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The Low Serum Vitamin D Levels as a Risk Factor for Cognitive Impairment in Parkinson's Disease: A Literature Review

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized not only by motor impairments but also by non-motor symptoms such as cognitive dysfunction. Cognitive decline in PD can progress to Parkinson's Disease Dementia (PDD), significantly impacting patients' quality of life. One of the factors suspected to contribute to cognitive impairment in PD is vitamin D deficiency. Several studies have shown that vitamin D deficiency is more common in PD patients compared to the healthy population. Low vitamin D levels are associated with poorer cognitive performance on neuropsychological tests and an increased risk of developing PDD. Vitamin D plays a role in modulating oxidative stress, regulating calcium homeostasis, and inhibiting inflammation, all of which contribute to the health of dopaminergic neurons in the substantia nigra. Vitamin D deficiency may be a risk factor for cognitive impairment in PD. Therefore, assessing vitamin D levels and implementing interventions such as supplementation and adequate sun exposure could be potential strategies in PD management to slow cognitive progression. Further studies are needed to determine the optimal dosage of vitamin D supplementation in PD therapy.

Keywords: vitamin D; Parkinson's disease; cognitive impairment; neuroprotection; vitamin D deficiency.

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive disorder characterized by both motor and non-motor symptoms. The hallmark motor symptoms include tremors, bradykinesia, rigidity, and postural instability.[1] Over time, research has revealed that PD is not solely a motor disorder but also includes non-motor symptoms such as cognitive impairment, autonomic dysfunction, sensory dysfunction, and sleep disturbances. While PD is traditionally classified as a movement disorder, non-motor symptoms, particularly cognitive impairment, are a highly prevalent feature.[2]

Over several years, PD patients may develop Parkinson's disease dementia (PDD), which is clinically defined as a progressive decline in cognitive function in patients with an established PD diagnosis. The cumulative prevalence of PDD is at least 75% among PD patients who survive beyond 10 years.[3] A recent meta-analysis reported that cognitive impairment affects approximately 40% of PD patients. Contributing risk factors include advanced age, lower education level, longer disease duration, higher daily levodopa dose, more severe motor symptoms, postural instability, gait difficulty subtype, lower quality of life, and higher levels of apathy and depression.[4]

Vitamin D has long been recognized for its roles beyond bone and calcium metabolism, including its involvement in immunity, cancer prevention, and more recently, cognitive protection.[5] Vitamin D, or 25-hydroxyvitamin D, originates primarily from dietary sources and ultraviolet B (UVB) radiation (wavelength 290–315 nm) from sunlight. Ultraviolet radiation is the primary source of vitamin D production.

Cognitive impairment is one of the most common and significant non-motor symptoms that can occur at any stage of Parkinson's disease (PD).[6] Vitamin D is a neurosteroid whose receptors are widely expressed in the nervous system, in addition to its calcium-related effects. Vitamin D regulates not only neurotrophic factors and neurotransmitters but also neurotoxic pathways and mitochondrial function, which have both neurotropic and neuroprotective roles.[7,8] Deficiency of vitamin D in circulation can lead to nigral dysfunction and its apoptosis.[9,10]

A recent study indicated that low serum vitamin D [25(OH)D] levels are associated with poorer cognitive performance, particularly in verbal fluency and memory tests.[11] Research by Evatt et al. found vitamin D deficiency in 55% of PD patients, 41% of

Alzheimer's disease patients, and only 36% of the control population, suggesting a higher incidence of vitamin D deficiency in PD patients.[12] Vitamin D may exert its neurocognitive effects through various mechanisms, including neuroprotection, oxidative stress modulation, calcium homeostasis regulation, and inhibition of inflammatory processes.

The hypothesis that low vitamin D levels may be linked to cognitive impairment in PD stems from its regulatory role in multiple physiological processes, including cell proliferation, differentiation, survival, oxidative stress resistance, hormone regulation, and immune system modulation.[13] Additionally, because vitamin D activates human T cells, its deficiency may hinder the immune system's ability to clear beta-amyloid plaques and Lewy bodies, which are implicated in the pathogenesis of PD and dementia.[14] Vitamin D receptors are widely distributed throughout the body and brain, supporting the notion that vitamin D plays a crucial role in normal central and peripheral nervous system function.[15,16]

Over the past two decades, numerous studies in developed countries have explored the relationship between low vitamin D levels and cognitive impairment in PD patients. However, research on serum vitamin D levels in populations from South Asia, particularly in Indonesia—a country with year-round sun exposure—is still limited, especially regarding its association with cognitive impairment in vulnerable groups such as PD patients.

