MINI REVIEW

Parkinson's disease and vitamin D

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ABSTRACT

Vitamin D is a fat-soluble secosteroid that has long been thought to be an important regulator of bone metabolism, calcium and phosphorus homeostasis. Its action is enabled by binding to the Vitamin D Receptor (VDR), after which it modulates the expression of thousands of genes both directly and indirectly. Vitamin D is essential for brain development and mature brain activity, and it has been linked to a variety of neurological diseases, including Parkinson's Disease (PD). Nearly two decades ago, it was discovered that patients with Parkinson's disease had a higher rate of vitamin D deficiency than the general population. This finding is intriguing given vitamin D's neuroprotective effect, which can be mediated by neurotrophic factors, nerve growth regulation, or protection against cytotoxicity. Vitamin D deficiency appears to be related to disease severity and progression, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr (H&Y) scales, but not to age of PD onset or disease duration. Furthermore, lower vitamin D levels in Parkinson's disease have been linked to a higher risk of falling. While the link between vitamin D and motor symptoms appears to be plausible, the results of studies looking into the link between vitamin D and non-motor symptoms are conflicting. Furthermore, there is very little evidence that vitamin D supplementation can reduce clinical manifestations and disability in Parkinson's disease patients. However, given the positive balance of potential benefits versus risks, vitamin D supplementation for Parkinson's disease patients is likely to be considered in the near future, if further confirmed in clinical studies.

Key Words: *Parkinson's disease; Neuroprotection; Neurodegeneration; balance; Cognition; Disease progression*

INTRODUCTION

The prevalence of neurological disorders is increasing as the global population grows and the average lifespan improves. The scientific community is concentrating its efforts on the treatment and prevention of brain ageing. Inflammation, oxidative stress, mitochondrial dysfunction, lysosomal depletion, metal dysregulation, impaired RNA homeostasis, misfolding and aggregation of specific proteins such as alpha-synuclein, Amyloid (A), and hyperphosphorylated tau are all involved in degeneration. Lower serum vitamin D (or 25-hydroxyvitamin D) concentrations appear to be associated with psychiatric disorders such as depression, bipolar disorder, and schizophrenia, as well as neurological disorders such as dementia and Parkinson's Disease (PD) As a result, it has been proposed that maintaining adequate vitamin D serum concentrations may prevent disease onset and potentially improve clinical outcomes. We discuss vitamin D's role as a neuroprotective factor, changes in serum concentration during disease progression, and potential therapeutic applications [1].

Vitamin D: Vitamin D is a group of fat-soluble secosteroids that are either ingested or produced by skin exposure to ultraviolet light. There are two types of vitamin D: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Humans can also synthesize vitamin D in their skin during sunlight exposure, using the effect of Ultraviolet B (UVB) to convert the steroid precursor, 7-dehydrocholesterol, into

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activated vitamin D3 Vitamin D is activated by a double hydroxylation, first in the liver by 25-hydroxylase into 25-hydroxyvitamin D (25(OH)D) and then in the kidney by 1~hydroxylase, resulting in an active form of the vitamin, 1,25-dihydroxyvitamin D2 (1,25(OH)2D2) or D3 (1,25(OH)2D3). Although 25(OH) D is not biologically active, it can be detected in humans with normal serum concentrations ranging from 50 nmol/L to 250 nmol/L. There is agreement that the serum or plasma level of 25 (OH) D should be used to assess vitamin D status because it can reflect the contribution of both diet and skin synthesis [2,3]

Globally, there is no agreement among health agencies and scientific organisations on the cut-off values that define the normal threshold of serum 25(OH) D concentration, which can range from >25 to >50 nmol/L. Vitamin D sufficiency has been defined in various ways, but the general consensus is that deficiency corresponds to 25(OH)D levels less than 25 nmol/L-30 nmol/L. Up to 95% of 25(OH)D binds to vitamin D-binding protein (VDBP), 10% circulates in conjunction with albumin, and only 1% is unbound. Vitamin D is important for bone health, but it also plays a role in other systems, including the Central Nervous System (CNS) [4].

