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The Role of Vitamin D in the Disease Stage of Parkinson's Patients

Harun Nurdiansah Ahmad[1], Dewa Putu Gede Purwa Samatra[2], Anak Agung Raka Sudewi [2]

[1]Resident of Department of Neurology, Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia
[2]Department of Neurology, Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia.

Corresponding Author: Harun Nurdiansah Ahmad

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ABSTRACT

Parkinson's disease (PD) is a disorder of brain function that is pathologically characterized by degeneration of nerve cells in the brain, specifically the basal ganglia. Additionally, there is a loss of pigmentation in the substantia nigra, the presence of cytoplasmic inclusions called Lewy bodies, and a decrease in dopamine in the Substantia nigra Pars Compacta (SNC) and corpus striatum. Vitamin D may provide neuroprotection through the action of neurotrophic factors, which regulate neuronal growth, or through protection against cytotoxicity. In some studies, the synthesis of neurotrophic factors, including Neurotrophin 3 (NT3) and Glial Cell Line-derived Neurotrophic Factor (GDNF), was found to be upregulated by 1,25(OH)2D3. A number of studies have demonstrated a higher prevalence of vitamin D deficiency in individuals with Parkinson's disease (PD) compared to healthy controls. Following the discovery that Vitamin D Receptor (VDR) and 1α-hydroxylase, an enzyme responsible for converting vitamin D into its active form, are highly expressed in the substantia nigra, it was postulated that insufficient circulating vitamin D may contribute to the dysfunction or cell death observed in this region.

Keywords: Parkinson Disease, Substantia Nigra Pars Compacta, Glial Cell Line-derived Neurotrophic Factor, Vitamin D Receptor

INTRODUCTION

Parkinson's disease is a chronic, progressive disease with characteristic motor symptoms, including tremor, bradykinesia, rigidity, and postural instability (Jankovic, 2008). In addition to prolonged investigation, it has been established that PP encompasses not only motor symptoms but also non-motor symptoms. Non-motor symptoms in PP include impaired cognitive function, autonomic system dysfunction, sensory dysfunction, and sleep disturbance. These non-motor symptoms serve as diagnostic criteria for PP, and the absence of non-motor symptoms in the first five years is considered a "red flag" for diagnosis (DeMaagd, 2015; Yang et al., 2016; Williams et al., 2020).

Vitamin D, also known as 25-hydroxyvitamin D, is derived from two primary sources: food and ultraviolet B (UVB) radiation (wavelength, 290-315 nm) from sunlight. The latter affects the conversion of the steroid precursor, 7-dehydrocholesterol, in the skin, thereby influencing vitamin D levels. Therefore, insufficient sun exposure can result in inadequate vitamin D levels. In addition to its role in calcium and phosphorus

metabolism, vitamin D is also involved in inflammatory responses, glucose and lipid metabolism, and heart and vascular regulation. Vitamin D performs its biological functions by binding to vitamin D receptors (VDR), which constitute a superfamily of steroid hormone receptors. VDR is widely expressed in numerous tissues, including the kidney, bone, intestine, muscle, pancreas, and the central nervous system (Zhou et al., 2019).

Vitamin D may provide neuroprotection through the action of neurotrophic factors, which regulate neuronal growth, or through protection against cytotoxicity. In multiple studies, the synthesis of neurotrophic factors, including neurotrophin 3 (NT3) and glial cell line-derived neurotrophic factor (GDNF), was found to be enhanced by 1,25(OH)2D3. Riaz et al. and Wang et al. demonstrated that the neuroprotective effects observed in mouse models were correlated with the stimulation of neurotrophins induced by vitamin D. Vitamin D can upregulate nerve growth factor (NGF) through the action of the vitamin D receptor (VDR). In a rat model with peripheral nerve injury, administration of vitamin D2 resulted in a significant increase in axogenesis and axon diameter (Riaz et al., 1999; Wang et al., 2019; Fullard, 2020).

It is therefore important to gain an understanding of the role of vitamin D in this context, as it can be used to predict the progressivity of Parkinson's disease patients.

