

ORIGINAL ARTICLE

RELATIONSHIP OF VITAMIN D DEFICIENCY WITH NON- MOTOR FUNCTIONS OF PARKINSON'S DISEASE

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Abstract

Background: Parkinson's disease (PD), a neurodegenerative disorder is associated with substantial public health and economic burdens. Low levels of vitamin D are a common finding in patients of PD. The aim of the study was to investigate the relationship between the vitamin D level and non-motor symptoms of Parkinson's Disease **Methods:** This case-control study was conducted in Department of Neurology, BIRDEM General Hospital, Dhaka for a period of 12 months. A total of 120 participants, 60 patients with PD and 60 age and sex matched sample of healthy controls were enrolled and informed written consent was taken. Information on socio-demographic characteristics, clinical features, laboratory parameters and neurological examinations were assessed. A semi-structured questionnaire was used for data collection and data was analyzed with Statistical Package for Social Science (SPSS) version 24.0. **Results:** Age and gender was not significantly different between PD cases and controls. Mean vitamin D level was significantly lower among the patients with PD compared to controls (25.97±3.44 ng/ml vs 38.47±5.08 ng/ml, (p<0.01). Among all the cases of PD, 45% had akathisia, 36.7% had depression and 40% had insomnia. According to Modified Hoehn and Yahr score 53.3% patients were in stage 1-2, 26.7% in stage 2-3 and 20% in stage >3. The mean vitamin-D level was 28.43±2.43, 24.06±1.57 and 21.92±1.62 in stage 1-2, stage 2.5-3 and stage >3 respectively and vitamin D level decreased significantly with advancement in stages of PD (p<0.01). While assessing the depression in patients with PD, it was observed that stages of PD was significantly associated with severity of depression, patients with >3 stage of PD was moderately severe (16.7%) and severely depressed (16.7%) than patients with <3 stage PD (p=0.009). **Conclusion:** Importance should also be given for recognition of non- motor symptoms in PD patients, since these symptoms have an impact on patient's quality of life.

Keywords: Vitamin D Deficiency, Non- Motor Functions, Parkinson's Disease

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Introduction:

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD). The prevalence of PD increases with age; it affects 1% of the population over the age of 60¹. Over the last two decades, multiple studies have examined the

relationship between low levels of vitamin D and Parkinson's disease. Several studies concluded that, serum level of vitamin D is significantly lower in patients with PD compared to healthy controls in their studies.^{2,3} Vitamin D was proposed to alter cholinergic, dopaminergic, and noradrenergic neurotransmitter

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pathways in the central nervous system (CNS). Furthermore, vitamin D may play a role in neuronal plasticity and axogenesis. Several studies demonstrated that vitamin D ameliorates synthesis of neurotrophic factors and detoxification pathways which protect the integrity and structure of neurons.⁴ Vitamin D enhances the synthesis of dopamine through increasing the level and activity of the enzyme tyrosine hydroxylase. Distribution of vitamin D receptors (VDR) in the substantia nigra is altered in patients with Parkinson's disease.⁵ It has been demonstrated that vitamin D plays a role in dopamine synthesis through regulation of tyrosine hydroxylase gene expression. VDR is also highly expressed in putamen and caudate. Significant relationship was found between VDR gene polymorphism and Parkinson's disease. Vitamin D receptors were demonstrated in the promoter regions of ret, GDNFR- α , and neurturin genes which are strongly linked to PD.^{6, 7}

Parkinson's disease is associated with substantial public health and economic burdens, which are expected to increase in the future with a rapidly growing older population. Identification of modifiable risk factors may therefore have important public health implications. Despite epidemiological data from different studies revealed that vitamin D deficiency may contribute in the development of Parkinson's disease, but it still a matter of debate whether this relationship is a direct effect or that patients suffering from Parkinson's disease have decreased ambulation and sun exposure and, as a sequence, higher prevalence of vitamin D deficiency.⁸ Multiple epidemiological studies have shown that relative to controls, PD cases have lower serum/plasma levels of 25-hydroxyvitamin D (25(OH) D). Several studies concluded that, higher level of vitamin D in patients of Parkinson's disease were associated with better motor and non-motor function. In Bangladesh, there is limited study regarding the level of serum vitamin D in Parkinson's disease patients. The aim of this study was to assess the serum vitamin D level in patients with Parkinson's disease and to investigate the possible relationship between the serum vitamin D level and non motor symptoms in Parkinson's disease.

