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

Yahya A. Alzahrani1*, Mohammed A. Alomary2, Abdulmajeed A. Alzahrani2,3, Mawaddah M. Eskandarani4, Iman S. Aljabry5 and Yahya M. Alzahrani6

1Department of Pharmacy, East Jeddah Hospital, Ministry of Health, Jeddah, Saudi Arabia.
2Department of Pharmacy, King Fahad General Hospital, Ministry of Health, Jeddah, Saudi Arabia.
3Department of Clinical Pharmacy, Batterjee medical College, Jeddah, Saudi Arabia.
4Department of Clinical Pharmacy, Ibn Sina National College, Jeddah, Saudi Arabia.
5Department of Pharmacy, Jeddah Eye Hospital, Ministry of Health, Jeddah, Saudi Arabia.
6Department of Pharmacy, Directorate of Public Health, Ministry of Health, Makkah, Saudi Arabia.

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

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

*Corresponding author: E-mail: Chemist_007@hotmail.com;
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 SYNTHESIS

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 VITAMIN 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].

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 Amyloidogenesis 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...
Numerous studies have documented neurofibrillary tangles (NFT) aggregation of associated with vitamin D deficiency based on Type 1 DM has been also reported to be 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].

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
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 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 differentiation 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].
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
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].

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 kB (NF-kB) 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 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.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Llewellyn DJ, Langa KM, Lang IA. Serum 25-hydroxyvitamin D concentration and cognitive impairment. J Geriatr Psychiatry Neurol; 2009. DOI: 10.1177/0991988708327888.

2. Goodwill AM, Szoece C. A systematic review and meta-analysis of the effect of low vitamin d on cognition. J Am Geriatr So. 2017;65(10):2161–2168. DOI: 10.1111/jgs.15012.

3. Kimura N. Diabetes mellitus induces Alzheimer’s disease pathology: Histopathological evidence from animal models. International Journal of Molecular Sciences, 2016;17(4):503. DOI: 10.3390/ijms17040503.

4. Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer’s and Vascular Types. Biomed Res Int. 2014;2014:1–8. DOI: 10.1155/2014/908915.

5. Alzheimer association early signs and symptoms of alzheimer’s. Alzheimer’s Dement. 2019;1:1–88. Available:https://www.alz.org/alzheimers-dementia/10_signs.

6. Hurtado-Puerto AM, Russo C, Fregni F. Alzheimer’s disease in Neuromethods; 2018.

7. Bondi MW, Edmonds EC, Salmon DP. Alzheimer’s disease: Past, Present and Future. J Int Neuropsychol Soc. 2017. DOI: 10.1017/s135561771700100x.

8. Patterson C. World alzheimer report 2018 - the state of the art of dementia research: new frontiers, Alzheimer’s Dis. Int. London, UK; 2018. DOI: 10.1103/PhysRevLett.78.4414.

9. Albugami M. The demographic characteristics and the risk factors of dementia in saudi elderly. Am J Psychiatry Neurosci. 2019;6(1):1–8. DOI: 10.11648/j.ajpn.20180601.11.

10. Khemka VK, Ganguly A, Chakrabarti S, Ganguly U, Banerjee A, Roy D. vitamin d and alzheimer’s disease: Neurocognition to Therapeutics. Int. J. Alzheimers. 2015;2015:1–11. DOI: 10.1155/2015/192747.

11. Demay MB. The good and the bad of vitamin D inactivation. Journal of Clinical Investigation. 2018;128(9):3736–3738. DOI: 10.1172/JCI122046.

12. Deluca GC, Kimball SM, Kolansinski J, Ramagopalan SV, Ebers GC. Review: The role of vitamin D in nervous system health and disease. Neuropathology and Applied Neurobiology. 2013;39(5):458–484. DOI:10.1111/nan.12020.

13. Garcia E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. New clues about vitamin D functions in the nervous system. Trends in Endocrinology and Metabolism, 2002;13(3):100–105. DOI: 10.1016/S1043-2760(01)00547-1.

14. Mc Grath JJ, Eyles DW, Kinobe R, Smith S, Hewison M, “Distribution of the Vitamin D receptor and 1α-hydroxylase in human brain. J Chem Neuroanat. 2004;29(1):21–30. DOI:10.1016/j.jchemneu.2004.08.006.
15. Stumpf WE, O’Brien LP. 1,25(OH)2 vitamin D3 sites of action in the brain. Histochemistry. 2004;87(5):393–406. DOI:10.1007/bf00496810.

