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Serum 25-OH vitamin d levels in Parkinson's disease and its Correlation with severity of Disease

[1]Dr. Aatif Sanaie, Postgraduate Scholar, Postgraduate Department of Medicine, GMC Srinagar, Jammu & Kashmir, India.

[2]Prof. Omar Farooq, Professor, Neurologist, Postgraduate Department of Medicine, GMC Srinagar, Jammu & Kashmir, India.

[2]Prof. Samia Rashid, Professor, Postgraduate Department of Medicine, GMC Srinagar, Jammu & Kashmir, India.

[2]Dr. Javaid Basu, Consultant, Postgraduate Department of Medicine, GMC Srinagar, Jammu & Kashmir, India.

[2]Dr. Irfan Bhat, Consultant, Postgraduate Department of Medicine, GMC Srinagar, Jammu & Kashmir, India.

[2]Dr. Basharat, Consultant, Postgraduate Department of Medicine, GMC Srinagar, Jammu & Kashmir, India.

[1]Dr. Mohammad Sayeed, Postgraduate Scholar, Postgraduate Department of Medicine, GMC Srinagar, Jammu & Kashmir, India.

[1]Dr. Mufti Moin, Postgraduate Scholar, Postgraduate Department. Of Medicine, GMC Srinagar, Jammu & Kashmir, India.

Corresponding Author: Prof. Omar Farooq, Professor, Neurologist, Postgraduate Department of Medicine, GMC Srinagar, Jammu & Kashmir, India.

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Abstract

Background: The relationship between vitamin D status and Parkinson's disease (PD) remains unclear, and whether or not supplementation is beneficial beyond bone health in PD has yet to be determined. The most consistent finding in the literature is a higher prevalence of vitamin D deficiency and insufficiency in PD compared to controls. The main objective of the study was to find out if any association, at all, exists between serum 25-OH-vitamin D levels & severity of Parkinson's disease.

Methods: It was a cross-sectional observational study consisting of 200 patients meeting inclusion criteria. Vitamin D levels were estimated & severity of Parkinson's disease was measured using Modified Hoehn & Yahr (HY) staging scale. Data was collected and analysed.

Results: In our study, the mean age (years) was 65.64 ± 10.30 with 34.5 % participants belonging to 61-70 years age group. Hypertension and Diabetes constituted two main comorbidities. Mean BMI in our study was 28.89 ± 4.28 kg/m^2. The mean duration Of Illness (years) was 4.51 ± 3.16. In our study, the mean (SD) of S. Vitamin D (ng/mL) was 22.26 (8.65). The S. Vitamin D (ng/mL) ranged from 6.6 - 45.91. Our study showed significant correlation between Vitamin D levels & severity of Parkinson's Disease ($\chi 2 = 331.348$, $p = <0.001$).

Conclusion: Majority of the Parkinson's Disease patients are Vitamin D deficient. There is significant correlation between Vitamin D levels & Severity of Parkinson's

Disease. Further investigations are warranted to understand the mechanism of underlying association.

Keywords: Parkinson's Disease, Vitamin D, Modified Hoehn & Yahr Scale

Introduction

Parkinson's disease (PD) is a degenerative disorder of the central nervous system. It was first described in 1817 by James Parkinson, a British physician who published a paper on what he called "the shaking palsy." In this paper, he set forth the major symptoms of the disease that would later bear his name.[1] Parkinson's disease (PD) belongs to a group of conditions called motor system disorders, which cause unintended or uncontrollable movements of the body. The precise cause of PD is unknown, but some cases are hereditary while others are thought to occur from a combination of genetics and environmental factors that trigger the disease. In PD, brain cells become damaged or die in the part of the brain that produces dopamine--a chemical needed to produce smooth, purposeful movement.

The four primary symptoms of PD are

- Tremor: shaking that has a characteristic rhythmic back and forth motion
- rigidity: muscle stiffness or a resistance to movement, where muscles remain constantly tense and contracted
- bradykinesia: slowing of spontaneous and automatic movement that can make it difficult to perform simple tasks or rapidly perform routine movements
- postural instability: impaired balance and changes in posture that can increase the risk of falls.