Methods:

This case control study was conducted in the department of neurology, BIRDEM general Hospital from 1st July 2022 to 30th June, 2023. Adult patients e"18 years of age who fulfilled the criteria for Parkinson's disease based on the British Brain Bank criteria⁹ were included the study. Convenient sampling method was used. Patients with visual impairment or hearing loss affecting their ability to complete the tests, secondary Parkinsonism, Parkinson's plus syndrome and patient with clinically overt dementia, history of alcohol intake or drug abuse, major psychiatric Disorders, structural brain lesions in an MRI/CT scan study, on vitamin D supplements or medications that

affect the vitamin D level, chronic kidney disease patient were excluded from the study.

All collected data was checked very carefully to identify any error in collecting data. Before commencement of the study, formal ethical approval was taken from the ERC of BIRDEM General Hospital, Dhaka. The study group consisted of 120 participants, 60 patients with PD and 60 age and sex matched sample of healthy controls. Written informed consent was taken from every patient. Clinical neurological examination including H&Y staging was performed and the findings were recorded for each PD cases. Non-motor symptoms were also assessed like depression was assessed by PHQ-9 quick depression assessment questionnaire.¹⁰

All the data collected was than analyzed in SPSS/PC 24 software. Results were expressed by appropriate tables, figures and analytical discussion. Data was compiled and analyzed by using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean (standard deviation) and categorical variables as frequencies and percentages. Comparison were done by Chi-Square (χ^2) test and Fisher Exact test for categorical variable and independent student t-test and one-way ANOVA and Post-Hoc analysis for continuous variable where necessary. A probability (p) value of < 0.05 (p<0.05) was considered statistically significant.

Results:

This case control study was conducted in the department of Neurology, BIRDEM General Hospital, and Dhaka to see the relationship of vitamin D deficiency with non- motor functions of Parkinson's disease.

Table I

Distribution of the study participants according to age (n=120).

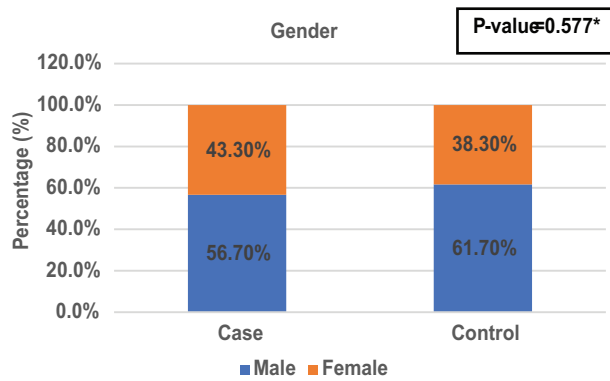
Age group (in year)	Case-group (n=60) n(%)	Control-group (n=60) n (%)	P-value
50 to 60	15 (25)	12 (20)	0.789*
61 to 80	40 (66.7)	42 (70)	
>80	5 (8.3)	6 (10)	
Mean \pm SD	68.4 \pm 9.43	69.8 \pm 9.37	0.456**

Cases group: PD patients.

Control group: Healthy controls.

P-value was determined by *Chi-square test and **Independent sample t test.

