Alzheimer's disease and the Possible role of vitamin D

Abstract:

Alzheimer's disease (AD) is a neurological illness that causes dementia. Despite the enormous global economic cost and impact on patients' immediate family members, there is no definitive cure, necessitating the development of improved therapeutic options. While memory and cognition are significantly impaired with Alzheimer's disease, the actual cause remains unknown. Among well-known hypotheses used to explain AD pathophysiology is Amyloid (A β) plaque development and aggregation hypothesis. There are now five FDA-approved medications that are used as therapy alternatives. All medications are used to treat symptoms of Alzheimer's disease. So, disease modifying treatments that target the AD pathological changes, are required. Those treatments may targeting suppression of the pathogenesis pathways. Vitamin D is generated in human epithelial cells through the photochemical formation and is also obtained through dietary resources. Calcium homeostasis and bone metabolism are two of the most well-known vitamin D impacts. Aside from that, non-traditional vitamin D benefits have recently acquired popularity. Vitamin D regulates the growth and activities of the central nervous system, which is an important but less understood function of the vitamin. Vitamin D's neuroprotective properties are associated with its effects on neurotrophin creation and secretion, neuromodulator synthesis, intracellular calcium homeostasis, and avoidance of oxidative nerve damage. The protective and therapeutic effects of vitamin D on neurodegenerative diseases are not intensively investigated

In this review, a comprehensive approach to understanding the pathogenesis of AD and the possible role of vitamin D in the protection and therapeutic of AD will be addressed.

Key words:

Alzheimer's disease, Central nervous system, Vitamin D, Genetic, Pathophysiology, Protection.

Introduction

Neurodegenerative disorders characterized by a gradual reduction of nerve cell functions or structure that may lead to neuron death. Neurodegenerative diseases included Huntington's disease (HD), Parkinson's disease (PD),Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) **(1)**. These disorders are considered incurable, and they cause a progressive decline in health to the point that neurons die. AD is commonest type of neurodegenerative disorders, about 75% of neurodegenerative cases **(2)**

The pathogenic hallmarks of Alzheimer's disease are thought to be aggregation of abnormal proteins in the brain, as amyloid beta (Aβ) and tau protein derivatives, then oxidative stress destruction and inflammations that caused disturbance in energy metabolism, localized synapsis failure, and deaths of the neurons **(3).**

Many licensed medications for Alzheimer's disease try to improve cognitive and reduce behavioral symptoms, however they only provide minor advantages to patients (Shen, 2022). As a result, there is more interest in non-pharmacological therapy to help people with Alzheimer's disease and their caregivers cope with their symptoms **(4)**.

The association between vitamin D and brain functions was discovered by researchers. The presence of receptors of vitamin D in the central nervous system suggests that vitamin D plays an essential role in the CNS, altering how people think, react, and learn. Some researchers refer to vitamin D as the “forgotten neurosteroid” **(5)**. Vitamin D also plays a significant function in reducing oxidative stress by increasing gene expression that code for antioxidant enzymes **(6)**. Vitamin D has neuroprotection, neurotrophy, neurotransmission, and neuroplasticity roles in the brain, so vitamin D deficiency may play role in dementia and AD progression **(7)**. Low levels of vitamin D associated with neurodegeneration disorders as Alzheimer's and Parkinson's diseases **(8)**.

Aim of this review was to summarize the mechanisms underlying Alzheimer's disease, shed light on the neuroprotective effects of vitamin D, association between vitamin D and Alzheimer's disease, and review possible potential vitamin D protective effects to Alzheimer's disorder.

Study design:

A systematic search of PubMed and Google scholar databases was made to retrieve the studies published about association between vitamin D and neurodegenerative diseases especially Alzheimer disease. The terms used for the PubMed and Google Scholar search are Neurogenerative diseases, Alzheimer disease, vitamin D protective effect, vitamin D therapeutic effect. The current search included studies conducted in humans, and animals and was restricted to English published researches. We also screened the reference lists of reviews and included the related researches in these lists.