Other symptoms may include difficulty swallowing, chewing, or speaking; emotional changes; urinary problems or constipation; dementia or other cognitive problems; fatigue; and problems sleeping.[2]

Parkinson's disease (PD) affects 1–2 per 1000 of the population at any time. PD prevalence is increasing with age and PD affects 1% of the population above 60 years. The main neuropathological finding is α-synuclein-containing Lewy bodies and loss of dopaminergic neurons in the substantia nigra, manifesting as reduced facilitation of voluntary movements. With progression of PD, Lewy body pathology spreads to neocortical and cortical regions. Autopsy studies show that the clinical diagnosis of PD is not confirmed at autopsy in a significant proportion of patients.[3]

Over the past decade, several studies have attempted to determine the relationship between hypovitaminosis D and the risk of Parkinson's disease, with conflicting results. Vitamin D refers to a group of fat-soluble secosteroids that can be obtained through dermal synthesis by exposure to sunlight or though dietary intake. Vitamin D itself is biologically inert and must undergo two hydroxylation's to become active. The liver converts vitamin D to 25-hydroxyvitamin D and then the kidney and other tissues convert 25-hydroxyvitamin D to the active form 1,25-dihydroxy vitamin D, also known as calcitriol. Vitamin D exerts its effects by binding to the vitamin D receptor (VDR), through which it directly and indirectly modulates the expression of hundreds to thousands of genes. Calcitriol is approximately 500–1000-fold more active than its precursor 25-hydroxy-vitamin D, but the latter is usually measured to estimate the systemic vitamin D status for several reasons. First of all, circulating concentrations of calcitriol are extremely low, approximately 1000-fold less than calcidiol. Moreover, 25- hydroxy-vitamin D is more stable and characterized by a longer half-life (~2–3 weeks) compared to the 1, 25- dihydroxy-vitamin D metabolite (~4–6 h).[4]

While originally known for its role in regulating calcium homeostasis and metabolism, vitamin D is now associated with many other health conditions, such as

cardiovascular disease, cancer, autoimmune disease and neurodegenerative disease, including Parkinson's disease (PD).[5] Multiple mechanisms have been proposed for the role of vitamin D in neurodegenerative diseases. Vitamin D may confer neuroprotection through the action of neurotrophic factors, regulation of nerve growth or through protection against cytotoxicity.[6] Vitamin D may also modulate the toxicity of reactive oxygen species. Nitric oxide is produced by inducible nitric oxide synthase (iNOS), an enzyme that is induced in CNS neurons and non-neuronal cells as part of an immune response.[7] At high levels, nitric oxide can damage neurons, and vitamin D has been shown to inhibit the synthesis of iNOS, thereby reducing levels of nitric oxide.[7,8] Lastly, vitamin D may exert a neuroprotective effect through reducing oxidative stress. In a study in which dopaminergic and non-dopaminergic neurons were exposed to glutamate, pre-treatment with vitamin D protected both cell types against cytotoxicity in a dose-dependent manner.[9]

Materials and methods

Study design: Our study design was cross-sectional observational study for a period of 18 months from January 2020 – July 2021.

Target Population: Clinically Established Parkinson's Disease patients attending SMHS Srinagar & SSH Hospital Srinagar outpatient department from January 2020 – July 2021.

Sample Size: 200.

Inclusion criteria

Patients aged 40 to 95 years with PD diagnosed by neurologist.

1. All patients who shall consent to participate in the study after seeking permission from them.

Exclusion criteria

1. Already taking vitamin D supplements or 1,25 vitamin D.
2. Familial or early onset PD (<40 years old).
3. Drug-induced Parkinsonism and ''Parkinsonism-plus'' syndromes.
4. Patients who did not consent or cooperate for participation in the study.

Clinically Established Parkinson's Disease patients attending SMHS Srinagar & SSH Hospital Srinagar outpatient department were included in the study (associated hospitals of GMC Srinagar). 369 patients were evaluated & after exclusion of ineligible patients 200 were enrolled in the study. Informed consent (oral and written) from all eligible patients was obtained. All the steps and methods in the study were approved by the Institutional ethics Committee, GMC, Srinagar. Patients recruited were provided with a unique identification code, particulars of which were known to the principal investigator only, this was done to avoid any bias while measuring serum Vitamin D levels. After recruiting eligible patients to this study, data collection (biodata, clinical history, baseline laboratory values) along with detailed history specifically related to Vitamin D intake was obtained. A point of care sample collection (POCSC) was done under all aseptic precautions. A total of 3 ml venous blood sample was obtained in clot activator vacutainer (Red top). All the samples collected were immediately labelled with unique identification code and taken to laboratory where serum was separated in a centrifuge at 1000 rpm for 10 minutes. Serum separation was done in biosafety cabinets and stored in Eppendorf vials labelled with unique identification code for each patient. Serum was the stored at -80° C in deep freezer, till analysis for vitamin D levels. Analysis was done using chemiluminescence immunoassay method using