The enzyme 1a-hydroxylase, which produces the active form of vitamin D, and Vitamin D Receptors (VDR) are both found in the brain. In reality, circulating 25-hydroxyvitamin D (25(OH) D can cross the blood–brain barrier and be hydroxylated into the active form 1,25OH2D in neuronal and glial cells. Vitamin D can activate both genomic and non-genomic pathways in the CNS.

Vitamin D Receptors (VDR) exist in the CNS in two forms: a nuclear receptor and a Membrane-Associated Rapid Response Steroid Binding Receptor (MARRS). VDR belongs to the nuclear receptor family of transcription factors, a steroid/thyroid hormone superfamily of transcription control factors that binds vitamin D to specific genomic regions and induces gene transcription (genomic pathway) when complexed with calcitriol. Vitamin D interacts to a membrane receptor called MARRS, which has various impacts on calcium and phosphate homeostasis, molecular chaperoning, immunomodulation, and activation of the protein kinase C, cAM, and MAP kinase pathways (non-genomic pathway). However, it has been discovered that the 1,25D3-MARRS receptor has a genomic effect, binding DNA and regulating gene transcription [3,5].

Vitamin D has a wide range of actions thanks to its receptors. The proto-oncogene tyrosine-protein kinase receptor Ret (C-Ret) and the GDNF genes, both implicated in antioxidant and neuroprotective regulation, can be upregulated by 1,25(OH)2D3.

Nurr1 and p57kip2 are also upregulated by 1,25(OH)2D3. collaborating and regulating the differentiation and maturation of DA neurons. Though vitamin D's primary function is bone health, its participation in brain development as well as adult brain neuroprotection has been well documented. The presence of 1,25(OH)2D3 in the cerebrospinal fluid (CFS) supports the presence of a catabolic pathway in the CNS. Vitamin D metabolites could flow through the blood–brain barrier.

Not only is 1-hydroxylase found in the brain (particularly in the cerebellum, cerebral cortex, and substantia nigra), but it has also been discovered that distinct neuronal populations can convert 1,25OH2D3 to 25OHD3. The existence of a high concentration of VDR and 1~hydroxylase in the Substantia Nigra (SN) suggests that PD and vitamin D may have a link.

Vitamin D and Parkinson Disease: Parkinson's Disease (PD), the second most prevalent neurodegenerative ailment, is marked by the motor symptomatologic triad of tremor, stiffness, and bradykinesia, with asymmetric involvement in the early stages. Other motor aspects that emerge clinically include Freezing of the Gait (FOG), postural instability, camptocormia, and Pisa-syndrome. Non-Motor Symptoms (NMSs) that might occur years before motor symptoms (autonomic impairment, orthostatic hypotension, sleep problems, olfactory impairment, sialorrhea, dysphagia, exhaustion, pain, cognitive and neuropsychiatric disturbances) are also common in Parkinson's disease. Treatment-resistant motor and non-motor symptoms become more apparent as Parkinson's disease progresses, and after 17 years of disease, over 80% of PD patients have Freezing Of Gait (FOG) and falls. The growth of neuronal Lewy Bodies and the progressive loss of Dopaminergic (DA) neurons in the Substantia Nigra Pars Compacta (SNpc) of the midbrain characterise the neuropathology of Parkinson's disease. These are -synuclein protein clumps that cause neuronal death and a reduction in the ability to manufacture dopamine. Excitotoxicity, apoptosis, oxidative stress, mitochondrial malfunction, inflammation, and other etiopathogenetic processes have all been linked to neurodegeneration [6,7].

