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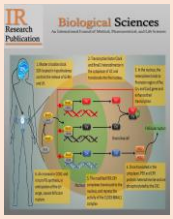

Emerging role of genetic factors related to Vitamin D in Alzheimer's disease

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ABSTRACT

Alzheimer's disease is an insidious progressive neurodegenerative disease. The pathological markers of AD are Aβ plaques and NF-tangles formation in the hippocampus, cortex region of the brain. Vitamin-D is a steroidal vitamin that plays an important role in AD and is a neuroprotective agent having anti-inflammatory, antioxidant, and anti-Aβ formation of APP in AD patients as reported in the recent literature. Vitamin D3 enhances the level of mitochondrial complexes I, II, III, and IV and decreases the level of NF-kB in the hippocampus and cortex region of the brain. It helps in the regulation of amyloid precursor protein in normal humans. But if is deficiency occurs, it causes a rise in the level of the Aβ protein plaque formation that leads to the onset of AD symptoms. It also has an ACE inhibiting property which is beneficial in AD. It attenuates the neuroinflammatory action in the hippocampus and reduces the neuronal degeneration in the cortex region of the brain. The goal of this review is to discuss the role of Vitamin D in AD and the genetics associated with AD.

Introduction

Alzheimer's disease (AD), the most common form of dementia in older individuals, is distinguished by gradual deterioration of memory and cognitive abilities generally characterized by extracellular Aβ deposits, abnormal tau protein buildup, and loss of neuronal connections and pyramidal neurons [1]. Multiple etiologic theories have been provoked, including mitochondrial dysfunction, genetic abnormalities, the development of neurofibrillary tangles, altered amyloid precursor processing, an inadequate amount of neurotropic agents, trace element neurotoxicity, an insufficient energy metabolism, and oxidative stress [2]. A common target in many neurological disorders and the majority of dementias is the hippocampus, a crucial area of the medial temporal lobe. It is generally known that many of the cognitive abnormalities seen in AD, especially those affecting long-term memory, are caused by damage to the hippocampus [3]. The cytoskeletal cellular abnormalities that develop in Alzheimer's disease are related to cognitive impairment and are linked to microtubule dysfunction [4]. An abnormally elevated amount of amyloid beta (Aβ) peptide across the brain is one of the distinguishing features of AD. Aβ peptide is often produced by neurons and brain barrier through an efflux transport mechanism as well as by being degraded by the proteinase

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Abbreviations: AD: Alzheimer's disease; Aβ: Amyloid beta; BBB: Blood-brain barrier; VDR: Vitamin D receptor; BMD: Bone mineral density; PTH: Parathyroid hormone; OH: Hydroxyvitamin; OH2: dihydroxyvitamin; HLA: Human leukocyte antigen; IL: Interleukin; ACE: Angiotensin-converting enzyme; APP: Amyloid precursor protein; ApoE: Apolipoprotein E; CSF: Cerebrospinal fluid; LDL: Low-density lipoprotein

enzyme within the brain tissues. A proposed theory suggests that late-onset AD, which accounts for more than 90% of all cases of AD, is marked by defective cerebral clearance of the Aβ peptide, which results in an abnormal increase in its brain level [5]. Cerebrovascular dysfunction has been linked to impaired Aβ peptide clearance through the blood-brain barrier (BBB), and low vitamin D3 levels have been linked to an increased risk of AD and vascular problems [6].

It has been established that the neuronal damage associated with AD and the cognitive deficits observed in older people are both strongly associated with oxidative stress, which is triggered by increased free radical formation and depleted endogenous antioxidant defenses [7]. Malnutrition increases the risk of dementia and AD. Recent research indicates that vitamin D, which is primarily recognized for its effects on calcium and bone metabolism, may also have neuroprotective properties and may be crucial for maintaining cognitive processes via a variety of pathways [8].

Vitamin D3 plays an important role in mitochondria such as enhancing the level of mitochondrial complex-I, II, III, and IV in the hippocampus and cortex region of the brain [9]. It plays an important role in neuroinflammation. It decreases the protein expression of NF-kB in the neurons of the hippocampus and cortex region of the brain as shown in Figure 1. AD and vitamin D have been examined together, although it's still unclear how exactly vitamin D affects the onset and course of AD [10]. Still, several possible processes have been given in Table 1.