Abbott ARCHITECT i2000SR immunoassay analyser in Department of Biochemistry, Government Medical College, Srinagar. On the basis of various guidelines, the serum Concentration of 30 ng/ml was taken as cut off for defining Vitamin D insufficiency, with less than 20 ng/ml as deficiency. [Table 1][10] Modified Hoehn & Yahr (HY) staging scale,[11] was used to calculate the severity. [Table 2]

Table 1: Classification of Vitamin D levels

Classification	**Value (in ng/ml)**
Danger of toxicity	>100
Normal/optimal	>30
Insufficient	21-29
Deficient	<20

Table 2: Modified Hoehn & Yahr (HY) staging scale

1.0	Unilateral involvement only
1.5	Unilateral and axial involvement
2.0	Bilateral involvement without impairment of balance
2.5	Mild bilateral disease with recovery on pull test
3	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severe disability; still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided

Results

In our study, the mean age (years) was 65.64 ± 10.30 with 34.5 % participants belonging to 61-70 years age group. Hypertension and Diabetes constituted two main comorbidities. Mean BMI in our study was 28.89 ± 4.28 kg/m2. The mean duration Of Illness (years) was 4.51 ± 3.16.

The mean (SD) of S. Vitamin D (ng/mL) was 22.26 (8.65). The median (IQR) of S. Vitamin D (ng/mL) was 22.56 (16.27-28.87). The S. Vitamin D (ng/mL) ranged from 6.6 - 45.91.

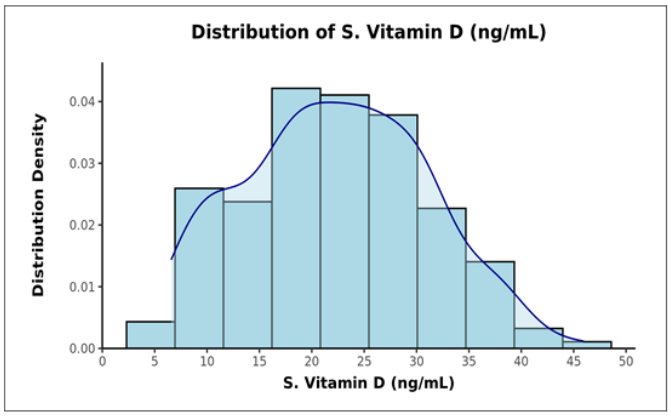

Figure 1: Distribution density of S. Vitamin D levels

Table 3: Distribution of the Participants in Terms of S. Vitamin D (n = 200)

S. Vitamin D	Frequency	Percentage	95% CI
<20 ng/ml (deficient)	82	41.0%	34.2% - 48.2%
20-30 ng/ml (insufficient)	79	39.5%	32.7% - 46.7%
>30 ng/ml (normal/optimal)	39	19.5%	14.4% - 25.8%

41.0% of the participants had S. Vitamin D deficiency (<20 ng/mL). 39.5% of the participants had S. Vitamin D insufficiency (20-30 ng/mL). 19.5% of the participants had S. Vitamin D levels normal/optimal (>30 ng/mL).

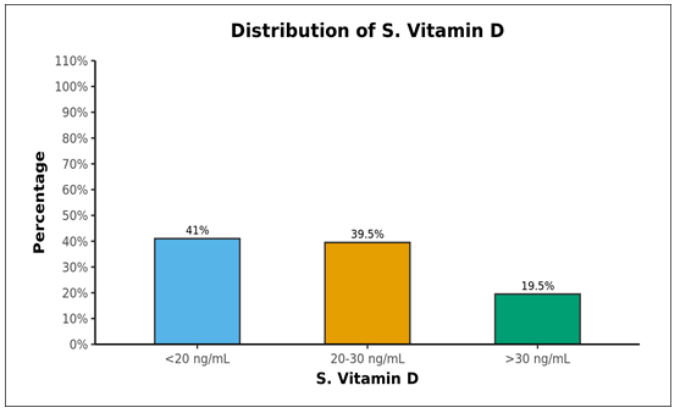

Figure 2: Distribution of Serum Vitamin D levels (Percentage)

Table 4: Comparison of the 6 Subgroups of the Modified HY Stage in Terms of S. Vitamin D (ng/mL) (n = 200)