16. Eyles D, et al. Developmental vitamin D deficiency alters the expression of genes encoding mitochondrial cytoskeletal and synaptic proteins in the adult rat brain. J Steroid Biochem Mol Biol. 2007;103(3–5):538–545. DOI:10.1016/j.jsbmb.2006.12.096.

17. Hanagasi H, et al. Association between Vitamin D Receptor Gene Polymorphism and Alzheimer’s Disease. Tohoku J Exp. Med. 2007;212(3):275–282. DOI: 10.1620/tjem.212.275.

18. Ross AC, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. Journal of Clinical Endocrinology and Metabolism, 2011;96(1):53–58. DOI: 10.1210/jc.2010-2704.

19. Holick MF, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. Journal of Clinical Endocrinology and Metabolism;2011. DOI: 10.1210/jc.2011-0385.

20. Grote J, Horst RL, Armas LAG, Heaney RP, Recker RR. Vitamin D 3 is more potent than Vitamin D 2 in humans. J Clin Endocrinol Metab.2010;96(3):E447–E452. DOI:10.1210/jc.2010-2230.

21. Mc T, Hugh et al. Ergocalciferol from mushrooms or supplements consumed with a standard meal increases 25-hydroxyergocalciferol but decreases 25-hydroxycholecalciferol in the serum of healthy adults. J Nutr 2012;142(7):1246–1252. DOI:10.3945/jn.112.159764.

22. J Hilger et al. A systematic review of vitamin D status in populations worldwide. Br J Utr. 2014;111(1):23–45. DOI:10.1017/S0007114513001840.

23. AlBuhaibran FS, et al. Time for an adolescent health surveillance system in Saudi Arabia: Findings from jeeluna. J Adolesc Heal; 2015. DOI:10.1016/j.jadohealth.2015.06.009.

24. Al-Mogbel ES. Vitamin D Status among adult saudi females visiting primary health care clinics. Int J Health Sci. (Qassim). 2014;6(2):116–126. DOI:10.12816/0005987.

25. Llewellyn DJ, et al. Vitamin D and risk of cognitive decline in elderly persons. Arch Intern Med. 2010;170(13):1135–1141. DOI:10.1001/archinternmed.2010.173.

26. Holick M, Schlogl M. Vitamin D and neurocognitive function. Clin Interv Aging. 2014;559. DOI:10.2147/cia.s51785.

27. Slavin Y, et al. Association between serum 25(OH) vitamin D and the risk of cognitive decline in older women. Journals Gerontol. - Ser A Biol Sci Med Sci; 2012. DOI:10.1093/gerona/gls075.

28. Eyles T, Sander D, Bickel H, Sander K, Förstl H. Vitamin D deficiency, cognitive impairment and dementia: A systematic review and meta-analysis. Dementia and Geriatric Cognitive Disorders. 2012;33(5): 297–305. DOI:10.1159/000339702.

29. Ballon C, et al. Vitamin D, cognition and dementia; A systematic review and meta-analysis. Neurology. 2012;79(13):1397–1405. DOI:10.1212/WNL.0b013e31826c197f.

30. Feart C, et al. Associations of lower vitamin D concentrations with cognitive decline and long-term risk of dementia and Alzheimer’s disease in older adults. Alzheimer’s Dement. 2017;13(11):1207–1216. DOI:10.1016/j.jalz.2017.03.003.

31. Matchar DB, et al. Vitamin D levels and the risk of cognitive decline in Chinese elderly people: The Chinese longitudinal healthy longevity survey. Journals Gerontol Ser A Biol Sci Med Sci. 2016;71(10):1363–1368. DOI:10.1093/gerona/glw128.

32. Karakis I, et al. Association of serum Vitamin D with the risk of incident dementia and subclinical indices of brain aging: The framingham heart study. J. Alzheimer’s Dis. 2016;51(2):451–461. DOI:10.3233/JAD-150991.

33. Pettersen JA, Fontes S, Duke CL. The effects of vitamin D insufficiency and seasonal decrease on cognition. Can J Neurol Sci. 2014;41(4):459–465. DOI:10.1017/S0317167100018497.

