

ORIGINAL ARTICLE

ASSOCIATION BETWEEN SERUM VITAMIN D LEVEL AND PARKINSON'S DISEASE: CASE CONTROL STUDY IN A TERTIARY LEVEL HOSPITAL, BANGLADESH

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Abstract:

Background: Parkinson's disease is a neurodegenerative disorder that is frequently observed in individuals who are 50 years of age or older. The etiology of this disease is still unknown, but research has shown the influence of factors like vitamin D acting as a hormone in Parkinson's disease. The current study aimed to explore the association between serum vitamin D levels and Parkinson's disease. **Methods:** In 2019 to 2020, the current researchers conducted this case control study on 50 patients with Parkinson's disease and 50 healthy subjects as the control group in the department of Neurology of Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh. Demographic information (age, gender, and education), serum levels of vitamin D in the two groups, disease duration, disease severity, and cardinal features of the disease in the patient group were investigated. Data were analyzed using the SPSS 25 software with the t-test, Kruskal Wallis, Mann-Whitney, and adjusted logistic regression. **Results:** The mean age of cases was 72.30 ±454 and the control group with a mean age of 60.08±8.305. Regarding the symptoms of the cases tremor 30 (60%), rigidity 5 (10%), bradykinesia 12(24%) and postural instability 3 (6%) and regarding disease duration(y) <5 year - 26 (52%), 5 to 10 years-17 (34%), >10years 7 (14%) and disease severity 1 to 2.5 - 26 (52%), 2.5 to 3 18 (36%) and >3 - 6 (12%) Serum vitamin D levels of males were 17.70±6.06 ng/mL in patients and 30.31±5.59 ng/mL in control groups, respectively which is clinically significant. Serum vitamin D levels of females were 20.03±5.75ng/mL in patients and 28.53±6.31ng/mL in control groups, respectively which is clinically significant (P=0.001). For the participants under 60 years of age, the mean serum vitamin D levels were 27.70±0.00 ng/mL and 30.78±5.44 ng/mL in patient and control groups, respectively. In participants aged 60 and older, the mean serum vitamin D levels were 18.40±5.91 ng/mL and 28.13±6.26 ng/mL in patient and control groups, respectively. These differences were statistically significant (P=0.001). Logistic regression analysis with adjusted demographic variables showed that the observed lower levels of serum vitamin D in cases compared with the control group was statistically significant(OR=4.17;95% CI:1.37, 12.71;P=0.012). **Conclusion:** There was a significant relationship between low serum vitamin D levels and the duration and severity of Parkinson's disease.

Keywords: Serum Vitamin D Levels, Parkinson's disease, Disease Severity, Duration of the Disease

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Introduction:

Parkinson's disease (PD) is a common complex neurodegenerative disorder characterized by a variety of motor and non-motor symptoms. As the disease progresses, PD symptoms can significantly affect the quality of life. Recently, it was reported that the median age-standardized annual incident rate of PD has raised to 14 per 100,000 people in high-income countries indicating that the burden of developing PD within a family is on the rise¹. To date, the exact pathogenesis of PD is still unclear, and no curative treatment is available. Thus, slowing down the progression of PD is of utmost importance. Vitamin D is a group of steroid derivatives, which can regulate the metabolism of calcium and phosphate. Recently, there are increasing evidences which show that Vitamin D plays an important role in cell modulation, such as proliferation, differentiation, immune regulation and so on.² In addition, an animal study found that vitamin D might have a neuroprotective function.³ Vitamin D deficiency is common in PD.⁴ However, it is argued whether vitamin D insufficiency is related to the etiology of PD. Two recent longitudinal studies suggested that the reduced serum vitamin D levels are significantly associated with risk of developing PD.^{5,6} This evidence provides the possibility of evaluating the risk of PD by using serum vitamin D levels as a biomarker.