Vitamin D

Vitamin D is a secosteroid hormone having precursors vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol), which are inactive, are together referred to as vitamin D. The skin may produce precursors after exposure to sunshine, or they can be consumed through food. The precursors are changed into 25-hydroxyvitamin D 3 [25-(OH)D3] vitamin D3 in the liver. The most active vitamin D metabolite, 1,25-dihydroxyvitamin D 3 [1,25(OH)2 D3], is created in the kidney by the hydroxylation of 25-(OH)D3 to this compound [18]. Vitamin D receptor (VDR) refers to the site where vitamin D metabolites act. Recently, it was shown that neurons also express the VDR, making them a possible target tissue for vitamin D metabolites [19]. The hypothalamus, substantia nigra, cortex, and hippocampus are among the areas typically impacted by AD and have high levels of VDR expression. It is unknown how essential adequate vitamin D sufficiency is for human cognitive function.

According to investigations, Bone mineral density (BMD) and its relationship to the biochemical indicators of AD patients were researched [20]. They discovered that those with AD had BMD that was significantly lower than that of age-matched controls. Additionally, they discovered that 26% of these patients had blood 25OHD3 deficits (5–10 ng/mL) and that 54% of them had osteomalacic levels (5 ng/mL). In another study, there was no significant difference in bone density between people with mild dementia and normal cognitive women; nevertheless, there were substantial changes in parathyroid hormone (PTH) and vitamin D levels across groups [21]. Since high PTH concentrations are associated with a 5-year deterioration in cognitive function in an older population, independent of ionized calcium levels and renal function, subclinical hypovitaminosis D is expected to occur often in demented patients. In addition, it was discovered that individuals with AD who had reduced BMD, lower blood ionized calcium levels, and 25OHD with compensatory hyperparathyroidism had a higher risk of hip fracture [22]. It is uncertain if a lack of vitamin D promotes or is a result of AD. Calcium levels are higher in neurons with neurofibrillary tangles compared to neurons without tangles in AD patients, according to nuclear microscopy examination of the samples from the patients [23],[24]. These results might suggest a connection between vitamin D and AD.

Genetic factor related to vitamin D in AD

According to studies, a number of genes in the MHC region increase vulnerability to AD. The MHC region's human leukocyte antigen (HLA) genes have been linked to an increased risk of AD. It has been observed that AD brains express more MHC class II glycoprotein on microglial cells [25],[26],[27]. It has been shown that AD retinae have substantially enhanced MHC class II expression [28]. Additionally, the number of HLA-DR and interleukin 2 (IL-2) receptor-positive cells was elevated in the postmortem brains of AD patients and correlated to Shalit et al, there was no change in the levels of CD4, presence of senile plaques [29]. According CD8, or

