Journal of Pharmaceutical Research International

32(35): 97-113, 2020; Article no.JPRI.63214
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

The Association of Vitamin D with Brain Cognitive Functions: A Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2020/v32i3530982
Editor(s):
(1) Dr. Syed A. A. Rizvi, Nova Southeastern University, USA.
Reviewers:
(1) Hima Ann Isaac, Sri Ramachandra Institute of Higher Education and Research, India.
(2) Blaženka Miškić, Josip Juraj Strossmayer University of Osijek, Croatia.
(3) Obodo Basil Nnaemeka, Ambrose Alli University, Nigeria.
Complete Peer review History: http://www.sdiarticle4.com/review-history/63214

Review Article

Received 19 September 2020
Accepted 23 November 2020
Published 17 December 2020

ABSTRACT

Vitamin D is a well-known steroid hormone that plays an important role in controlling bone levels of calcium, phosphorus, and overall mineralization. Several animal and human studies indicate that vitamin D hypovitaminosis may be linked to an increased risk of developing Alzheimer's disease and dementia. The objective of the present review is to summarize current knowledge of the effects of vitamin D deficiency and vitamin D intake on cognitive function. The possible underline mechanisms of these effects were also discussed. We reviewed the literature starting from 1986 to 2019 by searching PubMed, Cochrane, Semantic Scholar, Medline, Scopus, and Cochrane Library databases for all observational studies, randomized clinical trials, meta-analyses, and systematic reviews using the keywords "vitamin D and Alzheimer disease", "neuroprotective effect of vitamin D", "vitamin D deficiency and Alzheimer ", "role of vitamin D in neurodegenerative diseases ", " vitamin D and amyloidogenesis", "acetylcholine and vitamin D", and "memory and vitamin D ".We

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also referred to animal and in vitro studies that dealt with the possible mechanisms of actions of the neuroprotective effect of vitamin D. Our findings showed that Vitamin D supplementation improves cognitive performance via reducing amyloidogenesis, restoration of neurotransmission, maintaining calcium balance, regulating neurotrophic factors, anti-inflammatory action, apoptosis regulation, antioxidant, and vascular processes. This review might be open new horizons in the understanding of the molecular mechanisms of the disease and neurodegeneration and enable the development of new approaches in treatment and prevention of the disease.

Keywords: Vitamin D; cognitive function; alzheimer's disease; dementia.

1. INTRODUCTION

Vitamin D is a master steroid hormone that plays a significant role in bone homeostasis by regulating several minerals and hormones such as the controlling calcium, phosphorus. Apart from the critical vitamin D3 roles on the health and integrity of bone, findings obtained from numerous studies deliver convincing proof on the diversity of vitamin D functions in different body systems and tissues including brain [1]. In many studies, vitamin D deficiency was associated with cognitive impairment. In the 2017 systematic review and meta-analysis studies including over 19,000 participants, low vitamin D status was associated with cognitive decline (odds ratios (OR): 1.26) and poorer cognitive performance (OR: 1.24) among participants without dementia [2]. Clinical and animal studies have reported a possible neuroprotective role of cholecalciferol on cognitive function via reducing amyloidogenesis, restoration of neurotransmission, maintaining calcium balance, regulating neurotrophic factors, anti-inflammatory, apoptosis regulation, antioxidant activity, and vascular processes [3].

Alzheimer's disease (AD) is a long term non-curable progressive neurodegenerative disorder associated with progressive deterioration of memory ability and cognitive function that are necessary for conducting daily live activities [4]. By far, the AD is the most frequent cause of dementia, accounting for an estimated 60 to 80 percent of cases [5]. Early pathophysiological changes of AD have primarily appeared in the brain tissues that are located in the frontal and temporal lobes [6]. Those changes are associated with the accumulation of insoluble forms of amyloid- β (Aβ) plaques in extracellular spaces, as well as in the walls of blood vessels, and aggregation of the microtubule protein tau in neurofibrillary tangles in neurons [7]. The average duration of illness is 8–10 years, but the clinical symptomatic phases are preceded by preclinical and prodromal stages that typically extend over two decades [7]. Globally, the number of people living with dementia worldwide in 2018 was estimated at 50 million patients. This number is expected to be doubled to reach 75.63 million patients in 2030 and 135.46 million patients in 2050 [8]. In the kingdom of Saudi Arabia, there is a paucity in statistics of the prevalence of AD. However, it was estimated that there are more than 130.000 AD cases in the kingdom according to Saudi Alzheimer's Disease Association, the majority were females [9].

Therefore, the objective of the present review is to summarize current knowledge of the effects of vitamin D deficiency and vitamin D intake on the cognitive function. The possible underlying mechanisms of these effects will also be discussed.