S. Vitamin D (ng/mL)	Modified HY Stage						Kruskal Wallis Test	
	Stage 1	Stage 1.5	Stage 2	Stage 2.5	Stage 3	Stage 4	χ^2	p value
Mean (SD)	35.75 (3.57)	31.13 (0.14)	24.49 (3.46)	14.93 (2.59)	8.35 (1.10)	7.52 (0.95)	175.050	<0.001
Median (IQR)	35.85 (32.68-38.13)	31.16 (31.01-31.25)	24.67 (21.36-27.16)	15.85 (12.19-17.17)	8.31 (7.5-9.23)	7.52 (7.19-7.86)		
Range	31.36 - 45.91	30.96 - 31.28	18.63 - 30.76	10.9 - 18.59	6.6 - 10.14	6.85 - 8.2		

S. Vitamin D (ng/mL) was not normally distributed in the 6 subgroups of the variable Modified HY Stage. Thus, non-parametric tests (Kruskal Wallis Test) were used to make group comparisons.

There was a significant difference between the 6 groups in terms of S. Vitamin D (ng/mL) ($\chi 2$ = 175.050, p = <0.001), with the median S. Vitamin D (ng/mL) being highest in the Modified HY Stage 1 group.

Strength of Association (Kendall's Tau) = 0.83 (Large Effect Size)

The Box-and-Whisker plot below depicts the distribution of S. Vitamin D (ng/mL) in the 6 groups. The middle horizontal line represents the median S. Vitamin D (ng/mL), the upper and lower bounds of the box represent the 75th and the 25th centile of S. Vitamin D (ng/mL) respectively, and the upper and lower extent of the whiskers represent the Tukey limits for S. Vitamin D (ng/mL) in each of the groups.

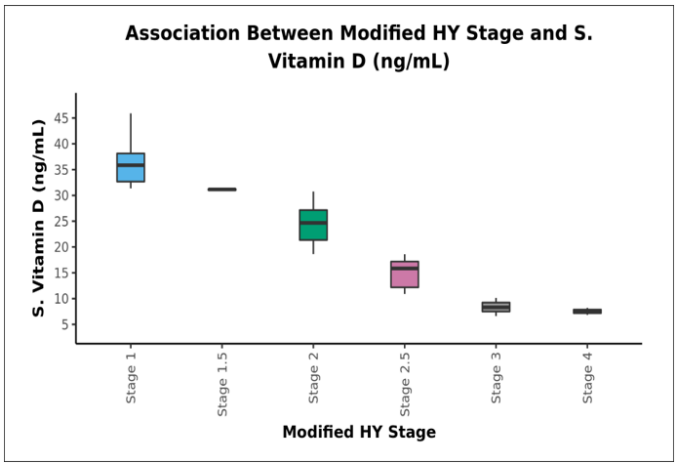

Figure 3: The Box-and-Whisker plot below depicts the distribution of S. Vitamin D (ng/mL) in the 6 groups of modified HY stage.

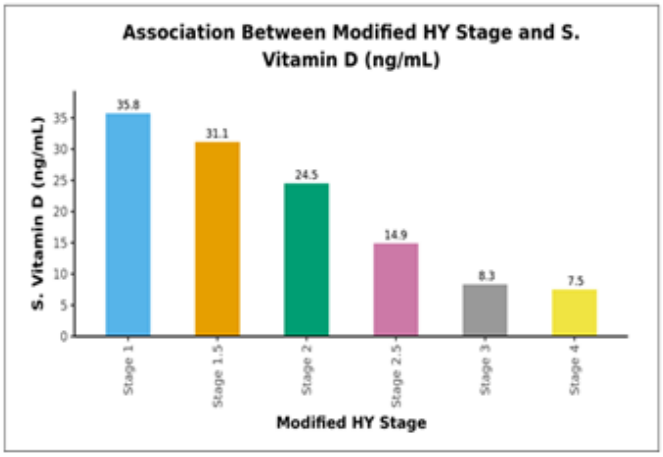

Figure 4: The bar graph depicts the means of S. Vitamin D (ng/mL) in the 6 different groups of modified HY stage.