Majority of the patients were aged between 61 to 80 years in both case (66.7%) and control (70%) groups. Mean age of the cases and controls was 67.98 \pm 10.4 years and 69.43 \pm 10.1 years respectively. No significant difference in age was observed between two groups (p>0.05). P-value=0.577*



Cases group: PD patients.
 Control group: Healthy controls.
 *p-value was determined by Chi-square test.
Figure 1: Gender distribution of the study participants (n=120).

Among all, in case group 56.7% (n=34) were male and in controls group 61.7% (n=37) were male. Regarding gender, no significant difference was observed between two groups (p=0.577).

In case group 80% were married, 35% had completed SSC, 41.7% were unemployed and 60% had socio-

economic status average. Besides, in control group, 76.7% were married, 33.3% had completed HSC, 41.7% were unemployed and 40% had socio-economic status average. No significant difference was found between both groups regarding socio-demographic profile.

Regarding co morbidities, no significant difference was observed between two groups (p>0.05). 28.3% and 25% of the case and controls had HTN respectively. Family history of PD was 31.7% and 11.7% in PD patients and healthy controls respectively (p=0.007).

Mean serum 25 Hydroxy vitamin D level in cases was 25.97±3.44 ng/ml and in controls was 38.47±5.08 ng/ml. Mean vitamin D level was significantly lower among the patients with PD compared to controls (p<0.01).

Vitamin D deficiency and insufficiency was significantly associated with PD (p<0.01), 5% and 78.3% of the patients had vitamin D deficiency and insufficiency compared to 1.7% in healthy controls respectively.

Table-II

Distribution of the study participants according to serum 25 Hydroxy vitamin D level (n=120).

Serum 25 Hydroxy vitamin D level (ng/ml)	Case-group (n=60) n(%)	Control-group (n=60) n(%)	p-value
Mean±SD	25.97±3.44	38.47±5.08	<0.01
Range	12-32	24-52	

Cases group: PD patients
 Control group: Healthy controls
 *p-value was determined by Independent sample t test.

Table-III

Distribution of the study participants according to vitamin D level (n=120).

Serum 25 Hydroxy vitamin D level (ng/ml)	Case-group (n=60) n(%)	Control-group (n=60) n(%)	p-value
Deficient (<20)	3(5)	1(1.7)	<0.01
Insufficient (20-30)	47(78.3)	1(1.7)	
Sufficient (30-100)	10(16.7)	58(96.7)	

*p-value obtained by chi-square test.

Table-IV*Clinical presentation of patients with PD (n=60).*

Clinical presentation	Frequency	Percentage
	(n)	(%)
Non-motor symptoms		
Akathisia	27	45
Depression	22	36.7
Pain	19	31.7
Constipation	11	18.3
Insomnia	24	40
Duration of the disease		
<5	35	58.3
5-10	22	36.7
>10	3	5
Modified Hoehn and Yahr score		
1-2	32	53.3
2.-3	12	26.7
>3	16	20

Among all the cases of PD 45% had akathisia, 36.7% had depression and 40% had insomnia. Majority had duration of disease <5 years (58.3%). According to Modified Hoehn and Yahr score 53.3% patients were in stage 1-2, 26.7% in stage 2-3 and 20% in stage >3.

Table-V*Association of depression with different stages of Parkinson's disease patients (n=60).*

Depression	Stage	Stage	Stage	p-value*
	1-2	2.5 to 3	>3	
None (0-4)	19(59.4)	12(75)	7(58.3)	0.009
Mild (5-9)	4(12.5)	1(6.3)	1(8.3)	
Moderate (10-14)	9(28.1)	3(18.8)	0	
Moderately severe (15-19)	0	0	2(16.7)	
Severe (20-27)	0	0	2(16.7)	

*p-value obtained by chi-square test.

While assessing the depression in patients with PD, it was observed that stages of PD was significantly associated with severity of depression, patients with >3 stage of PD was moderately severe (16.7%) and severely depressed (16.7%) than patients with <3 stage PD (p=0.009).