Pathogenesis of AD

Alzheimer's disease is commonest neurodegenerative illness with about 50 million person had AD disease **(9)**. In Alzheimer's disease neurons die irreversibly, especially in hippocampus and cortex. It is characterized by decline cognitive functioning (visuospatial issues, memory, and executive functioning), emotional control, and neuropsychiatric manifestations as apathy, depression, and agitation **(2)**. The diagnosis of AD based upon neurological examination and elimination of other causes of dementia; only an autopsy provides a definite diagnosis. Neuronal loss, brain atrophy, extracellular collection of senile plaques containing the peptide Aβ and neurofibrillary tangles (NFTs) made from hyperphosphorylated tau proteins, as well as loss of synapses and neurotransmission dysfunctions are all symptoms of Alzheimer's disease. **(10)**, as well as neuroinflammation **(11)** are pathogenic markers of AD.

Various mechanisms of neurodegeneration emerged, as amyloid plaque accumulation, inflammatory reactions, neurofibrillary degenerations, excitotoxicity of glutamate neurotransmitters, increased intraneuronal influx of calcium, oxidative stress reactions and mitochondrial dysfunctions, despite the fact that the pathophysiological a etiology of AD is unknown **(12)**.

It is still unclear what causes Alzheimer's disease in the vast majority of cases, except for a few of them where genetic abnormalities have been identified. By cleaving amyloid precursor protein (APP), neurotoxic A is produced, and senile plaques, a prominent neuropathological stigmata of AD, are made by the aggregation of soluble oligomers **(13)**. As previously mentioned, APP serves as two enzymes substrates. They are α-secretase and β-secretase, respectively. The two enzymes split APP's extracellular domain, resulting in 2 soluble N-terminal peptides, APPsα and APPsβ, and C-terminal

fragments CTFα and CTFβ attached to membrane of cells. Proteolysis occurs next. A third enzyme, γ-secretase, cleaves the transmembrane peptides CTFα and CTFβ inside membrane. This leads CTFα to release the p3 peptide and amyloid β (Aβ) into the extracellular space. The soluble peptide p3 shows no tendency to agglomerate. In contrast, amyloid β prefers to clump together **(14, 15)**. Amyloid-β has 40–42 amino acids. This differs because of site alteration at which γ-secretase cleaves protein chain **(16)**. A(1–42) is the most damaging form, as it accumulate and adheres to amino3-hydroxy-5-methyl- 4-isoxazolepropionic acid(AMPA)) receptors (receptor of glutamate) and Ca2+ channels, raising Ca2+ inflow and intracellular Ca2+ levels **(17)**. This leads local inflammatory reactions to neuronal cells apoptosis and death **(18)**.

A generates hydrogen peroxide during aggregation process, that potentiated by Cu2+ and Fe2+ ions. Electrochemically active Cu2+ ions trapped inside Aβ were capable of creating reactive oxygen species (ROS) **(19)**. The lipids peroxidation in neuronal cell membranes caused by these ROS causes glucose transporters and ion channel ATPases to malfunction. Because of oxidative stress generated by Aβ, the neurons' ion balance and metabolism are disrupted, making them vulnerable to death **(13)**. The creation of aggregates known as neurofibrillary tangles (NFTs) caused by tau protein hyperphosphorylation, a structural protein linked with cytoskeleton of neurons. These factors result in hampered neuron transmission and, eventually, neuron death **(20)** (Fig. 1).

