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IMPACT OF VITAMIN D ON NEUROCOGNITIVE FUNCTIONING

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ABSTRACT

Vitamin D plays a significant role in maintaining bone health by exerting its effect over homeostasis of calcium. Apart from this, vitamin D also has established its role in neurocognitive functioning. Vitamin D receptors are widely distributed in brain tissue, the biological active form of vitamin D has neuroprotective effects including amyloid peptide clearance, antioxidant and anti-inflammatory properties and potential defense against dementia related neurodegenerative pathways. Apart from reduced vitamin use, disturbed signaling and polymorphism in multiple associated genes, such as the vitamin D receptor increases the risk of AD or AD like neurodegeneration. Through antioxidative mechanisms, neuronal calcium control, immune system regulation, improved transmission of impulses, and detoxification mechanisms, vitamin D demonstrates functional characteristics that may prove its neuroprotective effects. This review encompasses the co-relation of vitamin D on the neurocognition and optimal brain health. This review also aims to examines the connection between gene-environmental effect and chronic vitamin D deficiency as a risk factor for developing sporadic AD, as well as the function and justification of vitamin D therapy studies. The discussion of this article provides the most recent findings of vitamin D and its therapeutic implications for older people including effects on the prognosis and course of dementia.

KEYWORDS: Neurocognition, Vitamin D, Dementia, Alzheimer's disease (AD), Brain signaling, cognitive, cognitive functioning, 25-hydroxyvitamin D., Aging.

INTRODUCTION

The prevalence of dementia is progressively increasing and aging population are more vulnerable to it.[1] Current incidence states that 55 million people have been affected with dementia and 60% of people affected reside in low and middle income countries.[2]Vitamin D deficiency prevails in all over the Indian subcontinent and is increasing exponentially with a prevalence of 70-100 %. This states that reduced vitamin D levels is having widespread prevalence and is undeniable in India.[3] Consequently, vitamin D deficiency risk factors include inadequate sunlight exposure, inadequate dietary intake of vitamin D-containing foods, and malabsorption syndromes such as Crohn's disease and celiac disease.[4,5] Vitamin D deficiency was found to be associated with weekly sun exposure and living location based on the multiple logistic regression model.[6] Vitamin D, In addition to maintaining a healthy mineralized skeleton as we age, plays a vital role in the development, growth.[7] Novel role of vitamin D is in maintaining calcium homeostasis, thereby maintaining bonehealth. It has been discovered that vitamin D receptors are found in many different tissues, which has led to a greater appreciation of vitamin D's other important functions.[8] Vitamin D has an influential role inthe body‘s immune system functions, including inflammatory markers and white blood cell counts.[9] Those who have vitamin D deficiency are also more likely to suffer from sleep disorders.[10] Low serum vitamin D could also contribute to autoimmune thyroid disease which includes Graves' disease (GD) and Hashimoto thyroiditis(HT).[11] Vitamin D levels also appears to protect against the development of atria fibrillation.[12] It has been found that vitamin D levels beneath 50nmol/l is also associated with increased rates of infection and sepsis. It is also noted that Infections with COVID 19, and severe disease will be aggrevated with vitamin D deficiency.[13] The word "vitamin d" supplementation refers to the consumption of cholecalciferol, ergocalciferol, calcidiol, and calcitriol. In nature cholecalciferol is the main form of vitamin D that nurtures the body. Throughout this review, we concentrate on cholecalciferol, which is the only form of vitamin D relevant to fortification and supplementation in the context of nutritional functions.[14] The elderly are particularly vulnerable to falls, which cause significant morbidity and mortality in those age groups. There is a strong association between vitamin D deficiency and muscle weakness, mostly in the proximal muscles. As a result, the walking speed is slowed, sitting to standing time is prolonged, quadriceps strength is reduced, Short Physical Performance Battery (SPPB) scores are poor, and falls are more likely.[15] Thus According to most prospective study investigators, Vitamin D concentrations are moderately to strongly inversely

associated with cardiovascular diseases, serum lipids, inflammation, glucose metabolism disorders, weight gain, infectious diseases, multiple sclerosis, mood disorders, declining cognitive function, impairment of physical functioning, and overall mortality.[16]