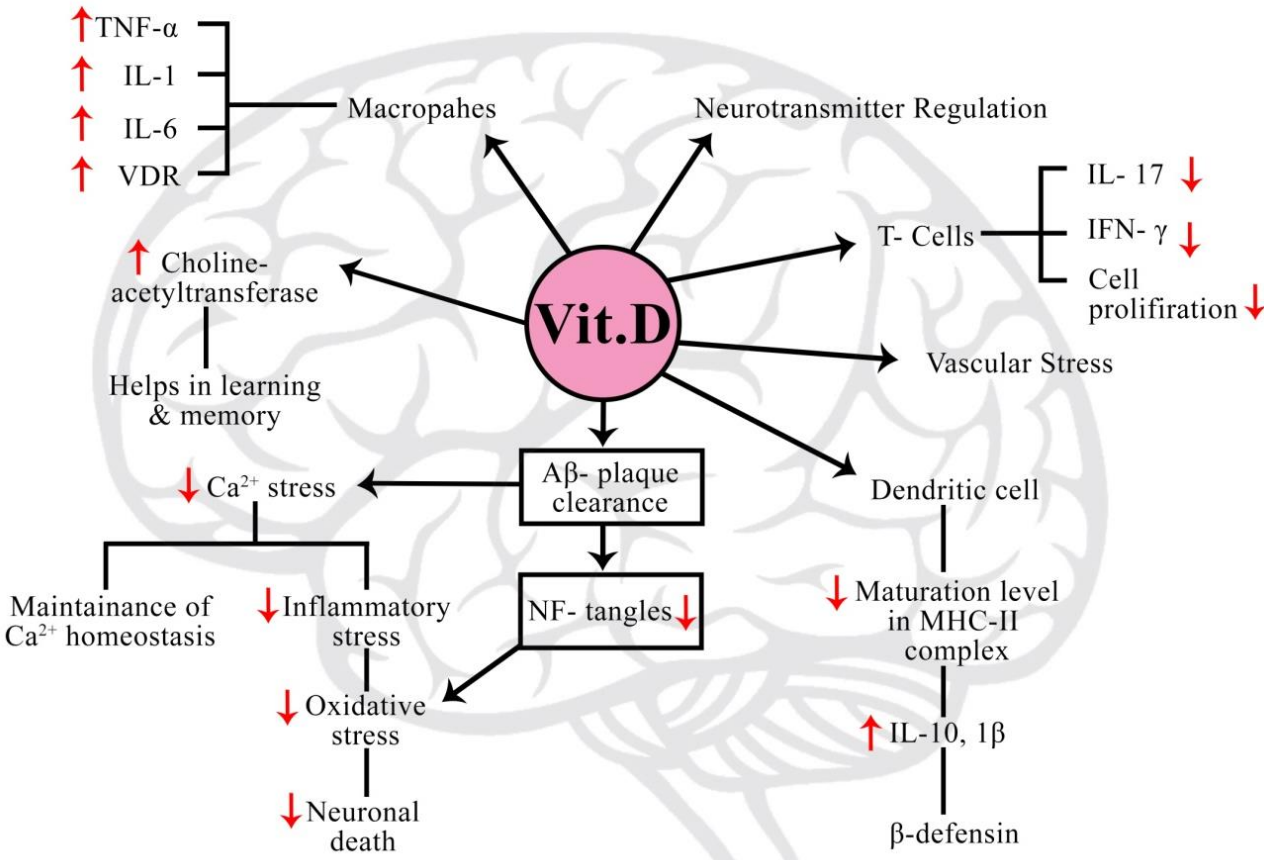

Figure 1. Role of Vitamin D in AD.

IL-2 in the moderate stage of AD with the although there was a modest rise in HLA-DR levels [30]. However, there was a considerable rise in HLA-DR and CD4 and a little drop in CD8 in the moderately severe stage, indicating that peripheral immune response in AD may be connected with the clinical stage of the illness. Additionally, after long-term therapeutic immunization with a DRB1*1501 allele-carrying Aβ peptide, the brain parenchyma was successfully cleansed of the substance, and brain microglial activation was decreased [31]. This indicates that HLA-DR alleles directly connect with certain Aβ T-cell epitopes due to the prevalent DRB1*1501 allele in this AD-causing animal strain.

The potential to connect molecular changes with epidemiological data is provided by genetic research. Polymorphisms, which are differences in DNA sequence, have both minor and subtle biological impacts. Both neurons and glial cells had VDR and 1α-hydroxylase, two enzymes that work together to create active vitamin D in the human brain. VDR was confined to the nucleus whereas 1α-hydroxylase was located throughout the cytoplasm in both neurons and glial cells [32]. VDR expression is downregulated in the hippocampus, which is more susceptible to AD, in individuals with AD [33].

In homogenates of postmortem brain tissue from AD patients, angiotensin-converting enzyme (ACE) activity was found, and it was related to the amount of Aβ plaque [34]. According to another investigation, increased neuronal and perivascular ACE immunoreactivity was also seen in the parietal cortex of AD [35]. Recently, it was shown that peripheral blood from AD patients with later onset had enhanced ACE activity; however, there was no relationship between this finding and the amount of Aβ present [36]. ACE has been shown to inhibit Aβ aggregation and to lower the levels of secreted Aβ in living cells; this effect was blocked by ACE inhibitor, whereas ACE inhibitor was reported to not affect cerebral Aβ levels and plaque deposition in vivo in another study. The role of ACE in AD is still controversial [37],[38],[39]. Long-term ACE inhibitor therapy increased Aβ deposition in aged amyloid precursor protein (APP) transgenic mice, even while short-term treatment with ACE inhibitors failed to boost Aβ formation in the brain [40]. In contrast to the D/D genotype, the ACE I/I genotype and I allele revealed an elevated risk of AD [41],[42]. In comparison to the D/D genotype, the I/I genotype has been associated with lower hippocampus and amygdale volumes as well as tendencies towards a higher brain Aβ-42 burden [43]. Additionally, genetic mutation of the VDR caused the RAS to be

Table 1. Different mechanisms of vitamin D in AD.