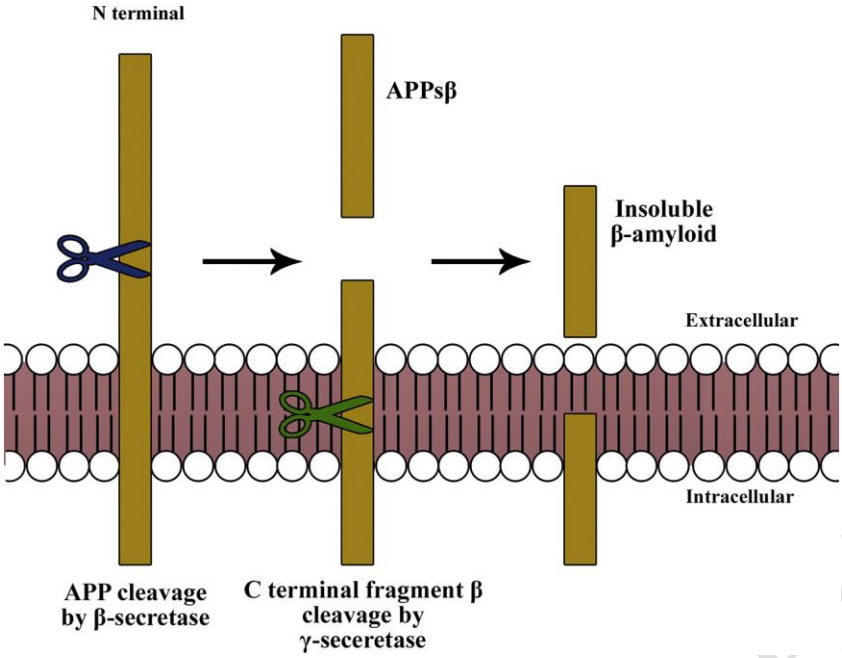

Fig. 1. Diagram showing insoluble amyloids β formation from amyloid precursor protein (APP) (13).

Vitamin D and neuroprotection

Vitamin D can be produced inside the body. It regulates calcium-phosphorus metabolism and has a variety of biological functions, including brain function and immune response modulation **(21-23)**. Vitamin D is made by irradiating a cutaneous molecule, 7-dehydrocholesterol (7-DHC), with ultraviolet B (UVB) rays. When UVB photons interact with 7-DHC, they make cholecalciferol, which requires two hydroxylation processes to become active form of vitamin D. The hydroxylation first takes place in the liver, where a 25 hydroxylase produces 25(OH)D, but the second hydroxylation is mostly dependent on the kidney 1,25 hydroxylase, which generates 1,25(OH)2D. Vitamin D's active form also created in a varies tissues, as brain, lung, placenta, prostate, and cells of immune system **(24, 25)**. Vitamin D binding protein (VDBP) carried 25(OH)D and 1,25(OH)2D from kidney and liver to other tissues, where active form of vitamin D combines with nuclear vitamin D receptor (VDR), resulting in non- genomic and genomic effects **(21, 26, 27)**.

The presence of the enzyme 25(OH)D3-1α-hydroxylase, which produces the active form of vitamin D, and VDR in the CNS, mainly in hypothalamus and dopaminergic neurons of the substantia nigra of the basal ganglia, indicate that vitamin D has both paracrine and

autocrine actions on CNS function **(28)**. A growing interest in vitamin D effects on CNS led many researchers to investigate 25(OH)D circulating values in AD patients **(29-35)**.

Vitamin D's active form linked to alterations in the formation and release of neurotrophic factors as nerve growth factor (NGF), which is essential for neuron development, and increased values of glial cell line-derived neurotrophic factor (GDNF). When vitamin D is given to hippocampus neurons, it greatly increases rate of neurons outgrowth **(36)**. Also, 1,25-(OH)2 D3 modifying acetylcholine synthesis *via* increased enzyme choline acetyltransferase (CAT) gene expression **(37)**. Vitamin D affects GABA-ergic neurotransmission genes expression **(38)** and enhanced tyrosine hydroxylase (TH) expression, essential for catecholamine generation **(39)**. The production of proteins that bind calcium (Ca2+) ions (e.g., parvoalbumin) and maintain homeostasis of cellular calcium, which is essential for CNS cell functions, is one of vitamin D's neuroprotective effects **(40)**. Elevated calcium in nerve cells leads to excitotoxicity due to enhancement release of stimulating amino acids, and other stimulating neurotransmitters, nitric oxide synthase (NOS) activation, reactive oxygen species (ROS) generation, proteases and lipases enhancement that leads to plasmic and mitochondrial membrane destruction. A disturbed in calcium ion transport and high calcium values stimulates lipid peroxidation and arachidonic acid pathway **(40)**.