DISCUSSION

Non-Motor Symptoms of Parkinson's Disease

Non-motor symptoms frequently observed in PD patients include autonomic dysfunction, cognitive impairment, neuropsychiatric disturbances, sensory dysfunction, and sleep disorders.[1] Cognitive impairment in PD can significantly impact daily activities to the same extent as motor symptoms. Cognitive impairment in PD ranges from mild cognitive impairment (PD-MCI) to severe cognitive decline in the form of Parkinson's disease dementia (PDD), with executive function being the most affected domain.[17,18]

Cognitive Impairment in Parkinson's Disease

The basal ganglia circuit is not only involved in motor preparation and execution but also plays a crucial role in learning, planning, executive function, and emotions. This explains the presence of non-motor symptoms in PD, particularly cognitive impairment.[14] Cognitive impairment in PD can range from mild to severe dysfunction.[17,18] Cognitive impairment significantly affects the quality of life of PD patients, increases caregiver burden, and raises healthcare costs. Longitudinal studies have shown that 25–50% of PD patients will develop PD-MCI or progress from PD-MCI to PDD within five years of diagnosis, and approximately 80% will develop PDD over the course of their disease.[17,20,21]

Community-based studies have reported PD-MCI incidence rates ranging from 20–60%, with 10% of PD-MCI patients progressing to PDD annually. [3,18,22]

Compared to age-matched controls, PD patients have a 3–6 times higher risk of developing dementia.[12] Uc et al. reported that the incidence of cognitive impairment in PD was 2.4% within the first two years of diagnosis and 5.8% at five years.[23] However, a study by Huang et al. in Taiwan found that cognitive impairment incidence was highest (11.98%) within the first six months post-diagnosis and declined over subsequent years, reaching 3.93% in the first year, 3.50% by the third year, and 2.20% in later years.[24] The cognitive domains affected by PDD include:

a. Executive Dysfunction Given that the pathophysiology of cognitive impairment in PD involves prefrontal circuits from the early stages, it is unsurprising that executive dysfunction is the earliest and most frequently observed cognitive impairment in PD patients. Executive dysfunction can be present even in the pre-motor stage. In some PD patients, executive dysfunction may remain the sole cognitive symptom throughout the disease course.[25]

b. Attention Deficits Attention is closely related to executive function, as both are regulated by the same circuitry—namely, the dorsolateral prefrontal circuit. However, despite sharing this circuitry, attention and executive function are distinct processes. Attention can be categorized into simple and complex attention, with complex attention assessments often incorporating elements of executive function evaluation. In early-stage PD, impairments may be found in complex attention, while deficits in simple attention are typically observed only in PDD patients. [25,26]

c. Memory Impairment Memory assessment in PD patients should include both implicit and explicit memory evaluations. Research has shown that both verbal and non-verbal memory, including facial recognition, are impaired in PD-MCI and PDD patients. The earliest memory functions affected in PD are immediate and delayed memory, while remote memory deficits emerge at the dementia stage. Implicit memory also begins to decline in the early stages of PD.[25]

d. Visuospatial Impairment Visuospatial dysfunction in PD patients is linked to posterior cortical dysfunction. Studies indicate that PD patients score lower on visuo-perceptual and visuospatial tests compared to age-matched controls. Additionally, visuospatial impairment in PD patients is not associated with their motor symptoms.[27,28]

e. Language Impairment The presence of language deficits in PD remains a topic of debate. Some studies classify language impairment as a distinct minor cognitive deficit in PD, while others argue that it is not an independent cognitive domain. This debate arises because language assessments, such as the phonemic verbal fluency test, inherently include executive function components.[25]

Pathophysiology of Cognitive Impairment in Parkinson's Disease

The pathophysiology of cognitive impairment in PD overlaps with that of PD itself, involving cortical-subcortical circuits and distinct histopathological features. In addition to formulating the motor circuit of the basal ganglia, Alexander and DeLong hypothesized the existence of five basal ganglia-thalamocortical circuits, where three of which are major circuits: the sensorimotor circuit, the associative and cognitive circuit, and the limbic circuit. [24] the foundation of all these circuits involves different regions of the striatum, pallidum, substantia nigra, thalamus, and prefrontal or frontal cortex, as illustrated in Figure 1.