34. Jia J, Hu J, Huo X, Miao R, Zhang Y, Ma F. Effects of Vitamin D supplementation on cognitive function and blood Aβ-related biomarkers in older adults with Alzheimer’s disease: A randomised, double-blind,
placebo-controlled trial. J Neurol Neurosurg. Psychiatry; 2019. DOI: 10.1136/jnnp-2018-320199.

35. Latimer CS, et al. Vitamin D prevents cognitive decline and enhances hippocampal synaptic function in aging rats. Proc Natl Acad Sci. 2014;111(41):E4359–E4366. DOI: 10.1073/pnas.1404477111.

36. Briones TL, Darwish H. Vitamin D mitigates age-related cognitive decline through the modulation of pro-inflammatory state and decrease in amyloid burden. J Neuroinflammation. 2012;9. DOI: 10.1186/1742-2994-9-244.

37. Zahrani YAA, Sattar MAAA, Alharthi SE, Alkreathy HM. Neuroprotective Role of vitamin d3 against insulin resistance and diabetic induced memory dysfunction in rats, Int J Pharmacol. 2019;15(6):724–730. DOI: 10.3923/ijp.2019.724.730.

38. Turner CP, et al. Widespread neonatal brain damage following calcium channel blockade. Dev Neurosci. 2007;29(3):213–231. DOI: 10.1159/000095221.

39. Basarsky TA, Parpura V, Haydon PG. Hippocampal synaptogenesis in cell culture: Developmental time course of synapse formation, calcium influx, and synaptic protein distribution. J. Neurosci. 1994;14(11):6402–6411 DOI: 10.1523/jneurosci.14-11-06402.1994.

40. Mantelas A, Stamatakis A, Kazanis I, Philippidis H, Stylianopoulou F, “Control of neuronal nitric oxide synthase and brain-derived neurotrophic factor levels by GABA-A receptors in the developing rat cortex,” Dev. Brain Res. 2003;145(2):185–195 DOI: 10.1016/j.devbrainres.2003.08.001.

41. Atlas D, Wiser O, Trus M. The voltage-gated Ca2+ channel is the Ca2+ sensor of fast neurotransmitter release. Cell. Mol. Neurobiol. 2001;21(6):717–731. DOI: 10.1023/A:101504105262.

42. Zanatta L, et al. 1α,25-Dihydroxyvitamin D3 mechanism of action: Modulation of L-type calcium channels leading to calcium uptake and intermediate filament phosphorylation in cerebral cortex of young rats. Biochim. Biophys. Acta - Mol. Cell Res. 2012;1823(10):1708–1719. DOI: 10.1016/j.bbrc.2012.06.023.

43. Gezen-Ak D, Dursun E, Yilmazer S. The effects of vitamin D receptor silencing on the expression of LVSCC-A1C and LVSCC-A1D and the release of NGF in cortical neurons. PLoS One; 2011. DOI: 10.1371/journal.pone.0017553.

44. Zhu Y, et al. Abnormal neurogenesis in the dentate gyrus of adult mice lacking 1,25-dihydroxy vitamin D 3 (1,25-(OH)2 D 3). Hippocampus. 2012;22(3):421–433 DOI: 10.1002/hipo.20908.

45. Landel V, Annweiler C, Millet P, Morello M, Féron F, Wion D. Vitamin D, Cognition and Alzheimer’s Disease: The Therapeutic Benefit is in the D-Tails. Journal of Alzheimer’s Disease; 2016. DOI: 10.3233/JAD-150943.

46. Grimm MOW, et al. Impact of vitamin D on amyloid precursor protein processing and amyloid-β peptide degradation in alzheimer’s disease. Neurodegener. 2014; 13(2-3):75–81.

47. Tse S, et al. Genomic and nongenomic signaling induced by 1α,25(OH)2-Vitamin D3 promotes the recovery of amyloid-β phagocytosis by alzheimer’s disease macrophages. J. Alzheimer’s Dis. 2018; 29(1):51-62. DOI: 10.3233/jad-2012-110560.

48. Masoumi A, et al. 1α,25-dihydroxyvitamin D3 interacts with curcuminoids to stimulate amyloid-β clearance by macrophages of alzheimer’s disease patients. J. Alzheimer’s Dis. 2009;17(3):703–717. DOI: 10.3233/JAD-2009-1080.