Although the aetiology of neurodegeneration in Parkinson's disease is unknown, interactions of genetic and environmental factors such as rural living, brain damage, pesticide exposure, alcohol intake, smoking, and other factors are very likely to have a role. Vitamin D insufficiency may be one of the key risk factors for Parkinson's disease, along with pesticides, medications, smoking, alcohol, and traumatic brain injuries. Other risk factors, such as tumours, smoking, and estrogenic hormones, appear to be inversely connected to Parkinson's disease. Because oxidative stress is one of the etiopathogenetic processes in Parkinson's disease, medicines having anti-inflammatory and antioxidant properties could be utilised to counteract it. Vitamin D serves as an antioxidant in the brain, and its shortage may be linked to the onset of Parkinson's disease. Many symptomatic drugs are currently available to help with PD symptoms, but no disease-modifying therapy shave been demonstrated to be beneficial. Vitamin D, owing to its neuroprotective properties, could be utilised as an additional treatment in Parkinson's disease patients to ameliorate symptoms and perhaps the illness's course [8].

We will discuss the most important and current results on vitamin D and Parkinson's disease in this review. We'll look at its putative neuroprotective properties, as well as its link to several clinical features of the disease and, lastly, a potential role for vitamin D as an additional treatment for Parkinson's disease.

Neuroprotective Effect of Vitamin D in Parkinson Disease: Vitamin D's involvement in Parkinson's disease has been extensively researched. Due to the loss of its protective effect, lower 25(OH)D levels may be responsible for dopaminergic neuronal death, which contributes to the development of PD. The exact mechanism through which vitamin D protects against Parkinson's disease is unknown. Many mechanisms have been linked to a neuroprotective effect against excitotoxic insults, including stimulation of neurotrophin release and the synthesis of Ca2+-binding proteins like parvalbumin, inhibition of the synthesis of Inducible Nitric Oxide Synthase (iNOS), Macrophage Colony-Stimulating Factor (M-CSF), and Tumour Necrosis Factor (TNF-), and induction of downregulation of LVSCC and upregulation of gluta. Furthermore, low vitamin D levels

are linked to high levels of C-Reactive Protein (CRP), an inflammatory marker. Overall, vitamin D's role in the production of growth factors such as Nerve Growth Factor (NGF), Ciliary Neurotrophic Factor (CNTF), Glial Cell-Derived Neurotrophic Factor (GDNF), Brain-Derived Neurotrophic Factor (BDNF), and neurotrophin 3 appears to be critical in the prevention of brain ageing (NT3) Vitamin D increases the levels of circulating neutrophins like NGF, GDNF, BDNF, NT3, CNTF, low-affinity p75 neurotrophin NT receptor (p75 NTR), and transforming growth factor (TGF)-b2, while decreasing the levels of neurotrophin 4 (NT4).

Vitamin D helps maintain intraneuronal calcium (Ca^{2+}) homoeostasis and cytosolic Ca^{2+} glial concentration by modulating the L-type Voltage Sensitive Ca^{2+} Channel (LVSCC), altering neuronal activity, and increasing parvalbumin and calbindin production. High Ca^{2+} concentrations are hazardous, causing an increase in Reactive Oxygen Species (ROS) and mitochondrial malfunction, as well as neuronal cell death. Vitamin D reduces excitotoxicity harm triggered by cytoplasmic Ca^{2+}, especially when calcium levels are suddenly increased. Vitamin D also has antioxidant properties, reducing the formation of free radicals and the production of Reactive Oxygen Species (ROS) by inhibiting nitric oxide synthase, lowering the activity of NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells), and increasing the activity of gamma glutamyl transpeptidase. Furthermore, vitamin D is a regulator of the Renin-Angiotensin System (RAS), and its malfunction could contribute to sympathetic dysfunction.

Given all of these important effects, vitamin D is anticipated to have a neuroprotective impact, which could slow the progression of neurodegenerative disease [9].