Studies on the association between vitamin D deficiency and Parkinson's disease have shown conflicting findings. One cohort study reported that there was insufficient evidence to support the hypothesis that vitamin D deficiency had a role in the pathogenesis of Parkinson's disease, or on the integrity of the dopaminergic system.⁷ However, recent studies have reported a high prevalence of vitamin D deficiency in patients with Parkinson's disease^{8,9} with an inverse relationship between serum levels of 25-hydroxyvitamin D and the severity of Parkinson's disease.¹⁰⁻¹² Vitamin D supplements have been shown to reduce the rate of deterioration of motor function, as determined by both the Hoehn and Yahr scale and the Unified Parkinson's Disease Rating Scale (UPDRS).¹³ Preclinical animal experiments have also shown that vitamin D treatment was beneficial in reducing neuroinflammation and dopaminergic neurodegeneration.¹⁴ However, controversy remains regarding the relationship between vitamin D status and the risk of Parkinson's disease. One study in Finland showed that increased vitamin D levels could reduce the risk of developing Parkinson's disease.¹⁵ A further prospective cohort study that included a 17-year follow-up period showed that there was no association between vitamin D levels and the risk of developing Parkinson's disease.⁴

Elderly individuals who are more than 60 years of age are most likely to develop Parkinson's disease¹⁶. For people who are more than 40 years of age, the incidence of Parkinson's disease is 37.55 and 61.21 per 100,000 person years, for women and the men, respectively.¹⁷ Worldwide, due to the increase in life expectancy, it has been predicted that the number of patients with Parkinson's disease who are more than 50 years of age will double by 2030.¹⁸

PD has been increasing; it is a major issue of public health concern currently as the average life expectancy at birth rises to 72 years in Bangladesh. Management of patients with PD in low and middle income countries to be too expensive that most governments are unable to afford, resources and budgets that are allocated are unable to meet the burden of treatment. The magnitude of PD in Bangladesh is not known as there are no national registries for this disease. However, studies have reported a higher prevalence of PD among increasing the age of patients. The association of Vit D and PD in our country is not exactly evaluated. If you evaluate the evaluated the relationship between Vit D and PD we should a make a further plan in treatment as well as prevention of PD. Limited data is available in association between serum Vitamin D levels and Parkinson's disease in Bangladesh. So we would like to embark on measuring the vitamin D levels in PD patients in Bangladesh to find out their association, so that the study result might open new era of future research regarding alternative management and as well as prevention of PD .

Methods:*Subjects:*

This case-control study was conducted on 50 PD patients and 50 healthy individuals as the control group who will attend in the Department of Neurology of Sir Salimullah Medical College & Mitford Hospital, Dhaka Bangladesh during one year (2019-2020) will be included in the study. Both groups were randomly selected and divided to two groups, according to their age (older than 60 and 60years and older). They were also classified in terms of education in three groups: higher than an secondary, secondary, primary education and illiterate. Inclusion criteria were having a diagnosis of PD in accordance with common criteria and four cardinal features based on UK Brain Bank Criteria, patient's consent, the possibility of taking blood samples to measure serum vitamin D levels, and access to patients and their information during the study.¹⁹ Exclusion criteria were based on the common criteria for this topic and those that were specifically related to this study, such as a history of bone disease or fractures, renal or liver failure, a history and current

risk of debilitating diseases, such as malignancies and some neurological disorders, such as Multiple Sclerosis (M.S), patients treated with corticosteroids or those who recently used medical supplements and those who refused to continue being in the study.²⁰

Study design, population and settings:

This study will be done in the Department of Neurology of Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh. Subject will included according to inclusion and exclusion criteria. Relevant history, examination and investigations will be done each patient. We will evaluate Vit D level of all PD patients. The normal serum reference range for total 25-hydroxyvitamin D is 20–100 ng/mL, and in this study, vitamin D insufficiency was defined as a serum level <30 ng/mL, and vitamin D deficiency was defined as a serum level <20 ng/mL. Patient should include after obtaining written consent. This study protocol will be approved by ethical committee of Sir Salimullah Medical College, Dhaka, Bangladesh.

Data collection and laboratory procedures:

All data including demographic information (age, gender, marital status, education, and occupation), serum vitamin D levels of the two groups, cardinal features, duration (time between the onset of symptoms until diagnosis and entry in the study, causes of PD and relevant laboratory investigations will done and recorded.