Table 5: Association Between S. Vitamin D [Groupwise] and Modified HY Stage (n = 200)

Modified HY Stage	S. Vitamin D				Chi-Squared Test	
	<20 ng/mL	20-30 ng/mL	>30 ng/mL	Total	$\chi 2$	P Value
Stage 1	0 (0.0%)	0 (0.0%)	29 (74.4%)	29 (14.5%)	331.348	<0.001
Stage 1.5	0 (0.0%)	0 (0.0%)	7 (17.9%)	7 (3.5%)		
Stage 2	11 (13.4%)	79 (100.0%)	3 (7.7%)	93 (46.5%)		
Stage 2.5	50 (61.0%)	0 (0.0%)	0 (0.0%)	50 (25.0%)		
Stage 3	19 (23.2%)	0 (0.0%)	0 (0.0%)	19 (9.5%)		
Stage 4	2 (2.4%)	0 (0.0%)	0 (0.0%)	2 (1.0%)		
Total	82 (100.0%)	79 (100.0%)	39 (100.0%)	200 (100.0%)		

Chi-squared test was used to explore the association between 'S. Vitamin D' and 'Modified HY Stage'.

There was a significant difference between the various groups in terms of distribution of Modified HY Stage ($\chi 2$ = 331.348, p = <0.001).

Strength of association between the two variables (Cramer's V) = 0.91 (High Association)

Strength of association between the two variables (Bias Corrected Cramer's V) = 0.9 (High Association)

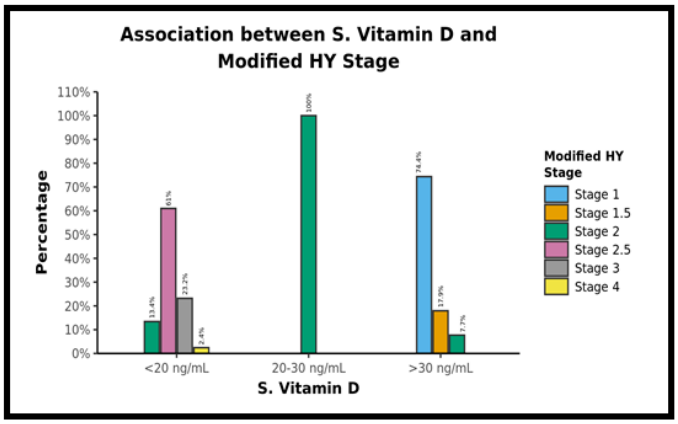

Figure 5: Association between S. Vitamin D & Modified HY stages.

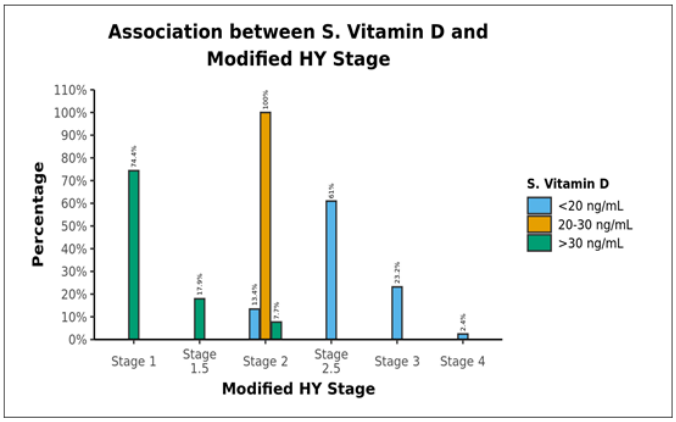

Figure 6: Association between S. Vitamin D & Modified HY stages.

Discussion

The relationship between vitamin D status and Parkinson's disease remains unclear, and whether or not supplementation is beneficial beyond bone health in PD has yet to be determined. While preclinical studies in animals and cell culture have shown promising neuroprotective effects of vitamin D, studies in humans have been inconsistent, likely in part due to differing methodologies and populations studied. The most consistent finding in the literature is a higher prevalence of vitamin D deficiency and insufficiency in PD compared to controls. The main objective of the study was to find out if any association, at all, exists between serum 25-OH-vitamin D levels & severity of Parkinson's

disease. For this purpose, we recruited 200 subjects from our institute who were diagnosed by neurologists.

In our study, the mean age (years) was 65.64 ± 10.30 with 34.5 % participants belonging to 61-70 years age group. Our results are comparable with the findings of Sato et al[12] and Zhu et al[13] where mean age of participants was 69.8 ± 6.1 and 64.6 ± 9.4 years respectively. Males 58% (116) outnumbered females 42% (84). In studies done by Evatt ML et al[14] and M. Sarić et al[15] males constituted 64.3% and 58.5% of study participants respectively which are comparable to our study. Hypertension and Diabetes constituted two main comorbidities. Hypertension was present in 58.5% (117) while as Diabetes was present in 17.5% (35). In a study done by Knekt et al[16] hypertension was present in 21.1% of the PD cases & diabetes was present in 2.7%. Mean BMI in our study was 28.89 ± 4.28 kg/m^2 which is comparable to the study done by F. van den Bos et al[17] which reported a mean BMI of 27.2 ± 4.0 kg/m^2 in PD patients. The mean duration Of Illness (years) was 4.51 ± 3.16.