DISCUSSION

DEFINITION

Parkinson's disease (PD) is a syndrome that presents with typical manifestations of parkinsonism. These symptoms arise due to denervation of the striatal dopaminergic system, which is pathologically characterized by degeneration of the basal ganglia, particularly in the substantia nigra pars compacta. This is accompanied by the presence of eosinophilic cytoplasmic inclusions, also known as Lewy Bodies. The term "parkinsonism" is used to describe the symptoms described by James Parkinson in his paper, including slowing of movement (bradykinesia), reduced spontaneous movement (hypokinesia), tremor, rigidity, and postural instability (Jankovic, 2008; PERDOSSI, 2015; Pradnyaning et al., 2020).

EPIDEMIOLOGY

Parkinson's disease represents the second most prevalent neurodegenerative disorder, following Alzheimer's disease. In general, Parkinson's disease manifests between the ages of 40 and 70, with an average onset above the age of 55. It is more prevalent in males than in females, with a ratio of approximately 3:2. The highest prevalence of Parkinson's disease is observed in the Caucasian race in North America and Europe, with a prevalence rate of 0.98% to 1.94%. The lowest prevalence is seen in the Black race in Africa, with a prevalence rate of 0.01%. According to data from the World Health Organization (WHO), the incidence of Parkinson's disease in Asia ranges from 1.5 to 8.7 cases per year in China and Taiwan. In Singapore, Japan, and Wakayama, the incidence is 6.7 to 8.3 cases per year, with an age range of 60 to 96 years. In Indonesia, it is estimated that approximately 10 individuals per year are diagnosed with Parkinson's disease. The number of individuals afflicted with Parkinson's disease is estimated to be between 200,000 and 400,000, with an anticipated impact on 876,665 individuals in Indonesia, representing 0.36% to 0.7% of the country's total population of 238,452,952. In terms of mortality, Indonesia ranks 12th in the world and 5th in Asia for Parkinson's disease, with a prevalence of 1,100 deaths in 2002. The Global Burden of Disease Study estimated the prevalence of Parkinson's disease in Indonesia to be between 117,531 and 178,755 cases in 2016. Additionally, the study estimated that there were 211,296 deaths from Parkinson's disease worldwide in 2016. (PERDOSNI, 2024; DeMaagd and Philip, 2015; Kalia and Lang, 2015).

PATHOPHYSIOLOGY of PARKINSON DISEASE

Studies on PD suggest that pathophysiologic changes associated with PD are already underway before the onset of motor symptoms. This pre-motor phase in PD is associated with the appearance of non-motor symptoms such as changes in cognitive function, sleep disturbances, and depression. Currently, the pre-motor phase is the subject of research for researchers as protection and prevention of PD is expected in the future (DeMaagd and Philip, 2015).

Until recent decades, PD was believed to be caused by idiopathic sporadic mutations. Technological advances in genetics, molecular biology and cellular immunohistochemistry are now proving that PD is caused by both genetic and environmental factors. There are several gene mutations associated with PD, one of the most widely discussed is related to synuclein α, while the histopathological characteristics of PD are the loss of pigmented dopaminergic neuron cells in the subtansia nigra and other pigmented nuclei, as well as the presence of eosinophilic cytoplasmic inclusions called Lewy bodies (DeMaagd and Philip, 2015; Wolters et al., 2006).

The basal ganglia are comprised of the caudate nucleus, putamen, nucleus accumbens, and globus pallidus, which is divided into an external segment (GPe) and an internal segment (GPi). Additionally, the substantia nigra is divided into two parts: pars compacta (SNC) and pars reticulata (SNR). The subthalamic nucleus (STN) is also included in this structure. The primary input impulse of the basal ganglia is the striatum. The striatum receives afferents from a number of areas of the cerebral cortex, including the motor cortex, premotor cortex, singulata, prefrontal cortex, and intralaminar nuclei of the thalamus. The principal output impulses from the basal ganglia are directed to the GPi and SNr, subsequently projecting to the thalamus and brainstem. Impulses that are directed to the thalamus exert a modulating influence on cortical activity. The primary neurotransmitter within the basal ganglia circuit is gamma-aminobutyric acid (GABA), whereas neurons within the STN utilize the excitatory neurotransmitter glutamate, and SNc neurons secrete dopamine (Magrinelli et al., 2016; Santens et al., 2003).

The progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) that project to the striatum via the nigrostriatal pathway results in a loss of dopaminergic function in patients with Parkinson's disease (PP). A reduction in dopamine levels within the striatum results in heightened activity within the GPi and SNr circuits, leading to GABA dysfunction and thalamus inhibition. Upon the loss of dopaminergic neurons reaching 50-80%, the ultimate consequence of this entire process is a reduction in the capacity of the thalamus to activate the frontal cortex, accompanied by a decline in motor activity, which is a hallmark feature of PP. The loss of dopaminergic neurons not only results in a reduction in thalamic activity but also an increase in cholinergic activity. This is due to the decreased inhibitory influence of dopamine, as evidenced by (DeMaagd and Philip.,2015; Magrinelli et al., 2016; Santens et al., 2003).

Another significant histopathological feature of PD is the presence of Lewy bodies, which are intracellular cytoplasmic aggregates comprising proteins, lipids, and other substances. In patients diagnosed with Parkinson's disease (PD), Lewy bodies are observed in dopaminergic neurons within the substantia nigra, manifesting as round bodies encased in a fluorescent halo composed of fat. The formation of Lewy bodies is thought to result from aberrant secondary proteolytic processes or the overproduction of specific proteins that are unable to be broken down by the typical degradation system. These processes are associated with genetic mutations that affect the metabolism of synuclein α protein. Firstly, a gene mutation results in the formation of excess synuclein α, which

leads to the accumulation of synuclein protein. Secondly, a mutation in the gene that controls the clearance of synuclein α from the cell via the proteasome pathway has been identified. These mutations involve malfunction of the ubiquitin proteasome system (UPS), causing proteins that have been bound by ubiquitin to not be broken down and instead become insoluble fibrils, as depicted in Figure 1 (DeMaagd and Philip, 2015; Ropper et al., 2014).

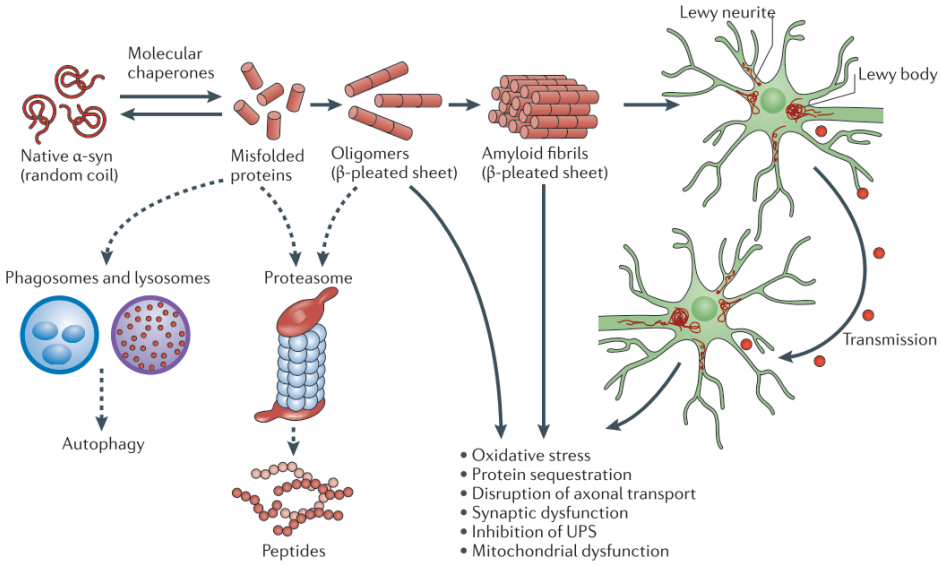

Figure 1 Hypothesis of Lewy body formation by synuclein a (Irwin, 2013)

CLINICAL FEATURES

The hallmark clinical manifestations of PD are primarily motor in nature. The motor symptoms of PD are highly variable and manifest differently in each individual. A consensus on the subtypes of PD has yet to be reached. However, it is widely acknowledged that there are two primary subtypes: (1) PD with dominant tremor symptoms and (2) PD with non-dominant tremor symptoms and typically described as akinetic-rigid syndrome and postural instability. Patients who do not fulfill both major subtypes are considered to be unclassified or mixed subtypes (Jankovic, 2008; Magrinelli et al., 2016; PERDOSSI, 2015).