49. Ito S, Ohtsuki S, Nezu Y, Koitabashi Y, Murata S, Terasaki T. 1α,25-Dihydroxyvitamin D3 enhances cerebral clearance of human amyloid-β peptide(1-40) from mouse brain across the blood-brain barrier. Fluids Barriers CNS; 2011. DOI: 10.1186/2045-8118-2-8.

50. Herrup K. The case for rejecting the amyloid cascade hypothesis. Nat. Neurosci. 2015;18(6):794–799 DOI: 10.1038/nn.4017.

51. Gong CX, Grundke-Iqbal I, Iqbal K. Targeting tau protein in alzheimers disease. Drugs and Aging. 2010;27(5): 351–365.

52. SEA, YMA Yahya, Al-Zahrani A, Mai A, Alim A Sattar. Vitamin D3 attenuates type 3 diabetic-associated cognitive deficits in rats via regulating neurotrophins and enhancing cholinergic transmission pathway; 2020.
53. Chiu KC, Chu A, Go V LW, Saad MF. Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. Am. J. Clin. Nutr. 2004; 79(5):820–825. DOI: 10.1093/ajcn/79.5.820.

54. Deleskog A, Hilding A, Brismar K, Hamsten A, Efendic S, Östenson CG. Low serum 25-hydroxyvitamin D level predicts progression to type 2 diabetes in individuals with prediabetes but not with normal glucose tolerance. Diabetologia. 2012;55(6):1668–1678. DOI: 10.1007/s00125-012-2529-x.

55. Forouhi NG, et al. Circulating 25-hydroxyvitamin D concentration and the risk of type 2 diabetes: Results from the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort and updated meta-analysis of Prospective studies. Diabetologia. 2012;55(8):2173–2182. DOI: 10.1007/s00125-012-2544-y.

56. Strugnell SA, DeLuca HF. The Vitamin D Receptor - Structure and Transcriptional Activation. Exp. Biol. Med. 1997;215(3): 223–228. DOI: 10.3181/00379727-215-44131.

57. Jones G, Strugnell SA, DeLuca HF. Current understanding of the molecular actions of vitamin D. Physiological Reviews. 1998;78(4):1193–1231. DOI: 10.1152/physrev.1998.78.4.1193.

58. Mathieu C and Badenhoop K. Vitamin D and type 1 diabetes mellitus: State of the art. Trends in Endocrinology and Metabolism. 2005;16(6):261–266. DOI: 10.1016/j.tem.2005.06.004.

59. Targher G, et al. Serum 25-hydroxyvitamin D3 concentrations and carotid artery intima-media thickness among type 2 diabetic patients. Clin. Endocrinol. (Oxf). 2006;65(5):593–597. DOI: 10.1111/j.1365-2265.2006.02633.x.

60. Hoyer S. The brain insulin signal transduction system and sporadic (type II) Alzheimer disease: An update. J. Neural Transm. 2002;109(3):341–360. DOI: 10.1007/s007020020028.

61. Hoyer S. Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. Eur. J. Pharmacol. 2004;490(1–3):115–125. DOI: 10.1016/j.ejphar.2004.02.049.

62. Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, De La Monte SM. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer’s disease: Link to brain reductions in acetylcholine. J. Alzheimer’s Dis. 2005;8(3):247–268. DOI: 10.3233/JAD-2005-8304.

63. Frölich L, et al. Brain insulin and insulin receptors in aging and sporadic Alzheimer’s disease. J. Neural Transm. 1998;105(4–5):423–438. DOI: 10.1007/s00720050068.

64. Farris W, et al. Insulin-degrading enzyme regulates the levels of insulin, amyloid - protein, and the -amyloid precursor protein intracellular domain in vivo. Proc. Natl. Acad. Sci; 2003. DOI: 10.1073/pnas.0230450100.

65. Zhao L. Insulin-Degrading Enzyme as a Downstream Target of Insulin Receptor Signaling Cascade: Implications for Alzheimer’s Disease Intervention. J. Neurosci. 2004;24(49):11120–11126. DOI: 10.1523/jneurosci.2860-04.2004.

66. Gedik O, Akahn S. Effects of vitamin D deficiency and repletion on insulin and glucagon secretion in man. Diabetologia. 1986;29(3):142–145. DOI: 10.1007/BF02427083.

67. Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. Int. J. Clin. 2003;57(4): 258–61. Available:http://www.ncbi.nlm.nih.gov/pubmed/12800453.

68. Kumar S, et al. Improvement in glucose tolerance and beta-cell function in a patient with vitamin D deficiency during treatment with vitamin D. Postgrad. Med. J. 1994; 70(824):440–443. DOI: 10.1136/pgmj.70.824.440.

69. Von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient-a randomised, placebo-controlled trial. Br. J. Nutr. 2010. DOI: 10.1017/S0007114509992917.

70. Maddaloni E, Cavallari I, Napoli N, Conte C. Vitamin D and Diabetes Mellitus. Front. Horm. Res. 2018;50:161–176. DOI: 10.1159/000486083.

71. Al-zahrani YA, Attar MAAA, Al-harthi SE, Akkreathy HM. Neuroprotective Role of Vitamin D3 Against Insulin Resistance and
Diabetic Induced Memory Dysfunction in Rats; 2019. DOI: 10.3923/ijp.2019.Research.

72. Reger MA, et al. Intranasal insulin improves cognition and modulates β-amyloid in early AD. Neurology. 2008; 70(6):440–448 DOI: 10.1212/01.WNL.0000265401.62434.36.

73. Benedict C, Frey WH, Schioth HB, Schultz B, Born J, Hallschmid M. Intranasal insulin as a therapeutic option in the treatment of cognitive impairments. Exp. Gerontol; 2011. DOI: 10.1016/j.exger.2010.08.026.

74. Skaper SD. The neurotrophin family of neurotrophic factors: An Overview. Methods in Molecular Biology. 2012;846:1–12. DOI: 10.1007/978-1-61779-536-7_1.

75. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu. Rev. Neurosci. 2001;24:677–736. DOI: 10.1146/annurev.neuro.24.1.677.

76. Sampaio TB, Savall AS, Gutierrez MEZ, Pinton S. Neurotrophic factors in Alzheimer’s and parkinson’s diseases: Implications for pathogenesis and therapy. Neural Regeneration Research. 2017;12(4):549–557. DOI: 10.4103/1673-5374.205084.

77. Scott J, Heumann R, Auburger G, Thoenen H, Korsching S. Levels of nerve growth factor and its mRNA in the central nervous system of the rat correlate with cholinergic innervation. EMBO J. 2018; 4(6):1389–1393 DOI: 10.1002/j.1460-2075.1985.tb03791.x.

78. Tai SK, Ma J, Leung LS. Medial septal cholinergic neurons modulate isoflurane anesthesia. Anesthesiology. 2014;120(2):392–402. DOI: 10.1097/ALN.0b013e3182a7cab6.

79. Blasko I, et al. Measurement of thirteen biological markers in CSF of patients with Alzheimer’s disease and other dementias. Dement. Geriatr. Cogn. Disord. 2006; 21(1):9–15. DOI: 10.1159/000089137.

80. Souza LC, et al. Indoleamine-2,3-dioxygenase mediates neurobehavioral alterations induced by an intracerebroventricular injection of amyloid-β1-42 peptide in mice; Brain. Behav. Immun. 2016;56:363–377. DOI: 10.1016/j.bbi.2016.03.002.

81. Deister C and Schmidt CE, “Optimizing neurotrophic factor combinations for neurite outgrowth,” J. Neural Eng. 2006: 3(2):172–179. DOI:10.1088/1741-2560/3/2/011.

82. Allen SJ, Watson JJ, Shoemark DK, Barua NU, Patel NK. GDNF, NGF and BDNF as therapeutic options for neurodegeneration. Pharmacol. Ther. 2013;138(2):155–175. DOI: 10.1016/j.pharmthera.2013.01.004.

83. Ghribi O, Herman MM, Forbes MS, DeWitt DA, Savory J. GDNF protects against aluminum-induced apoptosis in rabbits by upregulating Bcl-2 and Bcl-XL and inhibiting mitochondrial Bax translocation. Neurobiol. Dis. 2001;8(5):764–773. DOI: 10.1006/nbdi.2001.0429.

84. Straten G, et al. Influence of Lithium Treatment on GDNF Serum and CSF Concentrations in Patients with Early Alzheimers Disease. Curr. Alzheimer Res. 2011. DOI: 10.2174/156720511798192754.