Evidence revealed that vitamin D might protect against cognitive decline by its effects on neurotransmission, neuroprotection, synaptic plasticity, immune modulation, neuronal calcium regulation, and enhanced nerve conduction **(41, 42)**, with secondary protective effects on vascular systems and modifying vascular risk factors **(43)**. I*n vitro* studies showed that treatment with vitamin D had anti-inflammatory action by inhibiting interleukin (IL)-6 and tumor necrosis factor (TNF)-α generation **(44)** (Fig. 2). In this respect, Azhari and Maimanee **(45)** conducted cross section study on 343 females (18 to 59 years old) from King Abdul Aziz University, Jeddah, Saudi Arabia and measured their serum levels of 25-hydroxyvitamin D and assessed their cognitive levels using Brief Cognitive Status Exam (BCSE). They found that serum 25-hydroxyvitamin D levels were significantly correlated with cognitive status and severely deficient 25-hydroxyvitaminD was independent predictors for cognitive defect.

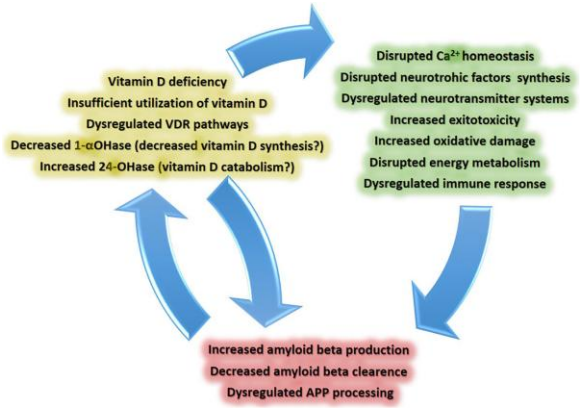

Fig. 2 Relation between amyloid β pathology and vitamin D in Alzheimer's disease **(46)**.

Genetic association between AD and vitamin D

From 1998 until first decade of 2000s, different chromosome 12 loci were thought to be risk loci for Alzheimer's disease **(47-51)**. The location is significant because VDR gene is also found in same place. VDR gene variant increase risk of Alzheimer's disease by 2 to 3 times **(52)**. Based on a genome-wide association study that enrolled 518 AD cases and 555,000 single nucleotide polymorphisms, Beecham et al. revealed that among a number of proximal candidate genes in 12q13 area, VDR is most likely genetic risk factor for AD (SNPs) **(51).** SNPs in VDR gene hypothesized to cause some alterataions in vitamin D-VDR pathway **(52-54)**. With the rs2228570 exception, none of the SNPs in VDR gene have a functional action (FokI site). Exon 2 of VDR gene has rs2228570, that results in a three-amino-acid elongated version of VDR **(55)**. Intron 8 of VDR gene has rs1544410 (BsmI site), rs7975232 (ApaI site), and rs757343 (Tru9I site) SNPs. The other SNP, rs731236 (TaqI site), present in exon 9 of VDR gene. The intronic SNPs believed to be in strong linkage disequilibrium with SNPs in 3′ untranslated region, which included in VDR gene expression regulation **(55)**.

Researches made over past 15 years revealed link between VDR polymorphisms and cognitive decline **(56, 57),** Alzheimer disease **(52, 54, 58)**, and Parkinsonism **(59, 60)**. Researches revealed that SNPs of megalin (low-density lipoprotein receptor-related protein 2-LRP2), a cell membrane vitamin D transporter, linked with Alzheimer's disease **(61, 62)** and cognitive decline **(57)**. Although, these researches strongly suggest role in genetic background of neurodegenerative diseases of genes related to vitamin D

metabolism, transport and receptors, more studies required to fully investigate the issue (Fig 3).