In our study, the mean (SD) of S. Vitamin D (ng/mL) was 22.26 (8.65). The S. Vitamin D (ng/mL) ranged from 6.6 - 45.91. Only 19.5% (39) participants had optimal Vitamin D levels (> 30 ng/mL). 39.5% (79) participants had Vitamin D insufficiency (20-30 ng/mL). Majority of the patients 41% (82) had Vitamin D deficiency (<20 ng/mL). Our results are in line with various studies performed over last two decades. Evatt ML et al[18] reported that more than half of the PD participants had Vitamin D insufficiency (<30 ng/mL) which is the case with our study as well. They also reported that 23% of PD cohort was Vitamin D deficient. In later study done by Evatt ML et al[14] majority (69.4%) of subjects were reported to have Vitamin D insufficiency & more than a quarter sujects (26.1%) had Vitamin D deficiency. F.van den Bos et al[17] also reported Vitamin D deficiency in 56.2% PD patients. Suzuki Met al[19] reported mean 25-OH Vitamin D levels of 21.1 ± 9.0 ng/mL & almost half (49%) PD patients showed deficient levels of 25-OH Vitamin D (<20 ng/mL) which are consistent with our study. Soliman et al.[20] regarding the incidence of Vitamin D deficiency, showed 84% of PD patients had Vitamin D deficiency & only 16% were found to have normal Vitamin D levels. There was also statistically significant difference between patients and controls in the mean value of Serum 25-OH Vitamin D levels (P value = 0.0001).

Our study showed significant correlation between Vitamin D levels & severity of Parkinson's Disease ($\chi 2$ = 331.348, p = <0.001). Participants in the Modified HY Stage 2.5, Stage 3, Stage 4 had the largest proportion of S. Vitamin D: <20 ng/mL. Participants in the group Modified HY Stage: Stage 2 had the largest proportion of S. Vitamin D: 20-30 ng/mL. Participants in the group Modified HY Stage 1, Stage 1.5 had the largest proportion of S. Vitamin D: >30 ng/mL. Sato et al[12] reported that Hoehn and Yahr stage correlated negatively with Serum 25-OH Vitamin D concentration (r= -0.766; p < 0.0001) & positively with serum calcium levels (r = 0.399; p =0.0009). Suzuki Met al[19] evaluated severity of PD by HY stage 1 to 5, there was a significant trend showing that as HY stage worsened, 25OHD levels became lower (P = .002): HY stage 1 to 1.5: 23.9 ± 10.9; HY stage 2 to 2.5: 22.4 ± 8.8; HY stage 3: 18.5 ± 8.5; HY stage 4 to 5: 14.5 ± 6.2. When severity of PD was evaluated by UPDRS, there were significant inverse associations between transformed 25OHD and transformed total UPDRS (P = .004). There were significant inverse associations in UPDRS Part I (P = .016), Part II (P = .010), and Part III (P = 0.016), but not in Part IV. Harvard Biomarker Study[21] showed that lower

Vitamin D levels are found in individuals with more advanced disease severity as measured by "gold standard" the clinical total UPDRS scale. M. Sarić et al[15] showed significant association with 25OHD concentration with the severity and stage of PD. UPDRS and HY score were significantly higher in vitamin D deficient group, compared to vitamin D sufficient group (p = .006, p = .002). They also showed significant relation between cognitive decline and vitamin D level (p = .034). Peterson AL et al[22] also showed that higher plasma Vitamin D levels are associated with better cognition and better mood in PD patients. Soliman et al.[20] showed a statistically significant negative correlation between Serum Vitamin D level and Modified Hoehn Yahr Staging, scores of motor, mentation, activities of daily living, medication, other complications, and total score of UPDRS.

Limitations

- The study was a single centre study conducted in North India, in an area itself having high prevalence of Vitamin D deficiency.
- The sample size was less as compared to the overall burden of disease in the area.
- The study did not recruit any controls for comparison of Vitamin D levels.
- No effect/follow up of patients receiving vitamin D supplementation during hospitalization was measured on discharge.

Conclusion

Majority of the Parkinson's Disease patients are Vitamin D deficient. There is significant correlation between Vitamin D levels & Severity of Parkinson's Disease. Further investigations are warranted to understand the mechanism of underlying association.

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