After inclusion in the study information on patient socio-demographics, clinical characteristics, causes of

PD and relevant laboratory investigations will done and recorded.

The serum vit D levels were measured by nanogram per milliliter (ng/mL), and the results were evaluated with 95% confidential interval. All the data will be collected and stored in Case Report Forms (CRF).

Data management and analysis:

All statistical analyses were performed using the Statistical Program for Social Science (SPSS) version 25, IBM Corp., Chicago, USA, 2017. Descriptive statistics, t-test, Kruskal Wallis and Mann-Whitney tests were used to explain the data, compare the two groups, and analyze nonparametric data, respectively. Moreover, logistic regression test was applied to adjust the eüect of confounding variables. P values of d”0.05 were considered signiücant in all of the afore mentioned tests.

Results:

We conducted this case-control study on 50 PD patients aged from 56 to 97 with a mean age of 72.30 ±454 and 50 healthy individuals aged from 45 to 85 as the control group with a mean age of 60.08±8.305. Regarding the symptoms of the cases tremor 30 (60%), rigidity 5 (10%), bradykinesia 12(24%) and postural instability 3 (6%) and regarding disease duration(y) <5 year - 26 (52%), 5 to 10 years-17 (34%), >10years 7 (14%) and disease severity 1 to 2.5 – 26 (52%) , 2.5 to 3 18 (36%) and >3 – 6 (12%) (Table: 1).

Table-I
Demographics and clinical features

Variables	Groups					
	PD		Control		p value	
	N	Percentage	N	Percentage		
Gender	Male	31	62	26	52	0.001
	Female	19	38	24	48	0.001
Age(y)	<60	1	2	25	50	0.001
	≥60	49	98	25	50	
Cardinal features	Tremor	30	60	-	-	
	Rigidity	5	10	-	-	
	Bradykinesia	12	24	-	-	
	Postural Instability	3	6	-	-	
Disease duration(y)	<5	26	52	-	-	
	5 to 10	17	34	-	-	
	>10	7	14	-	-	
Disease severity	1 to 2.5	26	52	-	-	
	2.5 to 3	18	36	-	-	
	>3	6	12	-	-	

[-] represent not applicable.

In Table: III Serum vitamin D levels of males were 17.70±6.06 ng/mL in patients and 30.31±5.59ng/mL in control groups, respectively which is clinically significant. Serum vitamin D levels of females were 20.03±5.75ng/mL in patients and 28.53±6.31ng/mL in control groups, respectively which is clinically significant (P=0.001). For the participants under 60 years of age, the mean serum vitamin D levels were 27.70±0.00 ng/mL and 30.78±5.44 ng/mL in patient and control groups, respectively. In participants aged 60 and older, the mean serum vitamin D levels were 18.40±5.91 ng/mL and 28.13±6.26 ng/mL in patient and control groups, respectively. These differences were statistically significant (P=0.001).

Table II

Comparison of mean serum vitamin D level in PD patients’ group and control group based on gender and age¹

Variables	PD	Control	P value
Gender			
Male	17.70±6.06	30.31±5.59	0.001
Female	20.03±5.75	28.53±6.31	0.001
Total	18.59±5.99	29.45±5.96	0.001
Age(year)			
<60	27.70±0.00	30.78±5.44	0.001
≥60	18.40±5.91	28.13±6.26	0.001
Total	18.59±5.99	29.45±5.96	0.001

¹Data are presented as mean ± SD.

According to the results presented in Table 3, mean disease severity was 2.65±1.11. At same level of disease severity, serum vitamin D levels were lower in males than females. The levels were also lower in patients with a disease severity of one to two than those with a severity of 2.5 to 3. Patients with a severity of more than three had lower serum

vitamin D levels compared with those having a score of 2.5 to 3. However, it is noteworthy that this findings was only significant in males (95%CI: 22.27-5.62; P = 0. 018). Mean PD duration was 5.80±4.16 years. While serum vitamin D levels decreased as the duration of the disease became longer, this result was completely reversed in patients’ affected by PD for more than 10 years, as their levels were increased. Overall, this was most remarkable and statistically significant in females (95%CI: 19.78-9.58; P=0. 049).