85. Forlenza OV, et al. Decreased Neurotrophic Support is Associated with Cognitive Decline in Non-Demented Subjects. J. Alzheimer’s Dis. 2015;46(2):423–429 DOI: 10.3233/jad-150172.

86. Revilla S, Suñol C, García-Mesa Y, Giménez-Llort L, Sanfeliz C, Cristófol R. Physical exercise improves synaptic dysfunction and recovers the loss of survival factors in 3xTg-AD mouse brain. Neuropharmacology; 2014. DOI: 10.1016/j.neuropharm.2014.01.037.

87. Gabriel C, et al. Akt-dependent Expression of NAIP-1 Protects Neurons against Amyloid-β Toxicity. J. Biol. Chem. 2005; 280(26):24941–24947 DOI: 10.1074/jbc.M413495200.

88. Narisawa-Saito M, Takahashi H, Nawa H, Wakabayashi K, Tsuji S. Regional specificity of alterations in NGF, BDNF and NT-3 levels in Alzheimer’s disease. Neuroreport. 2006;7(18):2925–2928. DOI:10.1097/00001756-199611250-00024.

89. Brown J, Bianco JL, McGrath JJ, Eyles DW. 1, 25-Dihydroxyvitamin D3induces nerve growth factor, promotes neurite outgrowth and inhibits mitosis in embryonic rat hippocampal neurons. Neurosci. Lett. 2003;343(2):139–143. DOI: 10.1016/S0304-3900(03)00303-3.
90. Van Der Meijden K, et al. Primary human osteoblasts in response to 25-hydroxyvitamin D3, 1, 25-dihydroxyvitamin D3and 24R, 25-dihydroxyvitamin D3. PLoS One. 2014;9(10). DOI:10.1371/journal.pone.0110283.

91. Cornet A, Baudet C, Neveu I, Baron-Van Evercooren A, Brachet P, Naveilhan P. 1, 25-Dihydroxyvitamin D3 regulates the expression of VDR and NGF gene in Schwann cells in vitro. J. Neurosci. Res. vol., no., pp., 1998;53(6):742–746 DOI:10.1002/(SICI)1097-4547(19980915)53:6<742::AID-JNR111>3.0.CO;2-#. DOI:10.1007/s001250051443.

92. Neveu I, Naveilhan P, Baudet C, Brachet P, Metsis M. 1, 25-Dihydroxyvitamin D3regulates NT-3, NT-4 but not BDNF mRNA in astrocytes. Neuroreport. 1994; 6(1):124–126. DOI:10.1097/00001756-199412300-00032.

93. Riaz S, Malcangio M, Miller M, Tomlinson DR. A vitamin D3 derivative (CB1093) induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabetic rats. Diabetologia. 1999;42(11): 1308–1313. DOI:10.1007/s001250051443.

94. Hayashi T, et al. Vitamin D3 attenuates cortical infarction induced by middle cerebral arterial ligation in rats. Neuropharmacology. 2002;39(5):873–880. DOI:10.1016/s0028-3908(99)00255-5.

95. Wang JY, et al. Vitamin D3attenuates 6-hydroxypalmitate-induced neurotoxicity in rats. Brain Res. 2001;904:67–75. DOI:10.1016/S0006-8993(01)02450-7.

96. Hasselmo ME. The role of acetylcholine in learning and memory. Current Opinion in Neurobiology. 2006;16(6):710–715. DOI:10.1016/j.conb.2006.09.002.

97. Perry EK, Smith CJ, Atack JR, Candy JM, Johnson M, Perry RH. Neocortical Cholinergic Enzyme and Receptor Activities in the Human Fetal Brain. J. Neurochem; 1986; DOI:10.1111/j.1471-4159.1986.tb00749.x.

98. Birks JS. Cholinesterase inhibitors for Alzheimer’s disease. Cochrane Database Syst. Rev; 2006. DOI:10.1002/14651858.CD005593.

99. Gezen-Ak D, Dursun E. Molecular basis of vitamin D action in neurodegeneration: the story of a team perspective. Hormones. 2018;89(1):557–60. DOI:10.1007/s42000-018-0087-4.

100. Wrzosek M, et al. Vitamin D and the central nervous system. Pharmacological Reports. 2013;65(2):271–278. DOI:10.1016/S1734-1140(13)71003-X.