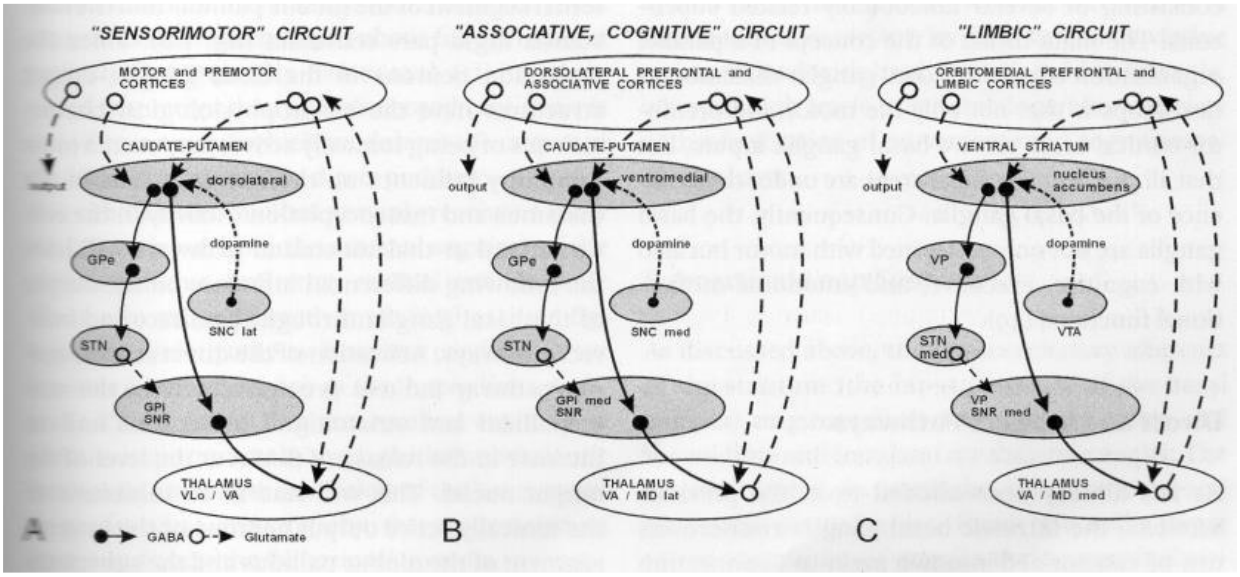

FIGURE 1: Representation of the Three Main Basal Ganglia-Thalamocortical Circuits. (According to Alexander and DeLong, as cited by Wolters et al., 2007).

The circuits that regulate cognition consist of two prefrontal circuits: the dorsolateral circuit and the orbital circuit. The dorsolateral circuit includes the dorsolateral prefrontal cortex (DLPFC), dorsolateral caudate nucleus, dorsomedial globus pallidus, and thalamus, while the orbital circuit consists of the orbitofrontal cortex (OFC), ventromedial caudate nucleus, dorsomedial globus pallidus, and thalamus. Within each of these circuits, there are also direct excitatory and indirect inhibitory pathways like the motor circuit. The neurotransmitters involved in these circuits resemble those in the motor circuit, so dopamine depletion can suppress both cognitive and behavioral output in patients with Parkinson's disease (PD).[29,30]

The prefrontal circuits primarily play a role in executive function. More specifically, the dorsolateral circuit regulates attention, working memory, and planning, and it is often impaired from the early stages of PD, whereas the orbital circuit is more involved in behavioral regulation and generally remains more intact. Dysfunction in these circuits leads to prominent executive impairment in PD patients, and as the pathological process progresses to the cortex, other cognitive dysfunctions will emerge.[30]

In addition to dopaminergic deficiency, non-dopaminergic systems are also involved in the pathophysiology of cognitive impairment in PD at various levels. The neurotransmitters affected in PD include serotonergic systems in the dorsal raphe nucleus, noradrenergic systems in the locus coeruleus and cortex, as well as cholinergic systems. Cholinergic neurotransmitters, found abundantly in basal brain nuclei and cortical areas, play a significant role in cognitive function. In PD patients, cholinergic activity reduction often overlaps with age-related cholinergic decline.[29] Functional imaging studies measuring acetylcholine activity have shown a decrease of up to 21% in the brains of patients with Parkinson's disease dementia (PDD) and only 13% in those with PD-mild cognitive impairment (PD-MCI). This hypothesis is further supported by evidence of cognitive impairment in elderly individuals treated with anticholinergics and the improvement of PDD symptoms with cholinesterase inhibitors. [17]