2. METHODS

We reviewed the literature starting from 1986 to 2019 by searching PubMed, Cochrane, Semantic Scholar, Medline, Scopus, and Cochrane Library databases for all observational studies, randomized clinical trials, meta-analyses, and systematic reviews using the keywords “vitamin D and Alzheimer disease”, “neuroprotective effect of vitamin D”, “vitamin D deficiency and Alzheimer”, “role of vitamin D in neurodegenerative diseases”, “vitamin D and amyloidogenesis”, “acetylcholine and vitamin D”, and “memory and vitamin D”, as well as their combinations regarding the effect of vitamin D in AD. We also referred to animal and in vitro studies that dealt with the possible mechanisms of actions of the neuroprotective effect of vitamin D.

3. VITAMIN D SYNTHSIS

The discovery of vitamin D (calciferol) as a vitamin was in the early 20th century, it is

identified as a prohormone. Calciferols are a group of lipophilic seco-sterols generally categorized into; ergocalciferol (vitamin D 2) and cholecalciferol (vitamin D3) [10]. Ergocalciferol is mostly present in the food, while, cholecalciferol is obtained by the effect of ultraviolet (B 297–315 nm) on the human skin from 7-dehydrocholesterol and existed in foods as well. Both forms of vitamin D are considered biologically inactive until it metabolized by two enzymatic hydroxylation reactions. The first hydroxylation reaction takes place in the liver through vitamin D 25-hydroxylase enzyme (CYP2R) on C-25 thus producing 25(OH) D or calcidiol when vitamin D binds carrier proteins in the skin transported to this activation site. While the second hydroxylation reaction in the kidney through the action of 25(OH) D-1-OHase enzyme (CYP27B1) hydroxylates 25(OH) D at C-1α position, which is ultimately becoming active form 1,25-dihydroxyvitamin D (1,25(OH)2D) or calcitriol. 1α-hydroxylase is closely controlled by feedback mechanisms from several factors including calcitonin hormone, parathyroid hormone, fibroblast growth factor 23, calcium, phosphate, and vitamin D itself [11].

Upon activation, a wide range of metabolic functions via both genomic and non-genomic pathways were influenced by vitamin D. Besides the regulatory effects on the intestinal calcium absorption and homeostasis of minerals, vitamin D3 binds and activates the vitamin D receptor (VDR) which interacts with the nuclear receptor retinoic acid X receptor (RXR). In the presence of 1,25(OH)2D3 the VDR/RXR complex binds small sequences of DNA known as vitamin D response elements (VDREs) and initiates a cascade of molecular interactions that modulate the transcription of a myriad of genes in tissues throughout the body [10].

4. VITAMIN D RECEPTORS IN THE BRAIN

Besides the endocrine functions of vitamin D, this vitamin is also expressed in different tissues and cells that exhibit autocrine and/or paracrine actions, including the CNS [12] .The original work of Stumpf et al, 2004, Garcion et al, 2002, and Eyles et al, 2007, demonstrated the existence of vitamin D metabolites, related enzymes, and receptors in the CNS, has which supported the hypothesis that vitamin D plays a role as a neurosteroid in particular regions of the brain regions, predominantly in those associated with learning and memory [13-16]. Stumpf and his colleagues were the first investigators who described the CNS 1,25 (OH)2D3 target sites, mainly in the neuroepithelial cells and proliferation regions. VDRs are distributed in different brain areas including the hippocampus, cingulate gyrus of the thalamus, nucleus accumbens, temporal lobe, amygdala, orbitofrontal cortex, and olfactory system of the adult brain [15]. Moreover, several considerable genetic studies have detected the presence of VDR genes polymorphisms that are associated with a high risk of cognitive impairment or AD. The first study that indicating a potential genetic relationship between AD and the VDR, back to 2007, where the researchers documented that the risk of AD rises by 2.3 times in VDR region polymorphisms [17].

5. VITAMIN D STATUS AND PREVALENCE OF VITAMIN D DEFICIENCY

Based on the Endocrine Society, 25(OH) D levels less than 20 ng/mL (50 nmol/L) is known as vitamin D deficiency, and 25(OH)D 21–29 ng/mL (52.5–72.5 nmol/L) is considered vitamin D insufficiency. While intoxication of vitamin D is recognized when 25(OH) D exceeded 150 ng/mL. The recommended doses to achieve sufficient levels are also still debated. For instance of such discrepancy, the recommended daily vitamin D.