S. No.	Effect	Mechanism	Reference
1.	Neuroprotection	There is evidence that vitamin D has neuroprotective qualities. It might be useful in protecting neurons against damage carried by factors such as oxidative stress, inflammation, and beta-amyloid plaques—all of those considered prevalent aspects of AD.	[11], [12]
2.	Anti-inflammatory effects	It was previously demonstrated that vitamin D reduces inflammation in the brain. It is thought that AD develops and progresses as a result of chronic inflammation, and vitamin D may help regulate this inflammatory response.	[13]
3.	Regulation of calcium homeostasis	Calcium homeostasis is essential for brain function and is mostly regulated by vitamin D. In AD, dysregulation of calcium levels has been linked to cell death and neural dysfunction.	[14], [15]
4.	Impact on amyloid-beta metabolism	According to certain research, vitamin D may have an impact on how amyloid-beta, a protein that causes plaques in the brains of AD patients, is metabolized. Amyloid-beta clearance-related regions of the brain have vitamin D receptors, and vitamin D may assist in controlling the production of enzymes involved in amyloid-beta metabolism.	[16]
5.	Neurogenesis and synaptic plasticity	The development of new neurons and synaptic plasticity, which is the capacity of synapses to become stronger or weaker over time and is essential for remembering and learning, constitute two additional mechanisms that vitamin D may influence and which may be compromised in AD.	[17]

overstimulated, increasing the synthesis of renin and angiotensin II, which led to excessive blood pressure and cardiac hypertrophy. Additionally, vitamin D has been shown to reduce ACE activity in bovine endothelial cells [44].

In addition to playing a significant genetic role in AD, apolipoprotein E (ApoE) plays key roles in both local and systemic lipid transport. Those who carry at least one ApoE ∈4 allele are more likely to develop AD [45]. The cerebrospinal fluid (CSF) of AD patients has been observed to considerably differ from normal levels of ApoE [46]. Low-density lipoprotein (LDL) and acetyl-LDL specific saturable receptors in macrophages are induced by calcitriol; the LDL receptor of 1,25OHD-induced macrophages was discovered to have selectivity for ApoB and E-containing lipoproteins [47]. In ApoE knockout mice, an animal model with dyslipidemia, severe oxidative stress, and significant atherosclerosis following uninephrectomy, animals showed reduced plaque formation and calcification with vitamin D analog therapy (paricalcitol) compared to control groups [48].

A nuclear protein called poly(ADP-ribose) polymerase-1 (PARP-1) is involved in both neuronal death and survival under stressful conditions. Poly(ADP-ribose) Peripheral blood mononuclear cells from moderate cognitive impairment patients exhibit increased polymerase cleavage [49]. Increased PARP activity has been documented in AD and proposed as a diagnostic indicator for AD [50]. The amount of PARP polymers increased with aging in the brains of an Alzheimer's mice model, and A-activated PARP polymers caused astrocytic metabolic failure and neuronal death in response to oxidative stress [51]. AD risk is strongly correlated with the PARP-1 gene. While the Ht1-TC haplotype showed a protective effect against AD as compared to control persons, the PARP haplotypes Ht3-TT and Ht4-CC were substantially related to an elevated risk of AD [29]. Additionally, calcitriol administration resulted in a reduction in PARP-1 levels in NB4 acute promyelocytic leukemia cells [52]. Inhibition of PARP-1 by vitamin D occurs in a concentration-dependent manner in human keratinocyte cells [53]. Nicotinamide also promoted the vitamin D-induced downregulation of PARP in human myeloblastic leukemia cells [54]. Dexamethasone and vitamin D may have an anti-inflammatory impact because of their capacity to reduce microglial activation, according to PARP attenuation in the hippocampus tissue of rats given these medications [55].