The histopathological features of cognitive impairment in PD patients are heterogeneous, found not only in subcortical but also in cortical regions. Lewy bodies can be detected in the cortex and limbic structures alongside beta-amyloid plaques and neurofibrillary tangles (NFTs).[17,31] A post-mortem study found that only 38% of PDD cases exhibited pure Lewy body pathology, whereas 59% showed both Lewy body and beta-amyloid pathology, and 3% exhibited Lewy body, beta-amyloid, and NFT pathology.[32] There is also a positive correlation between beta-amyloid deposition in the cortex and cognitive impairment in PD patients.[31]

Genetic mutations are also suspected to contribute to cognitive impairment in PD, such as mutations in the alpha-synuclein gene and apolipoprotein E4 (APOE4). Alpha-synuclein in fibrillar form can be found in the cortex of PD patients, forming Lewy bodies alongside dysfunction in the ubiquitin-proteasome system (UPS).

The pathological process of Lewy body formation from alpha-synuclein may also trigger the development of beta-amyloid and NFTs, and vice versa, as illustrated in Figure 2.

Ultimately, the pathological interactions between these three factors lead to further degeneration of cortical and subcortical neurons.[17]

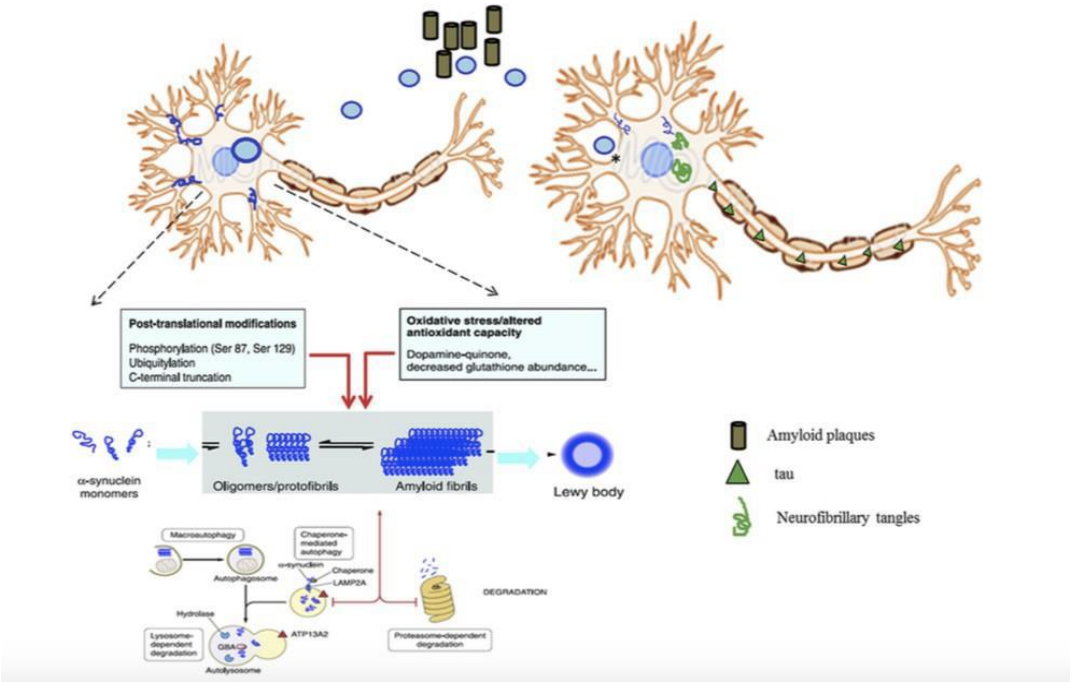

FIGURE 2: Interaction of α-synuclein, β-amyloid, and NFTs (Lin and Wu, 2015).