Supplementation is 600 IU for all ages up to age 70 and 800 IU after age 71 according to the institute of medicine (IOM) [18], while 400 IU for children aged 0-1 year and 600 IU/day for children aged 1-18 years . For all men and women older than 18 years 1500-2000 IU daily as recommended by the Endocrine Society [19]. Vitamin D3 is reported to be 87% more potent in raising and maintaining serum 25(OH)D levels compared to vitamin D2, and it provides a two-to three-fold greater storage capacity of vitamin D in adipose tissue [20]. Additionally, vitamin D2 supplementation may even suppress endogenously formed vitamin D3 [21]. Hilger et al., 2014 conducted A systematic review including 195 studies and enrolled more than 168,000 participants from forty-four countries, the authors stated that the individuals had 25(OH)D less than 20 ng/mL (50 nmol/L) represent 37%, while individuals above 30 ng/mL (75 nmol/L) form 11.9% only [22].

Despite the Kingdom of Saudi Arabia (KSA) being among the top countries in the world in terms of exposure to sunlight, Saudis strongly suffer from vitamin D deficiency this may due to lack of exposure to the sun on a daily basis, prolonged stay indoors, or in places away from sunlight, the use of shades on vehicle windshields and consuming junk food low in nutrients. A recent study conducted over 12,000 adolescents in all 13 regions of the KSA and the result showed a fearfully high prevalence of deficiency of vitamin D (96%) among Saudis adolescents defined by 25-(hydroxy) level of vitamin D below 20 ng/ ml [23]. Another cross-sectional study was carried out on a total of 465 young adult Saudi females aged 19 to 40 years old who were selected from primary health care centers of King Abdulaziz medical city, Riyadh, KSA, the result showed that 79.1% of participants exhibited severe vitamin D deficiency (serum 25(OH) D < 10 ng/ml), while 20.9% exhibited vitamin D insufficiency (serum 25(OH) D between 10–20 ng/ml) [24].

6. VITAMIN D AND COGNITIVE IMPAIRMENT

The correlation between vitamin D deficiency and cognitive functions has been evaluated by both cohort and cross-sectional studies but, so for, a very limited number of interventional studies have been performed. Most of them measured the vitamin D level in the blood, mainly in the geriatrics population group, few studies used dietary intake of vitamin D as an indicator of its level. The observed findings of such studies are either measure the incidence of dementia, cognitive performance, or AD. According to a 2017 systematic review and meta-analysis of 26 observational and 3 intervention studies including over 19,000 participants, low vitamin D status was associated with cognitive decline (odds ratios (OR): 1.26) and poorer cognitive performance (OR: 1.24) among participants without dementia [2]. Llewellyn et al, 2010 reported a greater risk of poor performance on Mini-Mental State Examination (MMSE) by losing 3 or more points in a longitudinal observational study, was conducted for 6 years in 175 adults with 10 ng/ml of 25(OH) D as baseline level versus 157 those with 30 ng/mL of 25(OH) D [25]. Holick and Schlogl, 2014 stated that the risk of cognitive dysfunction was up to 4 times higher in vitamin D-deficient individuals (<25 nmol/L) in comparison with sufficient individuals (>75nmol/L) [26].

Slinin et al. 2012 followed up more than 4 years the link between vitamin D deficiency and cognitive impairment among the geriatrics community (>65 years), and the results showed that women with lower levels had an increased risk of cognitive decline: odds ratio (95% confidence interval), 1.58(1.12–2.22) for women with levels <10 ng/mL (25 nmol/L), and 1.31 (1.04–1.64) for those with levels 10–19.9 ng/mL (25–49 nmol/L) compared with women with baseline 25(OH)D level ≥30 ng/mL (75 nmol/L) [27]. A meta-analysis of 5 cross-sectional and 2 longitudinal studies including 7,688 participants documented a positive relationship between individuals who have vitamin D deficiency and increased risk of cognitive decline (OR 2.39, 95% CI 1.91-3.00; $p < 0.0001$) [28]. Balion et al. 2012 study was compared levels of 25(OH)D to the mean MMSE scores and reported a greater average of MMSE scores in those subjects with a higher level of 25(OH) D [29]. Moreover, the role of vitamin D status in cognition was evaluated in 369 participants and researchers concluded that individuals who had lower vitamin D levels experienced a rapid rate of cognitive impairment. Additionally, AD risk was three-fold in vitamin D deficient people with a hazard ratio of 2.85 [30]. A 2016 study found that vitamin D deficiency increased elderly Chinese individual's risk of developing dementia by over twofold. In addition, dementia risk increased as vitamin D levels decreased [31]. Research published in 2016 found that severe vitamin D deficiency was independently associated with future risk of mild cognitive impairment and dementia among elderly individuals [32]. Also, Pettersen et al, 2014 found that both vitamin D insufficiency and seasonal decline of vitamin D levels are correlated with lower scores related to cognitive performance [33]. Recently, a randomized, double-blind, placebo-controlled trial was reported that daily oral vitamin D supplementation (800 IU/day) for 12 months significantly improvements plasma Aβ42, APP, BACE1, APP mRNA, BACE1mRNA ($p<0.001$) levels and information, arithmetic, digit span, vocabulary, block design and picture arrange scores ($p<0.05$) in the intervention group over the control group [34].

