vitamin D concentration has been reported by Chen et al. 2018 in their meta-analysis, which included 10 cohort research studies involving over twenty thousand recruits [44]. However, a meta-analysis of 6 prospective studies, including over 1000 Alzheimer's patients on the concentration of vitamin D and AD risk by Yang et al. 2019, noted no significant association between the two [45].

A meta-analysis done by Pinzon et al. 2023 involving 6 studies consisting of 10,884 individuals presented evidence in favor of low levels of vitamin D aggravating the risk of AD [46]. Pinzon et al. 2023 further noted that a vitamin D level of less than 25ng/ml was related to a higher risk of AD compared to individuals with vitamin D levels equal to or more than 25ng/ml [46].

Neurodegeneration may result from neuroinflammation and oxidative stress [2]. AD possibly develops due to 2 forms of neuropathological alterations, the first being amyloid plaques and neurofibrillary tangles accumulation within the brain. The other change involves neural and synaptic loss [2,47]. Vitamin D's possible advantage and association with AD have been observed in several studies. Vitamin D may promote amyloid plaque clearing, as has been noted by human and animal studies [47,48]. The active form of vitamin D has been found in neural cultures to regulate Aβ processing pathway-related gene expression [49]. This implies that vitamin D deficiency may disrupt the regular expression of genes, leading to AD pathology [9] (Figure 1).

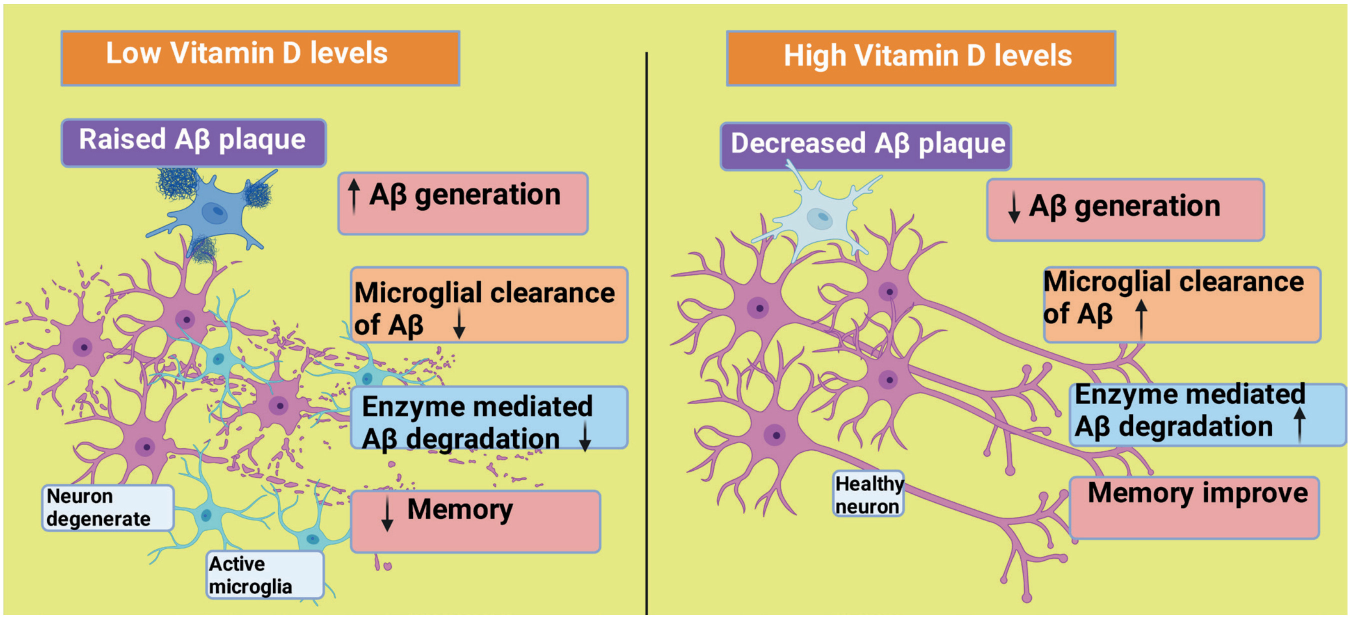

Figure 1: Depicting vitamin D's possible role in reducing Alzheimer's Disease and the effects of vitamin D deficiency on amyloid plaque formation.

Notes: ↑: Increase, ↓: Decrease.

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Even though the mechanisms involved in the other neuroprotective roles of vitamin D remain unclear, vitamin D has been reported to improve cognition via neurotrophy, neuroplasticity, neurotransmission, and neuroprotection [38]. Neuroinflammation may be prevented by vitamin D by inhibition of IL-6 and TNFα [51,52]. Vitamin D increases interleukin-10 expression and thus influences immune activation of microglia. VDR activation also regulates microglia polarization and reduces oxidative stress [53]. Long-term activation of astrocytes causes exacerbation of AD progression [54]. Reactive astrocytes augment the inflammatory response in neurodegenerative disorders, and the administration of vitamin D lowers the activation of astrocytes [55].

Vitamin D has a positive role in lowering inflammation and promoting cognition. Neuroinflammation may be a significant cause of progression of the condition like Alzheimer's Disease. As has been observed, vitamin D administration may help slow down the progression of this debilitating condition. The importance of vitamin D in neuroprotection needs to be showcased, and further research should be done to understand the mechanisms by which vitamin D can promote brain health. There should also be extensive research on other micronutrients that may halt or prevent the development of Alzheimer's Disease.

CONSENT FOR PUBLICATION

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including any accuracy or integrity issues.

DISCLOSURE

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All authors contributed significantly to the work, whether in the conception, design, utilization, collection, analysis, and interpretation of data or all these areas. They also participated in the paper's drafting, revision, or critical review, gave their final approval for the version that would be published, decided on the journal to which the article would be submitted, and made the responsible decision to be held accountable for all aspects of the work

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