Role and Metabolism of Vitamin D

Vitamin D has two different precursor molecules, D3 and D2, each with distinct molecular structures. [33] Vitamin D3, known as cholecalciferol, is primarily obtained through sunlight exposure, while vitamin D2, known as ergocalciferol, comes from dietary sources. Vitamin D3 serves as the body's main source of vitamin D and is synthesized in the skin upon exposure to sunlight, with optimal production occurring between 10:00 AM and 3:00 PM.[34] A 30-minute exposure to sunlight can generate approximately 10,000–20,000 IU of vitamin D. Additionally, vitamin D3 can be obtained from animal-based foods such as egg yolks, meat, fish oil, or dietary supplements. Meanwhile, vitamin D2 is available through oral medication or plant-based foods.[35]

Vitamin D plays a crucial role in bone health regulation, calcium metabolism, and various functions within the cardiovascular, endocrine, and nervous systems. It has anti-inflammatory, antioxidant, and neuroprotective properties. Moreover, vitamin D influences homeostasis, and glucose metabolism, and may contribute to diabetes prevention.[35] As a neuro-steroid hormone, vitamin D regulates neurotransmitters and neurotrophins, enhancing neurotrophic factors such as the Nerve Growth Factor (NGF), which supports brain health. It also aids in preventing β-amyloid accumulation and promotes β-amyloid clearance. [5]

Vitamin D3 has been shown to improve nerve demyelination and support axonal regeneration. [36] Additionally, it stimulates neurotransmitters and neurotrophins, play a role in enzyme formation for neurotransmitter synthesis and detoxification mechanisms. [36,37] The function of vitamin D receptors varies depending on the cell type; for example, vitamin D receptors on endothelial cells influence vascular structural and functional changes, modulated by Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, nitric oxide, and extracellular matrix components. [38–40] Both vitamin D2 and D3 are used as medications or supplements. However, studies have shown that serum 25(OH)D2 levels are higher when vitamin D3 is used compared to D2. [33,41] The active form of vitamin D derived from D3 also has a higher affinity for the vitamin D receptor (VDR). Despite these differences, both precursors undergo largely similar metabolic pathways and are collectively recognized as vitamin D.

Vitamin D is a prohormone and is initially inactive; it must undergo a series of enzymatic and non-enzymatic activation processes.[33] The synthesis of vitamin D3 occurs in the epidermis through a non-enzymatic process. Approximately 90%–95% of vitamin D3 in the human body is produced in the skin under the influence of sunlight. Ultraviolet B (UVB) radiation breaks the B-ring bond of 7-dehydrocholesterol (pro-vitamin D3), resulting in the formation of provitamin D3 in the epidermis. In the next step, a double bond forms between the carbon atoms that were split in the B-ring through a temperature-sensitive and non-enzymatic process, ultimately completing the conversion of provitamin D3 into vitamin D3.[33]

Once synthesized in the skin, vitamin D3 is released into the systemic circulation, where all its forms are transported by binding to vitamin D-binding protein (VDBP) in the serum. Vitamin D3 undergoes two hydroxylation processes: the first occurs in the liver, where it is converted into 25-hydroxyvitamin D3 [25(OH)D3] by the cytochrome P450 25-hydroxylase enzyme. 25(OH)D3 is the main circulating form of vitamin D and serves as the best parameter for estimating the body's vitamin D levels.

The second hydroxylation takes place in the kidneys, where the enzyme 1-alpha hydroxylase converts it into the active hormonal metabolite 1,25-dihydroxyvitamin D3 [1,25(OH)2D3].[42] The primary site of 1,25(OH)2D3 production is in the proximal renal tubules; however, mRNA for this enzyme has also been found in dendritic cells and macrophages, utilizing a different pathway. Circulating vitamin D is associated with the vitamin D receptor (VDR) and its carrier protein, vitamin D-binding protein (VDBP).[43]

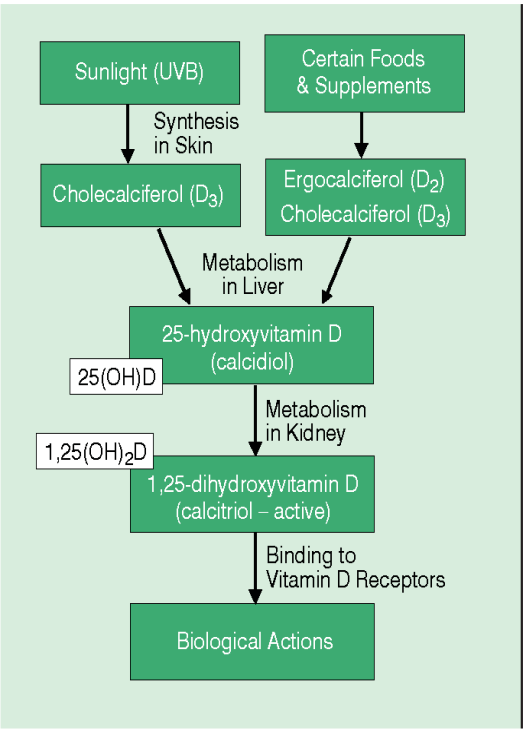

FIGURE 3: Vitamin D Metabolism (Leavitt, 2008).