101. Kumar PT, Antony S, Nandhu MS, Sadanandan J, Naijil G, Paulose CS. Vitamin D3 restores altered cholinergic and insulin receptor expression in the cerebral cortex and muscarinic M3 receptor expression in pancreatic islets of streptozotocin induced diabetic rats. J. Nutr. Biochem. 2011;22(5):418–425. DOI:10.1016/j.jnutbio.2010.03.010.

102. Alrefaie Z, Alhayani A. Vitamin D improves decline in cognitive function and cholinergic transmission in prefrontal cortex of streptozotocin-induced diabetic rats. Behav. Brain Res. 2015;287(2):156–162. DOI:10.1016/j.bbr.2015.03.050.

103. Peeyush K, Savitha B, Sherin A, Anju TR, Jes P, Paulose CS. Cholinergic, dopaminergic and insulin receptors gene expression in the cerebellum of streptozotocin-induced diabetic rats: Functional regulation with Vitamin D3 supplementation. Pharmacol. Biochem. Behav. 2010;95(2):216–222. DOI:10.1016/j.pbb.2010.01.008.

104. Dorey E, Chang N, Liu QY, Yang Z, Zhang W. Apolipoprotein E, amyloid-beta, and neuroinflammation in Alzheimer’s disease. Neuroscience Bulletin; 2014. DOI:10.1007/s12264-013-1422-z.

105. Livingston G, Cooper C, Psychological, behavioural and psychosocial interventions for neuropsychiatric symptoms in dementia: What works, what does not and what needs more evidence?. in Dementia, Fifth Edition. 2017:235–243.

106. Mirza S, et al. Type 2-diabetes is associated with elevated levels of TNF-alpha, IL-6 and adiponectin and low levels of leptin in a population of Mexican Americans: A cross-sectional study. Cytokine. 2012;57(1):136–142. DOI:10.1016/j.cyto.2011.09.029.

107. McInnes J, et al. Tau association with synaptic vesicles causes presynaptic dysfunction. Nat. Commun. 2017;8:15295. DOI:10.1038/ncomms15295.

108. Georgopoulou S, Kartalou GI, Paouri E, Zenelak S, Tzara O, Peripheral Tumor Necrosis Factor-Alpha (TNF-α) Modulates Amyloid Pathology by Regulating Blood-Derived Immune Cells and Glial Response.
in the Brain of AD/TNF Transgenic Mice. J. Neurosci. 2017;37(20):5155–5171.
DOI:10.1523/jneurosci.2484-16.2017.

109. Cekanavičiute E, Buckwalter MS, Astrocytes: Integrative Regulators of Neuroinflammation in Stroke and Other Neurological Diseases. Neurotherapeutics, 2016;13(4):685–701.
DOI:10.1007/s13311-016-0477-8.

110. Decourt B, Lahiri D, Sabbagh M. Targeting Tumor Necrosis Factor Alpha for Alzheimer’s Disease. Curr. Alzheimer Res; 2016.
DOI:10.2174/15672050136661609301105
51.

111. Shamim D, Laskowski M. Inhibition of Inflammation Mediated Through the Tumor Necrosis Factor a Biochemical Pathway Can Lead to Favorable Outcomes in Alzheimer Disease. J. Cent. Nerv. Syst. Dis. 2017;9:1–10.
DOI:10.1177/1179573517722512.

112. Birch AM, Katsouri L, Sastre M. Modulation of inflammation in transgenic models of Alzheimer’s disease. Journal of Neuroinflammation; 2014.
DOI: 10.1186/1742-2094-11-25.

113. Jadhav NJ, Gokhale S, Seervi M, Patil PS., Alagarasu K. Immunomodulatory effect of 1, 25 dihydroxy vitamin D3 on the expression of RNA sensing pattern recognition receptor genes and cytokine response in dengue virus infected U937-DC-SIGN cells and THP-1 macrophages. Int. Immunopharmacol. 2018;62:237–243.
DOI:10.1016/j.intimp.2018.07.019.

114. Erbaş O, Solmaz V, Aksoy D, Yavaşoğlu A, Saçman M, Taşkiran D. Cholecalciferol (vitamin D 3) improves cognitive dysfunction and reduces inflammation in a rat fatty liver model of metabolic syndrome. Life Sci. 2014;103(2):68–72.
DOI:10.1016/j.lfs.2014.03.035.