In the early days of research into PD, it was believed to be a purely motor disorder. However, as more research has been conducted, it has become evident that non-motor symptoms are also present in almost all PD patients. Non-motor symptoms of PD include olfactory dysfunction, impaired cognitive function, psychiatric disorders, sleep disorders, autonomic dysfunction, pain, and fatigue. These non-motor symptoms manifest in the early phase of PD and are even associated with the preclinical stage of PD. Non-motor symptoms of PD have been demonstrated to have a greater impact on quality of life than motor symptoms (Jankovic, 2008; Kalia and Lang, 2015).

MOTOR SYMPTOMS OF PARKINSON'S DISEASE

The classic motor symptoms of PP, also known as the Parkinson's Triad, include bradykinesia, tremor, rigidity, and postural instability. The initial manifestations observed in patients with PP are typically characterized by slowed movement and tremors, while postural instability resulting from the loss of postural reflexes is a symptom that typically manifests later in the disease process. In the advanced phase, postural deformities will also manifest (Jankovic, 2008; Santens et al., 2003; PERDOSSI, 2015).

Tremors typically manifest unilaterally, with a frequency of 4-6 Hz, and are almost always discernible in the distal regions of the extremities. Hand tremors are typically described as either supination-pronation or pill-rolling movements. Resting tremor in PP is transient and disappears during movement and during sleep. The most characteristic symptom of PP is bradykinesia, which is the slowing down of movement. Bradykinesia is defined as a combination of impaired planning, initiation, and execution of movements, as well as difficulty performing consecutive movements. Rigidity is defined by an increased resistance and a cogwheel phenomenon, which can be identified through the examination of passive movements of the arms and legs. Additionally, rigidity may be observed in proximal extremities, including the neck, shoulders, and hips, as well as in distal regions, such as the wrists and ankles (PERDOSSI, 2015; DeMaagd and Philip, 2015; Jankovic, 2008).

NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE

Non-motor symptoms are symptoms that are frequently observed in patients with PD. The non-motor symptoms of PD include autonomic dysfunction, cognitive disorders, neuropsychiatric disorders, sensory disorders, and sleep disorders (Jankovic, 2008).

Cognitive impairment in patients with PD can result in significant limitations in daily activities, comparable to those observed in motor impairment. The cognitive impairment observed in patients with PD can range from mild cognitive impairment or Parkinson's disease mild cognitive impairment (PD-MCI) to severe cognitive impairment in the form of Parkinson's disease dementia (PDD). Executive function is the domain most severely affected (Lin and Wu, 2015; Yang et al., 2016).

The symptoms of sensory disturbances and autonomic disorders are infrequently identified as components of PP. Olfactory dysfunction (hyposmia) is a sensory disturbance associated with the early phase of PP and is linked to an increased risk of PP developing within the following two years, with a 10% increased risk. Community-based studies have documented a prevalence of autonomic dysfunction in patients with PP as high as 50%, with 47% of these cases presenting with orthostatic hypotension (Lin and Wu, 2015; Yang et al., 2016).

STAGE OF PARKINSON DISEASE

A number of rating scales have been developed for the evaluation of motor impairment and disability in patients with PD. However, not all of these scales have been demonstrated to possess satisfactory levels of validity and reliability. At present, two rating scales are recommended for use in this context: the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr scale (PERDOSSI, 2015; Jankovic, 2008; Wolters et al., 2006).

The Hoehn and Yahr scale and its modifications provide an assessment of disease progression based on the observation of symptoms and disability. This scale is more commonly utilized in routine clinical practice, comprising stages 0 (asymptomatic) through 5 (fully assisted). The research conducted by Martinez et al. demonstrated that the H&Y scale is an acceptable, reproducible, and valid measure of disease progression. The study yielded excellent interrater reliability (kappa test, 0.93) and reliability (test-retest, 0.97). The validity test conducted by Martinez et al. yielded a score of 63.2% from 19 raters (Stebbins et al., 2013; Martinez et al., 2017; Wolters et al., 2006; PERDOSSI, 2015).

VITAMIN D

Vitamin D is a neurotrophic hormone that can be produced endogenously by the human body and is fat soluble. Additionally, it can be obtained exogenously from food sources such as dairy products, fish, and supplements that play a role in the process of calcium and phosphate homeostasis and

also bone metabolism (Greenhagen et al., 2019). Two forms of vitamin D are most commonly known: vitamin D3, or cholecalciferol, which is usually derived from sun exposure, and vitamin D2, or ergocalciferol, which is derived from food (Habib et al., 2020a; Yammine et al., 2020; PINZON et al., 2021).