Cognitive dysfunctions are core features of psychotic disorders with substantial impact on daily functioning. Recent studies have found that cognitive dysfunctions are related with the fact of vitamin D deficiency.[17] The brain contains many vitamin D receptors, including neurons and glial cells.[18] It also contains genes that encode enzymes involved in vitamin D metabolism. Consequently, the current review aims to discuss the recent evidence of vitamin D signaling in the brain, including its synthesis through alternative pathways and binding to different receptors as well as focuses on role of vitamin D deficiency and vitamin D supplementation in cognitive functioning.

ASSOCIATION OF VITAMIN D IN NEUROCOGNITIVE FUNCTIONING

Cognition is understood as the factors which isassociated to knowledge, learning, and understanding, as nicely as the capability to strengthen these functions. Cognitive decline and changes in brain structure, such as decreased white matter volume in the prefrontal cortex, are well-discussed items in the literature as key features of the aging process. In addition, there are other factors that can cause structural and functional cognitive changes in healthy individuals, those are Diet, sleep quality, physical training. It therefore emphasizes that vitamins and minerals can contribute to the development and maintenance of brain health, regardless of age.[19] vitamin D is an example of pro – hormone which is then biotransformed into 1,25 dihydroxyvitamin D3 by two back to back metabolism.[20] It then mediates its action by binding to the vitamin D receptor which is majorly located in all types of cells. Several clinical trial models, demonstrate the action of vitamin D on the brain function. Vitamin D deficient diet has substantial affect on the brain function and the structure.[21] The primary exposure of 1,25 dihydroxyvitamin D 3 through the genomic actions, was on the vitamin D receptor, also known as VDR which is mainly expressed in the brain region.[22] Five genes were identified `which were involved to affect the brain function, and could be considered as an etiological factor for the neurodegenerative disorders. The genes were VDR, CNKSR2, LPL, Slc1a1, C3.[23] The distribution of vitamin D was determined by the study which evaluated the distribution of 1,25 dihydroxy vitamin D3 receptor in the central nervous system of rats which concluded, the distribution of vitamin d receptors in cortex, thalamus, and amygdala and hippocampus. This study provided a base for the analysis of functional role of vitamin D in the neurocognition.[24] The distribution of vitamin D receptors were larger in the neural and the glial cells, and the distribution pattern was same in rats and the humans. The enzyme that is responsible for the formation of vitamin D in the brain that is 1alpha-hydroxylase (1alpha-OHase), was also found distributed in the CNS.[25] Cognitive impairment is seen mainly in dementia, AD, which possesses a major public concern. AD is characterized as a gradually progressing neurological disorder whose pathological attributes originate in the brain which includes amyloid beta protein accumulation as senile plaques in the brain, as well as formation of neurofibrillary tangles.[26] A clinical study conducted with rats showed that there was restoration of the suppressed synaptic plasticity upto the baseline with the vitamin D supplementation.[27] subsequently the rats who were fed with the diet deficient in vitamin D were observed with high amyloid beta plaque load with exponential increase in the cognitive impairment compared to that of the control group. Thus concluding the neuroprotective effect of the vitamin D.[28] Vitamin D has a significant effect on the macrophages, activation of these macrophages causes pathological engulfment of the amyloid beta plaques, thereby increasing their clearance and reducing the progression of AD.[29] Vitamin D had a significant effect on the cognitive functioning and vitamin D supplementation showed reduction in disease progression.