7. NEUROPROTECTIVE ROLE OF VIRAMIN D IN DIFFERENT ASPECTS OF ALZHEIMER DISEASE PATHOGENESIS

The exact mechanisms that linked vitamin D to the pathology of AD are yet to be fully understood, although a number of processes at play during the development of the pathology have been shown to be targeted by the vitamin D signaling system. In view of the mode of action of this steroid hormone, its biological roles will probably be varied, extending from anti-amyloidogenic to neurotransmitters maintenance, calcium balance regulation, controlling neurotrophic factors, modulation of inflammation, apoptosis regulation, antioxidant, and vascular processes. Several efforts have made crucial contributions for explaining the mechanism of action of vitamin D in an AD-like brain.

7.1 Vitamin D Improves Cognitive Performance in Rodent Behavioral Tests

Vitamin D supplementation in animal models shown memory and cognitive functions improvement accompanied by a reduction in AD neuropathological hallmarks. Latimer et al , 2014 reported that an enriched vitamin D diet was superior to the low level of vitamin D containing food (1,000 and 100 IU / Kg, respectively) in the enhancement of escape latency performance in the Morris water maze (MWM) [35]. Similarly, Briones and Darwish, 2012 administered 1,25(OH)2D3 subcutaneously to both young and aged rats (6 months and 20 months, respectively) for three weeks, and demonstrated a reduction of cognitive decline [36]. Also, Al-Zahrani et al, 2019 documented that rats treated with vitamin D3 displayed a significant improvement of the discrimination index (DI) between the familiar and novel object in a novel objective recognition task, as apparent by the significant rise of the DI in different doses of vitamin D3 (100,500 and 1000 IU/kg/day), combined treatment of vitamin D3 and rivastigmine and rivastigmine monotherapy versus positive control ($P<0.05$) [37]. In other work, vitamin D3 treatment significantly enhanced memory and learning functions through decreasing the escape latency, increasing time spent in the target quadrant of MWM in various doses of vitamin D3 (100,500 and 1000 IU/kg/day), combined treatment of vitamin D3 and rivastigmine and rivastigmine monotherapy versus positive control ($P <0.05$) [37].

7.2 Vitamin D Modulates L- Type Voltage-Gated Calcium Channels (L-Vgccs) in the Brain

Calcium signaling plays a central role in neuronal cell development. Accordingly, the L-VGCCs are highly expressed during development and their functions are critical for developing neurons [38], as well as for synaptogenesis [39]. One of the ways in which Ca2+ channels influence neuronal activities is via signaling pathways that control gene expression and that involve transcription factors such as cyclic AMP response element-binding protein (CREB) [40]. Also, the critical role of L-VGCC regulating the secretion of neurotransmitters must be considered [41]. A high level of calcium in the brain leads to neurotoxicity, and one action of vitamin D within the brain is associated with a reduction in calcium levels. Vitamin D has been shown to downregulate or modulate L-type voltage-gated calcium channels (L-VGCCs) [42]. This occurs through the downregulation of L-type voltage-sensitive calcium channel (L-VSCC)-A1C subunit mRNA and protein, mediated by VDR mechanisms. Vitamin D treatment has also been shown to downregulate L-VSCC-A1D subunit mRNA, but this does not occur via VDR [43]. While in the 8-week-old mice dentate gyrus, LVGCCs were upregulated in the absence of 1,25 (OH)2D3, which in turn enhances cell proliferation and neurogenesis [44]. Vitamin D also regulates the gene expression of a number of calcium-binding proteins, including parvalbumin and calbindin D28k [43], and proteins associated with calcium homeostasis [16] . The evidence suggests that the effects of vitamin D on calcium occur via both genomic and nongenomic actions [42].