It is well-established that exposure to sunlight for a period of approximately 30 minutes can result in the production of between 10,000 and 20,000 International Units (IU) of vitamin D. However, it should be noted that this process occurs at a significantly slower rate for individuals with darker skin tones, with the required exposure time being between 20 and 30 times longer (Shipton E.A and Shipton E.E., 2015). In the skin, 7-dehydrocholesterol is converted into pre-vitamin D3 with the assistance of ultraviolet B (UVB) exposure. This is then isomerized into vitamin D3. Studies in animals have demonstrated that the distribution of vitamin D3 is most abundant, with approximately three-quarters present in adipose tissue. Additionally, smaller levels have been observed in the skin, muscle tissue, and liver. Vitamin D is transported into the bloodstream and to the liver by binding to vitamin D-binding protein. Subsequently, the enzyme cytochrome P450 will hydroxylate it into the pre-hormone 25-hydroxyvitamin D (calcidiol/25(OH)D3). 1,25-dihydroxyvitamin D [1,25(OH)2D] is the biologically active form of vitamin D, whereas 25(OH)D circulates in the blood and predominantly binds to proteins and albumin. Furthermore, 25(OH)D can be metabolized in the kidney by CYP27B1 into the active form (1.25-dihydroxyvitamin D [1.25(OH)2D3]), also known as calcitriol (Shipton E.A and Shipton E.E., 2015; Qu et al., 2017; Dalia et al., 2019; Greenhagen et al., 2019).

The primary cause of vitamin deficiency is its limited synthesis in the skin, which can be attributed to inadequate sun exposure, excessive use of sunscreen products, limited outdoor activity, and low intake of foods containing vitamin D. Additionally, other studies have identified several contributing factors, including aging, pigmented skin, smoking, obesity, air pollution, malabsorption, and decreased synthesis due to liver or kidney disease, as potential causes of vitamin D deficiency (Holick and Chen, 2008).

The distribution of 25(OH)D3 is predominantly in adipose tissue, comprising approximately 35% of the total, with serum concentrations accounting for 30%, muscle tissue for 20%, and other tissues for 15%. Consequently, individuals with obesity are at an elevated risk of developing vitamin D3 deficiency (Habib et al., 2020).

25-hydroxyvitamin D [25(OH)D] is a biomarker for monitoring vitamin D levels, which can be quantified through analysis of blood samples. A 25(OH)D concentration of 20 to 30 ng/mL is indicative of vitamin D insufficiency, while a concentration below 20 ng/mL is indicative of deficiency (Qu et al., 2017; Algaows et al., 2021; Shaheen Anodiyil et al., 2021; Veronica, 2021).

VITAMIN D AND PARKINSON'S DISEASE

The role of vitamin D in the pathogenesis of Parkinson's disease has been the subject of extensive investigation. Low levels of 25(OH)D may be responsible for dopaminergic neuronal death, which will affect the progression of PP in the absence of its protective effect (Pignolo et al., 2022).

The precise mechanism of action of vitamin D in protecting against Parkinson's disease (PD) remains unclear. However, numerous mechanisms appear to be correlated with neuroprotective effects related to excitotoxicity (Zhou et al., 2019).

1,25(OH)2D3 has been demonstrated to stimulate the release of neurotrophins and the synthesis of Ca2+ binding proteins, such as parvalbumin, which in turn inhibits the synthesis of inducible nitric oxide synthase (iNOS), macrophage colony-stimulating factor (M-CSF), and tumor necrosis factor α (TNF-α). The stimulating factor (M-CSF) and tumor necrosis factor α (TNF-α) have

been observed to downregulate the L-type voltage-sensitive Ca^{2+} channel (LVSCC) and upregulate γ-glutamyl transpeptidase activity. A low concentration of vitamin D is also associated with elevated levels of C-reactive protein (CRP), which serves as a marker of inflammation. It can thus be concluded that vitamin D plays a role in preventing brain aging, as its primary function is to produce growth factors, including NGF, CNTF, GDNF, BDNF, and NT3 (Pignolo et al., 2022).