VITAMIN D SIGNALLING IN THE BRAIN

The widenumber of ligands present on the site of action facilitates the activation of brain signaling. Vitamin D beinga lipophilic moiety transports into the cell via diffusion through the blood brain barrier (BBB). Vitamin D metabolites in larger concenteration bind to vitamin D binding protein (DBP), thus leaving a small concenteration of free fraction.[30] Based onfree hormone hypothesis, the portion of free fraction of vitamin D found in blood or extracellular fluidbinds to carrier proteins can diffuse into the intracellular space and bind to its receptors, thus exerting its biological effects.[31] The clinical study conducted by Fu X et al, showed the presence of vitamin d metabolites in brains of rodents and humans thus endorsing their clinical role.[32] The vitamin D binding protein (DBP) is present in cerebrospinal fluid and vitamin D metabolites are likely to bind to these proteins. However, various clinical diseases, such as multiple sclerosis, have an impact on how DBP is expressed in the central nervous system (CNS). This leads to varying concenteration of unbound vitamin D metabolites, thus making difficult to quantify.[33]

ROLE OF VITAMIN D RECEPTOR IN DEVELOPMENT OF ALZEIHMERS DISEASE

Vitamin D receptors plays an important role as a mediator in modulating the actions of neurosteroid vitamin D. There exists potential association between alzheimers disease and the Vitamin D receptor polymorphism suggesting that people with these polymorphisms are more susceptible to alzheimers disease.[34] The clinical study conducted by Sutherland MK et al on postmortem AD brain endorsed that The

amount of the VDR mRNA pool is downregulated in Alzheimer hippocampus CA1 cells, and this reduced level may contribute to the decrease in calbindin-28k expression.[35] Binding to VDR, a ligand-dependent nuclear transcription factor found in numerous system organs and tissues throughout the body, promotes the biological activity of active vitamin D.[36] The genetic risk factor for late-onset AD is the vitamin D receptor (VDR) gene, was found to have its loci on chromosome 12q13.[37,38] VDR gene polymorphisms play a significant role in AD and MCI. However, due to small sample sizes and limited statistical power, such findings are conflicting and ambiguous. Despite the fact that a prior meta-analysis demonstrated the link between VDR TaqI and ApaI polymorphisms and AD susceptibility.[39] Glial fibrillary acidic protein (GFAP) stained cells in primary rat hippocampus cultures are an indicator of the presence of VDR in the astrocytes.[40] The expression of vitamin D in ~~growing~~ brains suggests a possible role for the vitamin in cellular development and differentiation.[41] In developing hippocampus neurons, Bartoccini and colleagues have demonstrated the fast partitioning of VDR into the lipid-rich microdomains inside the nuclear membrane. These microdomains resemble those in the plasma membrane in terms of their characteristics.[42] The clinical vitamin D deficiency during development phase can have an impact on adult brain functioning.[43] Vitamin D controls the transcription of several genes by attaching to the nucleus,creating a heterodimer with RXR, and then translocating to the DNAs vitamin D response region[44-45] According to the findings from the studies, VDR is highly expressed in the regions of the central nervous system (CNS) that are crucial for cognition, including the substantia nigra, hippocampus, hypothalamus, and thalamus.

EVIDENCES LINKING VITAMIN D AND DEVELOPMENT OF ALZHEIMERS DISEASE

Numerous mechanisms can allow vitamin D to have an impact on neurocognition, including the induction of neuroprotection, modulation of oxidative stress, control of calcium homeostasis, and inhibition of inflammatory processes.[46] Additionally, amyloid phagocytosis and clearance, vasoprotection, are all aided by vitamin D and its metabolites. The most common cause of dementia in older adults is Alzheimer's disease, and infarcts frequently coexist with the pathology of the disease. Cerebrovascular lesions reduce the threshold of the AD-type alterations required to trigger cognitive loss, according to several studies.[47] All studies in an AD-like context have shown that vitamin D treatment reduces the amyloid burden, regardless of the model tested, the dosage, the choice of molecule, and the time of treatment, suggesting a relationship between vitamin D function and amyloidogenesis.[48] The astrocytic reactivity, NGF levels, and TNF levels were all increased in brains of treated mice with decrease of Aβ along with the behavioural alterations. It's interesting to knowhow vitamin D regimen affectsAβPPbeing processed, resulting in different AβPPend products.[49] In a recent study conducted by Latimer CS et al found that a high vitamin D3 diet lasting for about half a year prevented the decline in cognitive functioning in aging rodents.[50] Other test was performed where subcutaneous injections of 1,5 dihydroxy vitamin D 3 was administered for young and aged rats for 21 consecutive days. It was observed that there was a cessation of cognitive impairment only in aged animals.[48,51] The multiple functions of vitamin D through out the central nervous system incriminate in the prevention and therapy of disorders such as dementia and AD.[52]