As a result, low vitamin D levels may cause the loss of dopaminergic neurons in the brain, which may contribute to the development of Parkinson's disease. Vitamin D levels in Parkinson's patients were found to be lower than in sex- and age-matched healthy controls. Many research looked into the impact of a low 25-hydroxyvitamin D level, hypothesising that a low vitamin D concentration could be a risk factor, and found that vitamin D deficiency (50nmol/L) was associated with a higher risk of PD than insufficiency (75nmol/L). In a cross-sectional investigation, blood 25(OH)D concentrations were found to be lower in PD patients compared to Alzheimer's disease patients, as well as lower levels compared to age- and sex-matched healthy controls. These findings could be explained by the fact that PD patients have a longer clinical history and are more immobile than AD patients, resulting in less sunlight exposure and, as a result, a lack of skin synthesis. Though decreased mobility and hence sunshine exposure in individuals with PD are reasonable explanations for lower 25(OH) D levels, 25(OH) D concentrations in PD patients with appropriate sunlight exposure are considerably lower than in healthy controls.

In comparison to controls, Ding et al. found reduced 25(OH) D3 and total 25(OH) D blood concentrations in PD patients. In a post hoc analysis, it was discovered that participants with the lowest quartile of 25 (OH) D serum concentrations had a higher incidence of PD than those with the highest quartile of 25 (OH) D serum concentrations. Further research looked into the link between increased sun exposure (>15 minutes per week) and a lower incidence of Parkinson's disease. It was proposed that persistently low vitamin D levels could have a role in the etiology of neurodegenerative diseases, including Parkinson's disease.

Outdoor activities and subsequent sunlight exposure were found to be inversely linked with PD in a case–control study.

Many writers, however, believe that there is insufficient data to support vitamin D's role in PD aetiology. In a prospective research, Shrestha et al. discovered no link between serum 25(OH) D and the risk of Parkinson's disease. Many authors have focused their attention on the role of Vitamin D Receptor (VDR). in dementia because of the potential relevance of vitamin D in neurodegeneration VDR is found in neurons, astrocytes, and oligodendrocytes throughout the CNS, but especially in the substantia nigra, cortex, subcortex, hippocampus, hypothalamus, thalamus, and vessel walls. The presence of VDR and 1-alpha-hydroxylase, the enzyme that converts 25(OH) D to its active form 1, 25-dihydroxyvitamin D (1, 25(OH) D), in the substantia nigra highlights the role of vitamin D in PD, implying that vitamin D hydroxylation and activation are also completed in the Central Nervous System (CNS), and that a vitamin D deficiency causes dopaminergic neurons to die. Motor impairment in VDR knockout mice supports the importance of vitamin D in PD etiopathogenesis, and genotypes in the VDR gene have been identified that are connected to several PD traits [10].

The presence of VDR in animal and human brains has been established in numerous studies, and vitamin D treatment has been shown to boost Dopamine (DA) production. This could be attributed to increased production of Tyrosine Hydroxylase (TH), which is the rate-limiting synthesis enzyme for dopamine, as well as an increase in neuronal survival in DA neurons in vitro and in vivo. Vitamin D therapy lowers 6-hydroxy dopamine's dopaminergic toxicity, and animals lacking the Vitamin D Receptor (VDR) have markedly reduced motor function. Several genetic association studies looked for a link between VDR Single Nucleotide Polymorphisms (SNPs) and PD, suggesting the possibility that vitamin D plays a role in PD risk. VDR polymorphisms were linked to both risk and age at onset of PD in a Genome-Wide Association Study (GWAS) [11].

As a result, as some research have revealed, the response to vitamin D therapy in PD patients is determined by the VDR genotype.

CONCLUSION

In this review, we summarized the current evidence on vitamin D's potential role in a variety of physiological activities, ranging from immune response modulation to brain development and ageing regulation. We talked about how blood levels of 25(OH)D may be linked to PD symptoms and clinical development, as well as how it might be used to enhance clinical manifestation in PD patients.

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