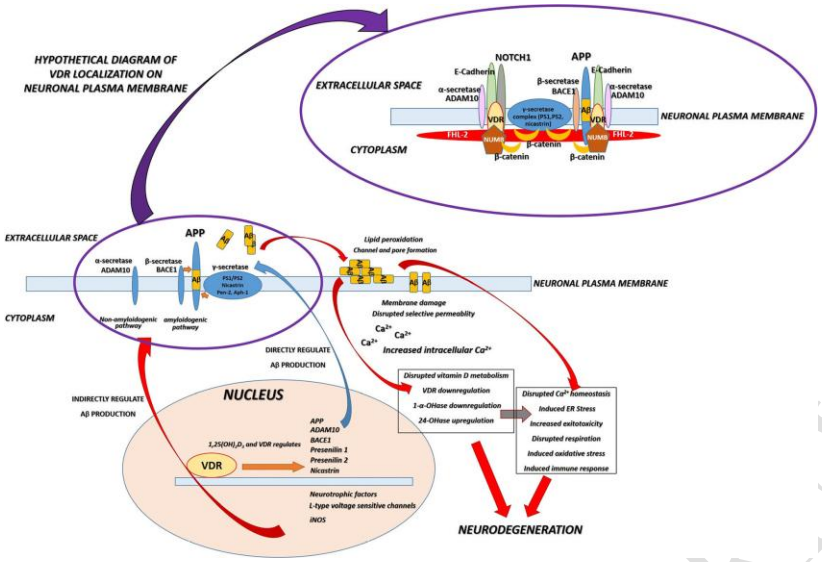

Fig. 3 Hypothesis of association between vitamin D receptor (VDR) and Aβ-induced neurodegeneration **(63)**.

Vit D status and risk of AD

As the population continues to age, it is more important to identify modifiable risk factors for Alzheimer's disease in terms of lifestyle and diet. Moreover, to possibly modifiable risk items for Alzheimer's disease like obesity, hypertension, type 2 diabetes mellitus, and smoking, vitamin D deficiency has been proposed to play a possible predictive role **(7)**. Vitamin D important for maintaining cognitive functions in old age people **(64)**. Vitamin D receptors found in CNS areas essential for memory formation and cognition and included in plaque removal **(65, 66)**.

The link between vitamin D deficiency and cognitive defect had been studied in several systematic reviews and clinical trials, with varied results. A meta-analysis study comparing people with dementia to those without found that those with AD had lower vitamin D levels **(67)**. A meta-analysis of cross-sectional researches reported low serum vitamin D concentrations associated with AD prevalence **(68, 69)**. In 2004, **Littlejohns et al. (32)** enrolled 1658 person, of them 171 acquired dementia (102 Alzheimer disease of 171 dementia cases) for 5.6 years follow-up duration. Results showed that persons had

25(OH)D serum value less than 25 nm/L posed 2-folds risk of AD onset versus those persons with more than 50 nm/L. **Licher et al. (33)** found that subjects with vitamin D less than 25 nmol/L (defined as vitamin D deficiency) had elevated risk of having dementia versus those with more than 50 nmol/L (vitamin D sufficiency), but this finding were insignificant. Meanwhile, longitudinal studies (follow-up duration 13.3 years) showed that lower the baseline 25(OH)D values, the elevated AD developing risk. Another meta-analysis of 18,974 adults revealed that severe vitamin D deficiency (less than 10 ng/ml) increased dementia risk by 54% **(70)**. A meta-analysis of 5 cohort researches revealed that sufficient vitamin D linked with lower risk of dementia and AD **(71)**. **A** meta-analysis study **(72)** that included six researches **(32, 73-77)** involving 14,618 person reported significant positive associations between vitamin D deficiency (less than 20 ng/ml) and risk of AD and dementia. In elderly and young patients (30–60 years old), low vitamin D values were linked to significant losses in cognitive functioning, according to a cross-sectional analysis utilizing Pearson's correlations **(78)**.

In contrary, Ulstein et al. **(79)** reported lack relation between vitamin D values and AD development. Karakis et al. (80) analyzed 1663 non-demented persons for 9 years follow-up duration, and reported lack link between 25(OH)D values and AD incident. In Middle East, a prospective cohort research of 13,044 people revealed that lower vitamin D values evaluated in middle age were not linked with faster cognitive deterioration during a 20 years follow-up duration **(81)**. A systematic review also found no evidence of link between cognitive deterioration and plasma 25(OH)D values **(82)**.

Current research has not fully confirmed pathophysiological processes underpinning the potential impacts of vitamin D values on risk of dementia and Alzheimer's disease, although different theories suggested. A deposition and tau protein tangles in brain tissue are two putative pathogenic pathways discovered thus far and used to identify clinical cognitive defect **(83)**. Vitamin D insufficiency causes an increase in Aβ deposition in the brain tissues, according to animal researches **(84)**. In human studies, vitamin D demonstrated to cause an increase in plasma Aβ, particularly in the elderly pearsons, implying a decrease in brain Aβ **(85)**. Vitamin D also affects the voltage-gated calcium channel that Aβ peptides target, implying that vitamin D helps restore calcium

homeostasis in neurons **(86)**. Vitamin D reduces glutamate neurotoxicity by increasing VDR expression and acting as an antioxidant hormone **(87)**.