7.3 Vitamin D Attenuates Amylooidogensis and Tauopathy

Several studies revealed that vitamin D administration; irrespective to the type of model tested, the dosage, the molecule selected, and the time of treatment reduces the burden of amyloid neurotoxicity, indicating an association between vitamin D function and amyloidogenesis [45]. Grimm and coworkers investigated the effect of a relative vitamin D deficiency on APP processing in vivo and in vitro in an animal

model, they concluded that vitamin D deficiency significantly increased Aβ accumulation due to high level and activity of the β-secretase enzyme, accompanied by neprilysin levels reduction [46]. 1,25(OH)2D showing an essential role in improving macrophages' capability to phagocytose soluble amyloid β protein released to surface in novel work in macrophages from AD patients [47]. Moreover, vitamin D diminished Aβ-42 deposition via reinforcing the phagocytosis capacity of the Aβ peptide [48], and facilitating the efflux of Aβ across BBB, subsequently reduced the amyloid plaques neurotoxicity [49] . SMAD 3 gene interacts with VDR, which is implicated in the processing of APP via transforming growth factor-beta (TGF-beta) signaling, this gene served as a transcription factor [49]. Inline, Shingo et al. found that the active form of vitamin D appears to enhance brain to blood Aβ efflux transport at the blood-brain barrier (BBB) leading to enhancement of its cerebral clearance [49].

Neurofibrillary tangles (NFT) aggregation of hyperphosphorylated tau protein is the second pathological hallmark of AD [50]. Latterly, the abnormal hyperphosphorylation of the tau protein received much attention as an AD drug target [51]. Aβ and Tau protein are responsible for the pathological cascade results in AD, i.e., loss of cognitive function, neuropsychiatric changes, and finally destruction of neurons. It was reported that decreased age-related Tau hyperphosphorylation was observed following the vitamin D administration. Interestingly, in our previous work, vitamin D3 administration showed a significant decrease($P<0.01$) in Aβ peptide and tau protein hippocampal tissue levels in all vitamin D3 treated group, reflecting the possible role of vitamin D3 in the enhancement of hippocampal Aβ peptide and tau protein clearance and this could contribute in the mechanism of its neuroprotective action [52].

7.4 Vitamin D Debilitate Brain Insulin Resistance

Numerous studies have documented an association between the status of vitamin D and diabetes risk. Vitamin D has been suggested to play a crucial role and one of the risk factor for developing insulin resistance and type 2 DM pathogenesis through influencing insulin sensitivity or function of β-cell, or both [53-55]. Type 1 DM has been also reported to be associated with vitamin D deficiency based on animal and human observational [56-58]. The prevalence of hypovitaminosis D was found to be higher in diabetic patients (24%; $P < 0.001$) than in controls (16%) in one study [59].

Mounting evidence supports the concept that AD profoundly denotes a metabolic disease in which brain utilization of glucose and production of energy is disturbed [60–62].

Abnormalities in the metabolic process have been associated brain insulin and insulin-like growth factor (IGF) resistance with impairment of signaling pathways that control survival of the neurons, energy production, expression of gene, and plasticity [63]. At the cellular level, diminishing of insulin/IGF signaling implicates in AD-type neurodegeneration via increasing: 1) the kinases activity that abnormally leads to tau phosphorylation; 2) AβPP expression and AβPP-Aβ accumulation; 3) levels of the endoplasmic reticulum (ER) and oxidative stress; 4) the reactive oxygen and reactive nitrogen species generation which in turn damage proteins, RNA, DNA, and lipids; 5) dysfunction of mitochondria; and 6) pro-inflammatory and pro-death cascades activation. On a functional basis, insulin/IGF resistance results in the down-regulation of target genes that are necessary for the homeostasis of cholinergic neurons, and it compromises systems that mediate neuronal plasticity, memory, and cognition [64,65].

Many studies support that supplementation of vitamin D may affect the homeostasis of glucose or improve insulin resistance [66,67]. Maintaining a normal level of vitamin D was reported to improve glucose tolerance in a study on one woman who had hypocalcaemia with vitamin D deficiency [68]. Insulin resistance was improved markedly after taking supplements of vitamin D in south Asian women as documented by a New Zealand study [69]. The ideal vitamin D level for improving insulin resistance has been reported to be 80 to 119 nmol/L, indicating additional evidence for an increase in the recommended adequate levels [70]. Recently, the insulin level in the hippocampus was significantly elevated, while the level of Aβ-42 significantly reduced after prolonged administration of vitamin D3 (100,500 and 1000 IU/kg/day) compared with non- vitamin D3 treated rats [71]. Similarly, Benedict et al, 2008 and Reger et al, 2011 stated that intranasal insulin administration for healthy individuals and AD patients resulted in the elevation of cognitive performance 72,73].

7.5 Vitamin D Regulates Neurotrophins

Neurotrophins are a family of proteins that includes; glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3). Neurotrophins are essential for the survival, maturity, and maintenance of particular neurons and also has been associated with controlling and coordinating the normal functioning of the hippocampal pathway, which is required in learning ability and memory capacity [74,75].