Role of Vitamin D in APOE regulation

Proteins such as APOE are involved in the body's lipid metabolism and transport, particularly the movement of cholesterol. The APOE gene contains three common alleles, which are APOE ε2, APOE ε3, and APOE ε4 [56]. Although the APOE ε2 allele may be protective, the APOE ε4 allele is the highest genetic risk factor for late-onset AD. It has been demonstrated that vitamin D interacts with the VDR to affect gene expression [57]. A vitamin D response element (VDRE) has been found in the promoter region of the APOE gene, indicating that vitamin D may directly control APOE expression by binding to the VDR and altering gene transcription [58]. Since chronic inflammation is linked to elevated APOE expression, vitamin D possesses anti-inflammatory qualities. It is possible that vitamin D indirectly affects APOE levels by lowering inflammation. Both vitamin D and APOE have been found to have an impact on cholesterol homeostasis and cholesterol metabolism, respectively [59]. Low levels of vitamin D can cause dysregulated metabolism of cholesterol, which can affect the expression of APOE. Indirect impacts of vitamin D's neuroprotective properties on APOE expression may exist. Vitamin D can protect neurons from harm and support neuronal health, which may have an impact on the expression of genes, such as APOE, linked to neurodegenerative illnesses like Alzheimer's [60]. All things considered, there is evidence that vitamin D may be involved in the control of APOE expression, although the precise processes underpinning this connection are still unknown.

Role of Vitamin D in APP regulation

The APP, a transmembrane protein, is implicated in the etiology of AD. It is broken down into different components by a variety of enzymes, including Aβ, which accumulates in the brain to form plaques that are characteristic of AD [61]. The function of vitamin D in the regulation of Aβ production and APP assessment has drawn attention in the context of AD. In the nucleus, vitamin D binds to VDRs and functions as a transcription factor to control the expression of target genes [62]. According to certain research, the expression of genes related to APP processing may be influenced by vitamin D/VDR signaling. Vitamin D may have an impact on the synthesis of Aβ by modifying the expression of these genes. The activity of α- and β-secretases, two enzymes that cleave APP, may be affected by vitamin D. In the Aβ area, α-secretase cleaves APP to produce non-amyloidogenic fragments, whereas β-secretase cleaves APP to produce Aβ [63]. According to some studies, vitamin D may favor the non-amyloidogenic route and lower the formation of Aβ by upregulating α-secretase activity and downregulating β-secretase activity.

Prolonged inflammation is associated with the pathogenesis of AD and can impact how the APP is digested. Due to its anti-inflammatory properties, vitamin D may influence Aβ production and APP metabolism indirectly by reducing brain inflammation [60]. The dysregulation of calcium homeostasis in AD is influenced by vitamin D. Aβ synthesis and APP processing can be impacted by calcium dysregulation. Vitamin D may have an indirect effect on APP metabolism by preserving calcium homeostasis [64]. The accumulation of harmful Aβ species and inappropriate utilization of APP may be lessened by vitamin D's neuroprotective actions, which maintain the integrity and function of neurons. Regarding data from in vitro and animal studies suggesting a potential role for vitamin D in controlling APP metabolism and Aβ production, human clinical studies have shown contradictory results [65].

Conclusion

Vitamin D has a positive effect on AD and enhances cognitive performance in some AD patients. Finding the proteins that connect vitamin D to AD pathogenesis has been made possible by genetic investigations. Additionally, vitamin D affects AD via non-genomic pathways. Patients with AD should have their vitamin D levels checked. Because of its receptor in the CNS and its active form of vitamin D3 metabolite, calcitriol is most effective for treating AD. However, because calcitriol prevents the liver's ability to produce serum 25OHD, monitoring serum 25OHD after taking it is not essential but calcium and PTH levels must be considered while changing the dosage of calcitriol. Calcitriol can both raise hypercalcemia and reduce PTH levels when vitamin D deficiency causes secondary hyperparathyroidism. Additional research on genetic factors related to vitamin D in AD is required.

Contribution of authors

Mr. Kamaljeet collected literature for this review article and writing the manuscript. Mr. Kamaljeet and Mr. Lovekesh Singh are the major contributors to writing, analyzing, drafting, and referencing the manuscript. Mr. Kamaljeet and Mr. Lovekesh Singh are major contributors to writing and drafting the manuscript as well as all authors read and approved the final manuscript.

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Conflict of Interest

The authors have declared that no competing interests exist.

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