Vit D can it prevent AD

Alzheimer's disease is a neurodegenerative disease that affects memory and function. Since they have lost their autonomy, patients find it difficult to acquire enough sunlight exposure to synthesize appropriate vitamin D. Similarly, for some people, getting adequate vitamin D-rich foods can be problematic. (88). Limitation of exogenous vitamin D result in low serum vitamin D levels in Alzheimer's patients. Durk et al. investigated effect of VDR in decreasing brain soluble and insoluble amyloid β peptides in mice. They demonstrated that VDR is promising therapeutic target for Alzheimer's disease prevention and therapeutic (84).

Vitamin D supplementation proven to be effective in AD patients in a small number of researches. Annweiler et al. revealed that combining vitamin D with memantine (an AD medicine) had better effects than treating individuals with memantine only **(89)**. Another research revealed that vitamin D intake for six months effective in mild cognitive defect cases (90). Lemire et al. revealed that memantine inhibits cognitive defect that accompanies vitamin D deficiency onset, suggests that AD cases must administered combining both vitamin D supplements and memantine **(91)**. One of two intervention researches revealed that vitamin D intake led to enhancement in cognitive performance in cases with senile dementia (92), while second study revealed that vitamin D treatment is an independent protecting factor in Alzheimer’s disease progression **(93)**. More evidence about the link between mild cognitive impairment and vitamin D may be helpful in the early stages of dementia, like mild cognitive impairment **(94)**. As a result, future prospective researches must look at link between vitamin D insufficiency and early stages of Alzheimer's disease and dementia.

Limitations of the review

In this review there is a lack of levels of vit D defect and severity of Alzheimer disease manifestations and associated pathology of the brain as degree of plaque deposits of the

brain. Another limitations are the studies that associated between supplements of vitamin D and decreased severity of AD after longitudinal study for long periods.

Conclusions

Alzheimer's disease is primary reason of dementia in patients over age of 65 all over the world. Even though the specific causes of AD disease have yet to be discovered, various possibilities exist to explain disease's pathophysiology. Patients with the severe form of disease will be unable to accomplish even most basic physical duties, and will be completely reliant on others for practically all of their daily activities. When illness is severe, they may have difficulty doing things like swallowing. Mostly, the cognitive defects happened in AD cases followed about twenty years of beginning of Aβ plaques aggregating. So, when one is suspected to have AD, they have undergone major neuron damage most of the time. Till now there is lack of cure therapy for AD. Approved used medications in AD therapy are symptoms improving therapy. They did not stop disorder progression but improve AD patients' memory decline to certain extent. Based upon current hypotheses, drugs that selectively inhibits β or γ secretase domain included in Aβ formation, drugs that can selectively inhibit Aβ accumulation, therapy that can dissolve Aβ plaques, neuroprotective therapy, neurogenerative therapy, tau phosphorylation inhibiting therapy, tau accumulation inhibiting therapy must be effective treatments.

Vitamin D has many functions in the treatment of dementia and AD, according to evidence from animal and cellular studies. According to cross-sectional and case-control researches, vitamin D levels in patients with cognitive defect are lower. In a small number of longitudinal studies, low vitamin D levels were connected to raised risk of cognitive defect, all-cause dementia, and Alzheimer's disease, but not in bigger studies with longer (18–20 years) follow-up periods. Clinical research examining the effects of vitamin D supplementation on cognitive outcomes have yielded conflicting results; however, a number of methodological flaws limit the applicability of these findings.

Future researches

There is still a lack of agreement on the exact quantity of vitamin D to use and the best age to start treatment for people who are at risk. Large double-blind, randomized, placebo-controlled trials with the appropriate dosage and duration may also give conclusive results. This collection of research implies that vitamin D could be a new paradigm for dementia and Alzheimer's disease prevention and treatment.

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