Spatial navigation is compromised with a decreased synthesis of neurotrophins [76].NGF is vital in the plasticity and survival of forebrain cholinergic neurons, which are memory-related [77]. In the deficiency of NGF, cholinergic neurons exhibit cell shrinkage, loss in fiber thickness, and reduction of transmitter-associated enzymes (ChAT and AChE), followed by a decrease of cholinergic transmission [78]. Blasko et al, 2006 noticed an elevation of the NGF Level in cerebrospinal fluid of AD patients [79]. Also, in an animal model, intracerebroventricular administration of amyloid β-42 for fourteen days produced a significant decrease of NGF protein expression, which contributes to the cognitive dysfunction observed in this animal model of AD [80]. GDNF is a critical growth factor for the growth, survival, and maintenance of dopaminergic neurons [81]. GDNF has been limited studied, and depletion of GDNF seems to be linked with the pathophysiology of AD [82].

A study conducted by Ghribi et al, 2001 proved that the administration of GDNF might protect against AD-like disease produced by the aluminum injection o in the rabbit [83]. Also, Basun et al, 2011 found a lower plasma GDNF level in the early stages of AD suggesting an adaptive process of the injured brain [84]. Similarly, a study reported that serum GDNF levels were significantly decreased in mild cognitive impairment (MCI) and AD patients [85]. Furthermore, in a transgenic mouse model of Alzheimer's, Revilla et al, 2014 have reported that GDNF was down-regulated, and this effect was reversed after six months of the exercise [86]. NT-3, a protein found in the hippocampus and neocortex, reduces the toxicity of neurons by amyloid-beta via limiting caspase-8, caspase-9, and caspase-3 cleavage. Moreover, NT-3 produces an up-regulation of neuronal apoptosis inhibitory protein-1 expression in neurons that promote the inhibition of Aβ-induced neuronal apoptosis [87]. Narisawa-Saito et al, 2006 reported a significant reduction in brain NT-3 levels in AD patients [88].

Vitamin D exerts an essential role in the neuronal di□erentiation and maturation through control of the neurotrophic agents' synthesis such as NGF, GDNF, and NT-3 [89]. It was reported that calcitriol and vitamin D analogs enhance NGF induction by increasing activator protein 1 (AP-1) binding activity in the NGF promoter, in mouse fibroblasts [90]. Synthesis of NGF [91], NT3 [92], and GDNF [92] were upregulated by 1,25-(OH) 2D3, whereas neurotrophin 4 (NT4) was downregulated [92]. Similarly, In an experimental model of AD, in which deficiencies in NGF synthesis have been reported; treatment of the animals with a 1,25-(OH)2D3 analog increases NGF production and prevents neurotrophic deficits [93]. Also, the stimulation of neurotrophin production by 1,25-(OH)2D3 was correlated with a neuroprotective effect [94]. Moreover, In animal models, treatment with 1, 25 (OH) 2D3 increased GDNF concentrations and reduced oxidative stress in Parkinson's disease [95]. Interestingly, in our recent unpublished work , different doses of vitamin D3 administration (100, 500 and 1000 IU /kg /day) for four months was found to be disease-modifying in AD as it significantly increased hippocampal levels of ; NGF ($p<0.001$) , NT-3 ($P < 0.05$), ($P < 0.01$), ($P < 0.001$) and ($P < 0.001$) respectively, and GDNF ($p<0.05$), ($p<0.05$) , ($p<0.001$) and ($p<0.001$) respectively compared with non-vitamin D3 - treated rats [52].

7.6 Vitamin D Enhances the Neurotransmission Pathway

Acetylcholine (ACh) and dopamine play a crucial role in facilitating learning and memory, and therefore, the disturbance in release of these neurotransmitters will result in memory impairment [96]. Acetylcholinesterase (AChE) is a key enzyme in the cholinergic nervous system. During the progression of AD, many different types of neurons deteriorate, although there is a profound loss of forebrain cholinergic neurons, which is accompanied by a progressive decline in acetylcholine [97] . Current AD therapy is mostly based on inhibitors of AChE, which enhance cholinergic transmission, but which have modest and transient therapeutic effects [98].