Discussion:

Parkinson's disease (PD) is a complex and progressive neurological condition characterized by postural

instability, rigidity, and resting tremor. In addition, PD is linked to a broad range of non-motor symptoms that heighten total disability.^{1,2} Majority of the patients were aged between 61 to 80 years in both case (66.7%) and control (70%) group with mean age of the case and control was 67.98±10.4 years and 69.43±10.1 years accordingly. Majority of the cases and controls were male. Similar age and gender distribution was also observed by a study.¹¹ Another study also found older age and male predominant among the PD patients.¹² Ageing remains the biggest risk factor for developing Parkinson's disease.¹⁵ As control group were age and gender matched with case group so no significant difference found between both groups.

Mean serum 25 hydroxy vitamin D levels in cases was 25.97±3.44 ng/ml and in controls 38.47±5.08 ng/ml. Mean vitamin D level was significantly lower among the Case groups. Similar study revealed a strong association between hypovitaminosis D and PD.¹³ Another study described that mean serum 25(OH)D concentrations were lower in PD than control participants (44.1±21.7 vs. 52.2±22.1 nmol/L, p < 0.05). A study also revealed that vitamin D has a significant impact on Parkinson's disease.¹⁴ Beyond regulating calcium homeostasis and bone metabolism, vitamin D has extensive impacts on a wide range of systems and tissues, including the CNS.¹⁵ There are accumulating evidences supporting the role of vitamin D deficiency in the pathogenesis of PD. Long-standing low vitamin D levels may lead to chronic loss of dopaminergic neurons in the central nervous system and, as a consequence, the development of Parkinson's disease.¹⁶

Among all the cases of PD 45% had akathisia, 36.7% had depression and 40% had insomnia. Majority had duration of disease <5 years (58.3%). A relevant study concluded that, constipation, urgency, insomnia, panic attack, light headedness and recent memory impairment were the most prevalent non motor symptoms in PD compared to controls.¹⁷ While assessing the depression in patients with PD, it was observed that stages of PD was significantly associated with severity of depression, patients with >3 stage of PD was moderately severe (16.7%) and severely depressed (16.7%) than patients with <3 stage PD. A study concluded that 31.25% of patients with PD had depression while 40.6% of patients had anxiety disorder. Depression was higher in females and patients with history of depression and low socioeconomic status (SES). Hoehn and Yahr scale accounted for 33.4% of variance for depression. Advanced disease stage and severity were independent predictors for depression while disease severity and younger age of onset were the main predictors for

anxiety. Depression has a negative impact on the overall quality of life of PD patients especially on physical and psychosocial domains.¹⁸

Current study revealed that Vitamin D level significantly decreases with the increased stage of Parkinson's disease patients which was similar to a previous study.¹⁹ A relevant study also revealed that Vitamin D deficiency seems to be related to disease severity and disease progression.²⁰ It was observed in another study that Vitamin D deficiency was significantly associated with disease severity of PD.¹³ The relationship between low vitamin D status and PD is supported by current study along with several studies. Vitamin D deficiency is evident in PD patient, and such deficiency significantly affected non-motor symptoms.

Conclusion:

In summary, this study results showed that mean vitamin D level was significantly lower among the patients with PD compared to controls. Importance should also be given for recognition and management of non- motor symptoms in PD patients, since these symptoms have an impact of patient's quality of life. Furthermore, multicenter longitudinal randomized researches are recommended to understand the role of vitamin D level.

Limitations of the study:

This was a single center study. Sample size was small. In this study, since there were no repeated measurements, so the results only reflect the period in which the study was conducted.

Conflict of Interest:

The authors stated there is no conflict of interest in this study.

Funding:

No funding.

Ethical Consideration:

Ethical measures were taken throughout the study period to maintain a high standard of confidentiality and anonymity of the participants. Formal approval was taken from the ethical committee of Sir Salimullah Medical College Mitford Hospital.

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