Table III

Comparison of mean serum vitamin D level in PD patients’ group based on disease severity and its duration according to gender¹.

Variables	Male, confidence interval 95%	Female, confidence interval 95%
Disease severity		
1 to 2.5	19.37±5.41	21.63±5.76
2.5 to 3	16.75±6.57	14.53±4.27
>3	11.80±2.12	21.15±4.26
P value	0.114	0.062
Disease duration(year)		
<5	16.88±6.05	20.80±5.57
5 to 10	19.78±6.82	17.50±6.24
>10	15.58±3.28	23.40±4.67
P value	0.376	0.337

¹Data are presented as mean ± SD.

As shown in Table 4, lower serum vitamin D levels are statistically significant in patients aged 60 years and older compared with those younger than 60 years of age in unadjusted logistic regression model(P=0.807). Based on this model, these levels were significant in patients with PD compared with the control group (OR = 0.99; 95%CI: 0.89-1.10; P = 0.804). Other variables were not statistically significant in this model. After removing the effects of the confounding variables, such as age, gender, and education based on adjusted logistic regression model, the difference in serum vitamin D levels between case and control groups was statistically significant (OR = 0.94;95% CL:0.85-1.04; P=0.200).

Table IV

The effect of vitamin D on PD patients using logistic regression with adjustment of age and gender effects

Variables	Crude logistic regression			Multivariate logistic regression			
	OR	CI (95%)	P value	OR	CI (95%)	P value	
Age(y)	<60	Ref	Ref	Ref	Ref		
	≥60	0.98	0.86-1.12	0.807	1.02	0.89-1.16	0.807
Gender	Female	Ref	Ref	Ref	Ref		
	Male	1.10	0.97-1.18	0.200	0.94	0.85-1.04	0.200
Group	Control	Ref	Ref	Ref	Ref		
	PD	1.01	0.92-1.12	4.17	0.99	1.37-12.71	0.012

Abbreviations: CI- confidence interval; OR- odds ratios.

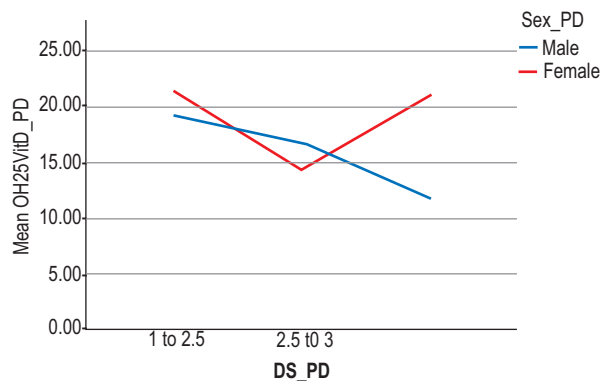


Fig.-1: Mean serum vitamin D level in PD patients based on disease severity according to gender.

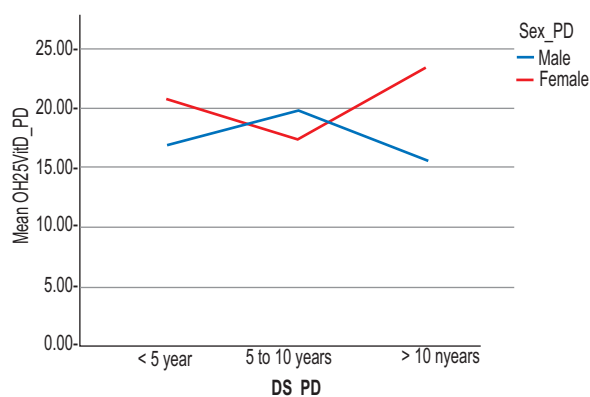


Fig.-2: Mean serum vitamin D level in PD patients based on its duration according to gender.