1,25(OH)D markedly regulates the genetic expression of acetylcholine, dopamine, serotonin, and γ aminobutyric acid in the hippocampus [99]. Vitamin D is an essential factor modifying the synthesis of several neuromediators like acetylcholine by elevating choline acetyl-transferase (CAT) gene expression and decreasing AChE activity [100]. Also, Kumar et al. 2011 demonstrated the neuroprotective role of vitamin D in the cerebral cortex by normalizing the altered cholinergic synaptic transmission in streptozocin-induced diabetic rats [101]. Similarly, Alrefaie and Alhyani , 2015 proved the beneficial role of vitamin D3 administration on cognitive performance [102], and concluded that this influence is mediated by improving the prefrontal cortex level of ACh in streptozotocin-induced diabetic rats. Also, supplementation of vitamin D3 for 14 weeks resulted in a 3-fold increase of dopamine level in the animal model [103]. In the recent work, the high vitamin D dose group (1000 IU/kg/day) significantly reduced AChE activity ($p<0.05$), and enhanced dopamine level ($p<0.001$) in the hippocampus of vitamin D3 - treated rats compared with a positive group [71].

7.7 Vitamin D Prevents Neuroinflammation

Besides being a progressive neurodegenerative disease, AD is considered one of the inflammatory brain disorders due to reactive astrocytes and microglia recruitment nearby the β amyloid plaques [104] . In AD, high levels of proinflammatory cytokines and chemokines surrounding the β amyloid plaques are also implicated in the triggering of an immune response. The activated cytokines mark Aβ deposition as inflammation sites for the glial cells in the affected brains [105]. Increased proinflammatory cytokines levels like interleukin-6 (IL-6), TNF-α, and interleukin-1β (IL-1β) have played a critical role in the pathogenesis of AD [106]. TNF-α amplifies neuroinflammation through different pathways, such as stimulation of microglial cells that destroy adjacent neurons by increasing the production of reactive oxygen species (ROS), the liberation of protease enzymes, upregulation of βAPP, and accelerating the βAPP processing to form insoluble Aβ peptide which in turn causes Aβ accumulation [107] . The accumulated Aβ oligomers directly react with microglia cell surface receptors and enhance nuclear factor κB (NF-κB) activity, further increasing the production of cytokines [108], resulting in the downward spiral of chronic inflammation. Also, astrocyte is another kind of CNS cells involved in AD pathogenesis. IL-1β and IL-6 are examples of proinflammatory cytokines that caused astrocytes activation, the activated astrocytes trigger inflammation by the liberating of cytokines such as IL-6 and tumor necrosis factor α (TNF-α) [109].

In the experimental models, The manipulation of TNF-α signaling resulted in the improvement of cognitive function. Moreover, the neuropathological characteristics of AD such as phosphorylated tau protein agglomeration, Aβ accumulation, and neuroinflammation induced by activated glial cells were all found to be mitigated by the inhibition of TNF-α pathway. It is noteworthy that blocking TNF-α signaling diminishes the massive stimulation of glial cells, maintaining them in a moderate stimulated state where they display neuroprotection by increasing the clearance of Aβ [110]. Shamim and Laskowski, 2017 determine that Aβ phagocytosis may be prevented by the presence of a higher level of pro-inflammatory mediators; IL-1β, TNF-α, and IL-6 in the brains of astrogliosis patient and eventually led to neural death [111]. According to Birch et al, 2014, there was a correlation between Aβ production and pro-inflammatory cytokines by observing that TNF-α and Interferon-gamma (IFN- γ) transcriptionally upregulate β-secretase, beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) [112].

The action of vitamin D as potent anti-inflammatory and immune-modulatory has long been discussed. In mice models, vitamin D reversed age-related inflammatory changes in the hippocampus [43]. The possible underlying mechanism of this neuroprotection may be due to inhibition of the brain proinflammatory cytokines [113]. Vitamin D therapy showed a partial reduction in several factors including tumor necrosis factor α (TNF-α) and Lipopolysaccharide-induced levels of mRNA encoding macrophage colony-stimulating factor (M-CSF) in cultured astrocytes [100]. Five months of supplementation with vitamin D3 in a mouse model of AD largely influenced the immune and inflammatory gene expression profiles translating into improved functional outcomes [45]. Erbaş et al, 2014 who investigated the effect of vitamin D3 on fatty liver in a rat model of metabolic syndrome and

reported cognitive function improvement and anti-inflammatory actions [114]. Inline, Tse et al. 2018 reported that administration of 1,25(OH)D for 3 weeks decreased pro-inflammatory cytokine Il-1β and amyloid burden of aged rats (20 months) [47]. Also, vitamin D, through selective blockade of NF-kB signaling pathway, results in a significant reduction in inflammatory IL-1β and TNF-α expression [115]. Moreover, Our previous work points out that vitamin D3 exhibited an anti-inflammatory effect as verified by the significantly diminished ($p<0.001$) TNF- α, IL-6, and IL-1β level in the hippocampal tissue and significantly decreased ($p<0.05$) of serum CRP level in vitamin D3-treated-group, compared to the positive control group [37].