The optimal circulating vitamin D levels remain a topic of discussion, with no established consensus. Levels between 20-30 ng/mL (50-70 nmol/L) are considered adequate, while levels below 20 ng/mL (<50 nmol/L) are classified as deficient.[44] According to the US Endocrine Society, vitamin D deficiency is defined as 25(OH)D levels below 20 ng/mL.[45] Dawson-Hughes et al. described the diagnostic criteria for serum vitamin D levels, measured as 25(OH)D concentration, as follows:[46]

a. Severe deficiency: 0-10 ng/mL
b. Deficiency: 10-20 ng/mL
c. Insufficiency: 20-30 ng/mL
d. Optimal: 30-80 ng/mL
e. Risk of toxicity: >100 ng/mL

Vitamin D in Parkinson's Disease

Various mechanisms have been hypothesized regarding the role of vitamin D in neurodegenerative diseases. Vitamin D exhibits neuroprotective properties by influencing neurotrophic factors, regulating nerve growth, or providing protection against cytotoxicity. Several studies have shown that the synthesis of neurotrophic factors, including neurotrophins 3 (NT3) and Glial Cell Line-Derived Neurotrophic Factor (GDF), is upregulated by $1,25(OH)_2D_3$.[47]

Studies by Riaz et al. and Wang et al. have demonstrated that vitamin D-induced neurotrophin stimulation correlates with neuroprotective effects in animal models. Through the Vitamin D Receptor (VDR), vitamin D can enhance the regulation of the Nerve Growth Factor (NGF). In animal models of peripheral nerve injury, mice exposed to vitamin D_2 showed significant increases in axogenesis and axon diameter.[48]

Oxidative stress is one of the etiopathogeneses of Parkinson's disease (PD), and vitamin D has antioxidant properties. Its deficiency may contribute as a risk factor for PD.[43] Although various treatments are available to manage symptoms and reduce disease severity, no Disease-Modifying Therapy (DMT) has been proven effective for PD. Considering its neuroprotective effects, vitamin D has the potential as an adjunctive therapy in PD to improve symptoms and disease progression.[48]

$1,25(OH)_2D_3$ stimulates the release of neurotrophins and the synthesis of calcium-binding proteins such as parvalbumin, which inhibit the synthesis of inducible nitric oxide synthase (iNOS), macrophage colony-stimulating factor (MCSF), and tumor necrosis factor-α (TNF-α).

This leads to the downregulation of L-Type Voltage-Sensitive Ca^{2+} Channels (LVSCC) and the upregulation of γ-glutamyl transpeptidase activity. Low vitamin D levels are also correlated with elevated C-reactive protein (CRP), an inflammatory marker. Thus, vitamin D is considered crucial in preventing brain aging due to its role in producing growth factors such as NGF, Ciliary Neurotrophic Factor (CNTF), Glial Cell-Derived Neurotrophic Factor (GDNF), Brain-Derived Neurotrophic Factor (BDNF), and Neurotrophins 3 (NT3).[47]

Based on previous hypotheses, recent research has increasingly focused on the Vitamin D Receptor (VDR). VDR is expressed in central nervous system (CNS) neurons, astrocytes, oligodendrocytes, substantia nigra, cortex, subcortex, hippocampus, hypothalamus, thalamus, and blood vessel walls. The presence of VDR and 1-alpha-hydroxylase—an enzyme that converts 25(OH)D into its active form, 1,25-dihydroxy vitamin D ($1,25(OH)_2D$)—in the substantia nigra suggests that vitamin D hydroxylation and activation occur within the CNS. A deficiency in vitamin D concentration may lead to dopaminergic neuron death.[47] Animal studies in which VDR was knocked out showed that vitamin D supplementation increased dopamine production. This effect was attributed to the increased expression of tyrosine hydroxylase (TH), which contributed to the survival of dopaminergic neurons. Furthermore, vitamin D administration reduced dopaminergic toxicity induced by 6-hydroxy dopamine, while VDR downregulation was associated with motor dysfunction in animal models.[47]