THE IMPACT OF VITAMIN D ON BRAIN OXIDATIVE STRESS AND AMYLOID BETA BREAKDOWN – THE POSSIBLE MECHANISMS

Although it bears adding, vitamin D also controls the metabolic features of amyloid precursor protein APP and amyloid beta. 1,25(OH)2D has promising role in restoring the macrophages' capacity to phagocytose soluble amyloid beta protein.[53] Vitamin D has the capacity to inhibit the buildup of amyloid β (Aβ)42 protein by promoting the phagocytosis of the Aβ peptide.[54] And fastening the blood-to-brain Aβ efflux over the BBB[55], which reduces the quantity of amyloid plaques.[56] NF-kB activation and ROS generation are both inhibited by 1,25(OH)2D, which provides further protection against cerebral endothelial dysfunction. Similarly, 1,25(OH)2D treatment was reported to protect the bEnd 3 cells (a mouse brain endothelial cell line) from hypoxic/oxidative stresses. This protective impact of vitamin D is due to its inhibitory influence on Ik-B phosphorylation and translocation of P 65 to the nucleus.[57] The clinical trial conducted after the treatment with different neurotoxins or glutathione production inhibitors, the results enodorsed that vitamin D led to increase in glutathione levels within the mesencephalic dopaminergic neurons.[58] vitamin D inhibits the production of inducible nitric oxide synthase and controls the activity of gamma glutamyl transpeptidase, a crucial enzyme in the metabolism of glutathione, in addition to exerting its antioxidant effects against free radicals produced by reactive oxygen and nitric oxide.[59] Using gene array it has been possible to investigate the expression of genes throughout the adult vitamin D-deficient rat brain as well as the expression of proteins in the prefrontal cortex and hippocampus. Vitamin D deficiency significantly changed the expression of 74 genes and 36 proteins involved in a variety of processes, including maintenance of the cytoskeleton, homeostatsis of calcium, neurohumoral transmission, and posttranslational alterations.[43-60] The in vitro oligomerization of amyloid beta has been demonstrated to be inibited by DBP, and it has also been proven to stop Amyloid beta induced hippocampal synapse loss and the subsequent memory impairment.[61] Neuroprotective effects of vitamin D against glutamate toxicity have been demonstrated in a clinical study. Vitamin D therapy shielded cultured rat cortical neurons against acute glutamate exposure via elevation of VDR expression and antioxidant effects.[61,62]

CONCLUSION

Vitamin D is a promising option for the prevention and treatment of AD and ADRDs because of its multitargeted neuroprotective activity. Vitamin D has a major role inneurocognition, including the induction of neuroprotection, modulation of oxidative stress, control of calcium homeostasis, and inhibition of inflammatory processes. Along with some other functions like amyloid phagocytosis and clearance, vasoprotection, are all aided by vitamin D and its metabolites.Vitamin D treatment reduces the amyloid burden in the brain which indicates a relationship between vitamin D and amyloidogenesis. Evidences demonstrated that ineffective utilization of vitamin D in elderly population may result in the alteration of clinical manifestations, thus causing negative outcomes of cognitive decline. However, due to a lack of specificity and inadequate data, Vitamin D Deficiency should not yet be employed as a diagnostic or prognostic biomarker of neurocognitive decline. Prior to considering DBP as a potential therapeutic modulator in AD, further confirmation with stronger epidemiological and molecular data is eagerly sought. Thus indicates the need of several prospective observational clinical studies endorsing the correlation of vitamin D and neurocognition is essential to consider vitamin D deficiency as a active biomarker for compromised neurocognition.

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