7.8 Vitamin D Protects Against Oxidative Stress

Oxidative stress, a process increased in the brain with aging, is induced by an imbalance in the redox state, involving the generation of excess reactive oxygen species (ROS) or the dysfunction of the antioxidant system [116]. The primary source of ROS is NADPH oxidase, and its activation contributes as a positive marker for oxidative stress. The main cell defense against attacks of free radicals is antioxidant enzymes, which preserve cell membrane and components of cytoplasm from damaging effects of ROS. Glutathione (GSH) peroxidase, superoxide dismutase (SOD), and catalase are the most important antioxidant enzymes [117]. SOD is considered the first line cellular antioxidant defense, despite the oxidative stress resulted from superoxide radicals.

The results in some experimental studies implied that vitamin D3 administration in diabetic mice helps to diminish the ROS formation by the suppression of the gene expression of NADPH oxidase [118,119]. Vitamin D3 reduces lipid peroxidation and improves the activity of SOD in the animal model [120]. There is a positive correlation between vitamin D and a high level of GSH [121]. It was reported that ROS elimination could be promoted by calcitriol through increasing the pool of GSH intracellularly, partially through regulation of gene expression of glutamate-cysteine ligase (GCL) and glutathione reductase (GR) [122]. GCL is an essential enzyme involved in the GSH synthesis. Also, the results of a clinical trial showed a significant reduction of plasma MDA level with vitamin D treatment in adult patients [123].

During AD, damaged neurons, microglia, and astrocytes produced reactive nitrogen species, these sequelae can upregulate the inducible nitric oxide synthase (iNOS) expression. Consequently, the level of NO will be increased and causing cell death due to suppression of mitochondrial and neuronal respiration further leading to the excitotoxicity of neurons [124].

Many studies revealed that vitamin D exerts antioxidant effects by blocking the synthesis of iNOS, regulation of gamma glutamyl transpeptidase activity, which is the rate-limiting enzyme involved in the glutathione metabolism [125]. Huang et al, 2015 found that 1,25(OH)2D3 diminish the expression of iNOS in reactive microglia, monocytes and macrophages, and reduce the response immune system, and decrease the apoptosis of brain inflammation in a rat model [126]. Also, Dursun et al, 2011 documented that vitamin D prevented Aβ-mediated iNOS expression in cortical neurons [127]. Recently, Vitamin D3 administration significantly ($p<0.05$) and dose-dependently inhibited cognitive impairment that was evaluated in the MWM test, with significant, decreases in Aβ-42 and nitric oxide synthase pathway through reduced hippocampal iNOS and NO overproduction ($p<0.05$) [52].

It was found that vitamin D increases the level of GSH in mesencephalic dopaminergic neurons even post-treatment with different glutathione synthesis inhibitors or neurotoxins [128]. Vitamin D also prevents cerebral endothelial dysregulation through inhibitory actions on the ROS production and nuclear factor κB (NF-κB) activation. Similarly, treatment of bEnd 3 cells (mouse brain endothelial cell line) with 1, 25(OH)2D was found to be protected from hypoxic/oxidative insults. The inhibitory action of vitamin D on IκB phosphorylation and P65 translocation to the nucleus accounts for this protective effect [129]. Recently, Vitamin D3 significantly alleviated cognitive deficits ($p<0.001$) in a novel object recognition test and further attenuated oxidative stress via significantly elevated GSH level and marked reduction of MDA and SOD level compared to a positive control [71].

8. CONCLUSION

Vitamin D is a well-known steroid hormone that plays an important role in controlling bone levels of calcium, phosphorus, and overall mineralization. In this review, observational

studies indicate that vitamin D hypovitaminosis may be linked to an increased risk of developing AD and dementia. While, cross-sectional studies only revealed correlations, not explained causality. The major limitation of these studies was the difficulty to compare due to heterogeneous methodologies, differing cutpoints defining the status of vitamin D, and criteria for dementia or cognitive impairment. Inverse causation is another concern in cross-sectional studies of the status of vitamin D and dementia, where dementia progression may cause vitamin D reduction. Future large prospective studies and RCTs are therefore needed to elaborate the causal linking between vitamin D status and dementia. Moreover, animal studies showed that Vitamin D supplementation improves cognitive performance via reducing amyloido-genesis, restoration of neurotransmission, maintaining calcium balance, regulating neurotrophic factors, anti-inflammatory action, apoptosis regulation, antioxidant, and vascular processes. This review might be open new horizons in the understanding of the molecular mechanisms of the disease and neurodegeneration and enable the development of new approaches in treatment and prevention of the disease.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/63214