Vitamin D and Cognitive Function in Parkinson's Disease

Vitamin D receptors (VDR) and vitamin D metabolites are highly expressed in the human brain and play a crucial role in maintaining various brain functions.[49] VDR is highly expressed in the substantia nigra, where it regulates dopaminergic neuron activity and synaptic plasticity.[50] Vitamin D exerts protective and therapeutic effects on the progression of Parkinson's disease (PD) by modulating dopaminergic neurons in the substantia nigra. It reduces oxidative stress and neuroinflammation in PD due to its anti-inflammatory and antioxidant properties. Several studies have highlighted the protective effects of vitamin D in managing PD.[51] The high expression of VDR in the substantia nigra (SN) further supports its role in regulating dopaminergic neuron activity and synaptic plasticity.[49]

Cognitive function can be assessed through screening tests such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). A study by Yan Lu et al. found that MMSE and MoCA scores were lower in patients with severe vitamin D deficiency compared to those with mild deficiency.[52] Serum vitamin D levels positively correlate with MMSE and MoCA scores, and this relationship remains significant even after adjusting for gender, age, and education level.

Both in vitro and in vivo studies have demonstrated the impact of vitamin D on cognitive function. [53,54] Vitamin D plays a role in protecting the brain from damage caused by age-related neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, by inhibiting inducible nitric oxide synthase (iNOS), which is upregulated during ischemic events.[55] Additionally, vitamin D regulates gamma-glutamyl transpeptidase activity, which increases glutathione concentration in glial cells. These cells provide protective effects on oligodendrocytes and help maintain neural conduction pathway integrity, which is essential for cognitive processes.[56] Evidence also suggests that vitamin D protects brain structures by modulating neuronal calcium homeostasis.[57] These findings indicate that vitamin D not only maintains calcium and phosphorus homeostasis but also prevents cognitive impairment by reducing the risk of cardiovascular and cerebrovascular diseases.

A large prospective study in the elderly population in France suggested that maintaining normal serum vitamin D levels may help prevent cognitive decline and the development of dementia.[58] Supporting this, Peterson et al. (2013) found that higher serum vitamin D levels correlated with better cognitive function and mood in PD patients through reduced Aβ deposition.[59] The cognitive-enhancing effects of vitamin D are associated with synaptic plasticity preservation and its modulation of neurotransmitter release, as documented in several preclinical studies. [60,61]

A study by Han Wu et al. (2022) reported a significant decrease in serum 25(OH)D levels in PD patients compared to controls. The study found that serum 25(OH)D was positively correlated with MoCA scores. In binary logistic regression analysis, an increase in serum 25(OH)D was identified as an independent protective factor against cognitive impairment in PD.[62] This finding is consistent with the results of Barichella M et al., which suggested that low serum 25(OH)D may be involved in the onset and progression of cognitive impairment in PD patients.[63]

Furthermore, cognitive dysfunction is also linked to the development of olfactory dysfunction in PD patients. Vitamin D deficiency is associated with the severity of olfactory dysfunction, which often precedes the onset of symptomatic PD.[64] The brain regions responsible for olfaction and cognition are closely related, and olfactory dysfunction, such as hyposmia, can predict PD-related dementia and motor severity. [65,66] A prospective study revealed that vitamin D supplementation could protect against PD progression by modulating dopaminergic neuron activity.[67] Additionally, exposure to sunlight for more than 15 minutes per week has been suggested as a preventive measure against PD progression.[68] Therefore, vitamin D supplementation and adequate sunlight exposure may be effective in preventing PD progression in high-risk individuals.

CONCLUSION

Vitamin D is known to play a role in protecting the brain from damage caused by age-related neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Ts levels in the blood influence oxidative and atherogenic processes both in the brain and systemically, potentially contributing to cognitive impairment in PD. Vitamin D may exert neuroprotective effects by promoting neurotrophic factors, regulating neural growth, and mitigating cytotoxicity. Therefore, evaluating vitamin D levels is essential as a biomarker for cognitive decline risk and as a guideline for supplementation in Parkinson's disease management and its associated complications.

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