Discussion:

The recent research showed a connection between PD and reduced levels of serum vitamin D, which becomes more noticeable in more severe cases of the disease ²¹. Ahmadi et al. also assessed the serum vitamin D concentrations in individuals with PD and similarly observed a correlation between these levels and increased severity of PD.²¹ In others research indicated that the occurrence of vitamin D insufficiency was greater in early PD patients compared to findings from earlier studies ^{22,23}. Furthermore, the inadequacy of vitamin D did not worsen as Parkinson’s disease advanced. They suggested conducting additional research to discover the correlation between vitamin D levels and PD.^{23, 24} Their results do not align with those of past research or with the current study. Certainly, the findings of the current research can validate the link between vitamin D concentrations and increased severity of PD.

This research found low levels of serum 25 hydroxyvitamin D in patients with PD, whereas serum 1,25-hydroxyvitamin D levels were normal in all

participants. Recent research found that patients with lower severities of PD had higher levels of 25-hydroxyvitamin D, but no significant correlation was observed between 1, 25-hydroxy vitamin D levels and PD severity ²⁵. Similar to Suzuki et al.’s research, this study examined 25-hydroxy vitamin D levels and found a significant association between a decrease in these levels and increased disease severity, demonstrating the consistency with past studies .²⁶

However, this correlation was not found in females. In their research, they found a notable link between consuming dairy products high in calcium, vitamin D, protein, and lactose, and an increased likelihood of developing PD.⁴ In the study, consuming calcium supplements, vitamin D, and protein from other sources did not lead to a higher risk of PD. Nevertheless, their findings regarding the connection between consuming vitamin D from dairy products and the heightened risk of PD did not align with the outcomes of this research²⁷. So, they concluded that vitamin D from sources other than dairy did not increase the risk of PD. This research found a notable link between decreased levels of vitamin D in the blood and the length of illness among female subjects.²⁸ Because most Iranian men work outside and have more sun exposure, they can obtain more vitamin D from this source compared to females. In this study, it was found that males had significantly lower levels of Vitamin D compared to females when considering disease duration, region, and type of work. Disability and crippling caused by PD could potentially result in a lack of Vitamin D intake and reduced exposure to sunlight, leading to an increased impact of disease duration in men compared to women. Females showed a higher risk of PD compared to males due to lower levels of vitamin D in their blood, possibly because they tend to have less exposure to sunlight, which could be attributed to societal factors like limited outdoor activities and more time spent indoors for household duties. ²⁹ There was a notable correlation between lower serum vitamin D levels in patients under 60 years old compared to the control group in the two age categories (under and over 60 years), which contradicts findings from other research.^{21,30} While age adjustment was not fully implemented in both patient and control groups, patients over 60 years old in the study showed a significantly greater decrease in serum vitamin D levels compared to those under 60 years old according to the unadjusted logistic regression model.

Furthermore, the researchers in the present study categorized the patients according to the main characteristics of PD, which was a novel approach in examining the connection between serum vitamin D levels and PD.² Nevertheless, serum vitamin D levels

were not significantly linked to these characteristics. The study assessed how age, gender, cardinal disease features, severity, and duration affect PD and serum vitamin D levels, highlighting the strengths of the study. Furthermore, this research confirmed the connection between lower serum vitamin D levels and PD after adjusting for gender, age variables.

Conclusion:

Our research revealed that PD patient showed a significant decrease in serum vitamin D levels when compared to the control group, as shown by logistic regression analysis considering gender, age, and education. Severity and duration of Parkinson's disease were linked to lower levels of vitamin D among patients. Our findings presented new evidence linking low vitamin D levels with PD, prompting consideration of vitamin D replacement in PD treatment decisions.

Limitations:

However, there were certain limitations on the datasets that we had collected. This research was restricted to a small sample size, so the authors recommend additional studies using larger sample sizes and focusing on the variables mentioned and other related ones.

Data Availability:

The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

Conflict of Interest:

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

Funding:

Funding from research grant from Ministry of Science and Technology, Bangladesh was received for this study.

Ethical consideration:

The study was conducted after approval from the ethical review committee of Sir Salimullah Medical College. The confidentiality and anonymity of the study participants were maintained.

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