Vitamin D has been demonstrated to induce an increase in the levels of circulating neurotrophins, including NGF, GDNF, BDNF, NT3, CNTF, the low-affinity p75 neurotrophin receptor (p75NTR), and TGF-β2. Additionally, it has been shown to induce downregulation of neurotrophin 4 (NT4) (Fullard et al., 2020).

Vitamin D plays a role in maintaining the equilibrium of intraneuronal calcium (Ca2+) and cytosolic glial Ca2+ concentrations, which serves to regulate L-type voltage-sensitive Ca2+ channels (LVSCC), modify neuronal function, and upregulate the synthesis of parvalbumin and calbindin. Elevated levels of calcium have been demonstrated to exert toxic effects, leading to an increase in the concentration of reactive oxygen species (ROS). This is attributed to a reduction in the capacity to reduce nitric oxide (NO) synthesis. This results in a reduction in the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and an increase in the activity of gamma glutamyl transpeptidase (Pignolo et al., 2022).

Furthermore, vitamin D plays a role in the renin-angiotensin regulatory system (RAS). Disturbances in vitamin D levels have been demonstrated to affect the functioning of the sympathetic system. In light of the aforementioned functions, it can be postulated that the neuroprotective effect of vitamin D may serve to attenuate the neurodegenerative process. Consequently, insufficient levels of vitamin D may contribute to the loss of dopaminergic neurons in the brain (Detopoulou et al., 2023; Pignolo et al., 2022).

Consequently, insufficient levels of vitamin D may contribute to the loss of dopaminergic neurons in the brain (Detopoulou et al., 2023; Pignolo et al., 2022).

A substantial body of research has examined the potential impact of diminished 25-hydroxyvitamin D levels on health outcomes. These studies have postulated that suboptimal vitamin D concentrations may confer an increased risk of developing Parkinson's disease (PD) and have identified a heightened risk associated with vitamin D deficiency (serum 25-hydroxyvitamin D levels <50 nmol/L) compared to vitamin D insufficiency (serum 25-hydroxyvitamin D levels <75 nmol/L). A cross-sectional study demonstrated that serum 25(OH)D concentrations were diminished in patients with Parkinson's disease (PD) relative to those with Alzheimer's disease (AD), as well as in age- and sex-matched healthy controls. These results may be explained by the longer clinical history and higher immobility in PP patients compared to AD patients, resulting in reduced sun exposure and consequent lack of vitamin D synthesis from the skin (Detopoulou et al., 2023; Fullard & Duda, 2020).

Another study demonstrated an inverse correlation between elevated UPDRS scores and both Hoehn and Yahr (H&Y) stage and reduced 25(OH)D3 and total 25(OH)D levels. The researchers concluded that decreased vitamin D concentrations were associated with increased disease severity, but not with disease duration or age of PP patients. These findings were corroborated by the DATATOP study, which demonstrated that 25(OH)D levels remain stable throughout the progression of PP. Suzuki et al. observed a deceleration of PP progression, as assessed by the H&Y scale, in activities of daily living, as well as quality of life, as measured by the Parkinson's Disease Questionnaire (PDQ-39), in a cohort of PP patients who received vitamin D supplementation. The Parkinson's

Disease Questionnaire (PDQ-39) was employed to evaluate the impact of vitamin D reintegration in patients with PP. The results demonstrated that the placebo group exhibited a more pronounced progression of PP, as evidenced by elevated UPDRS-III scores. Sleeman et al. concluded that lower baseline serum 25(OH)D levels were associated with more severe PP progression, as measured by the UPDRS-III scale. Moghaddasi et al. demonstrated that low 25(OH)D levels were associated with severe postural instability, freezing gait, and postural abnormalities (Calabresi et al., 2023; Magrinelli et al., 2016; Pignolo et al., 2022; Zhou et al., 2019).

CONCLUSION

To date, no studies have been conducted with the specific aim of evaluating the role of vitamin D in the progression of Parkinson's disease. The pervasive impact of this disease on patients' lives highlights the necessity of elucidating the role of vitamin D in the pathogenesis of Parkinson's disease. A number of studies have provided insights into the neuroprotective effects of vitamin D in the context of degenerative disorders such as Parkinson's disease. However, further research is imperative to ascertain whether vitamin D is a risk factor for Parkinson disease progression. It is hoped that this knowledge will motivate other researchers to further investigate the potential of vitamin D as a therapeutic modality in Parkinson disease management.

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