115. Condello C, Yuan P, Grutzendler J, Microglia-Mediated Neuroprotection, TREM2, and Alzheimer’s Disease: Evidence From Optical Imaging. Biological Psychiatry. 2018;83(4):377–387.
DOI:10.1016/j.biopsych.2017.10.007.

116. Moreira PI, et al. Role of oxidative stress in Alzheimer’s disease (Review). Oxidative Stress Neurodegener. Disord. 2016;519–522.
DOI:10.1016/B978-044452809-4/50153-8.

117. Birch-Machin MA, Bowman A. Oxidative stress and ageing. British Journal of Dermatology. 2016;175:26–29.
DOI:10.1111/bjd.14906.

118. Kitazawa S, et al. Anti-Oxidative Effect of Vitamin D Analog on Incipient Vascular Lesion in Non-Obese Type 2 Diabetic Rats. Am. J. Nephrol. 2013;37(2):167–174.
DOI:10.1159/000346808.

119. Labudzynskyi DO. Vitamin D(3) contribution to the regulation of oxidative metabolism in the liver of diabetic mice. Ukr. Biochem. J. 2015;87(3):75–90.
DOI:10.15407/ubj87.03.075.

120. Zhong W, Gu B, Gu Y, Groome LJ, Sun J, Wang Y. Activation of vitamin D receptor promotes VEGF and CuZn-SOD expression in endothelial cells. J. Steroid Biochem. Mol. Biol; 2014.
DOI:10.1016/j.jsbmb.2013.11.017.

121. Jain SK, Micinski D, Huning L, Kahlon G, Bass PF, Levine SN. Vitamin D and L-cysteine levels correlate positively with GSH and negatively with insulin resistance levels in the blood of type 2 diabetic patients. Eur. J. Clin. Nutr. 2014;68(10):1148–1153.
DOI:10.1038/ejcn.2014.114.

122. Kanikarla-Marie P, Jain SK. 1, 25(OH)2D3inhibits oxidative stress and monocyte adhesion by mediating the upregulation of GCLC and GSH in endothelial cells treated with acetacetate (ketosis). J. Steroid Biochem. Mol. Biol; 2016;159:94–101.
DOI:10.1016/j.jsbmb.2016.03.002.

123. Forooranzand F, et al. Calcium plus vitamin D supplementation influences biomarkers of inflammation and oxidative stress in overweight and vitamin D-deficient women with polycystic ovary syndrome: A randomized double-blind placebo-controlled clinical trial. Clin. Endocrinol. (Oxf); 2015.
DOI:10.1111/cen.12840.

124. Uberti F, Morsanuto V, Molinari C. Vitamin D in Oxidative Stress and Diseases. A Crit. Eval. Vitam. D - Basic Overv. 2017;48–72.
DOI:10.5772/64506.

125. Mokhtari Z, Hekmatdoost Z, Nourian M, “Antioxidant efficacy of vitamin D,” J. Parathy. Dis. 2017;5(1):11–16.
126. Chen H, et al. Associations between Alzheimer’s Disease and Blood Homocysteine, Vitamin B 12, and Folate: A Case-Control Study. Curr. Alzheimer Res. 2015;12(1):88–94. DOI:10.2174/1567205012666141218144035.

127. Dursun E, Gezen-Ak D, Yilmazer S. A new mechanism for amyloid-β induction of iNOS: Vitamin D-VDR pathway disruption. J. Alzheimer’s Dis. 2013;36(3):459–474. DOI: 10.3233/JAD-130416.

128. Ito R, Ihara H, Okada T, Ikeda Y. 1α,25-dihydroxyvitamin D3 enhances γ-glutamyl transpeptidase activity in LLC-PK1 porcine kidney epithelial cells. Mol. Med. Rep., 2014. DOI: 10.3892/mmr.2014.2436.

129. Won S, Sayeed I, Peterson BL, Wali B, Kahn JS, Stein DG. Vitamin D prevents hypoxia/reoxygenation-induced blood-brain barrier disruption via vitamin D receptor-mediated NF-kB signaling pathways. PLoS One; 2015. DOI:10.1371/journal.pone.0122821.

© 2020 Alzahrani et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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