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Could vitamin D deficiency have an impact on motor and cognitive function in Parkinson's disease?

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Abstract

Background: Multiple epidemiological data showed a significant higher prevalence of hypovitaminosis D in patients with Parkinson's disease (PD).

Objectives: 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 both motor and cognitive symptoms in Parkinson's disease

Materials and methods: A case-control study was conducted on 25 patients who fulfilled the criteria for diagnosis of idiopathic Parkinson's disease based on the British Brain Bank criteria, and 25 healthy volunteers. Selected PD patients were submitted for assessment of cognitive function using the PD - Cognitive Rating Scale (PD-CRS) and assessment of motor function using the Unified Parkinson's Disease Rating Scale (UPDRS). Serum 25 hydroxy vitamin D level was measured for all the included patients and controls.

Results: PD patients were found to have a significantly lower level of serum vitamin D than controls (P value = 0.001). There was a statistically significant negative correlation between the serum vitamin D level and the scores of motor, mentation, activities of daily living, medication complication, other complications, and the total score of UPDRS (P value = 0.01, < 0.001, 0.012, 0.017, 0.039, and 0.002 respectively). There was a statistically significant positive correlation between the serum vitamin D level and the scores of attention, working memory, immediate recall, delayed recall, naming, visuoperceptual abilities, visuoconstructional abilities, alternating verbal fluency, action verbal fluency, and the total score of PD-CRS (P value < 0.001 in all parameters).

Conclusion: Vitamin D deficiency is evident in PD patient, and such deficiency significantly affected both motor and cognitive symptoms.

Keywords: Parkinson's disease, Vitamin D, PD-CRS, UPDRS

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease; it affects 1–2/1000 population at any time. The prevalence of PD increases with age; it affects 1% of the population over the age of 60 [1]. Compared to other Arab countries, the prevalence of PD disease is higher in Nile valley governorates of Upper Egypt [2]. Several epidemiologic studies have suggested an inverse relationship between circulating vitamin D levels and the risk of PD. Serum level of vitamin D is significantly lower in patients with PD compared to healthy controls [3–5], and serum 25 hydroxy vitamin D (25(OH)D) concentration progressively decreases with the increase in severity of motor symptoms of Parkinson's disease [6].

In a meta-analysis on the relationship between the vitamin D level and PD that included 20 studies (1 interventional, 14 observational, and 5 rodent studies), serum levels of 25(OH)D in PD patients were lower than in controls and higher levels of vitamin D were associated with better motor functions in most of the included studies [7]. Moreover, higher levels of vitamin D in PD patients were associated with better mood and cognitive function [8].

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Vitamin D was proposed to alter cholinergic, dopaminergic, and noradrenergic neurotransmitter pathways in the central nervous system (CNS) [9]. Furthermore, vitamin D may play a role in neuronal plasticity and axogenesis [10]. Several studies demonstrated that vitamin D ameliorates synthesis of neurotrophic factors and detoxification pathways which protect the integrity and structure of neurons [11].

Vitamin D enhances the synthesis of dopamine through increasing the level and activity of the enzyme tyrosine hydroxlase [12]. Furthermore, vitamin D was assumed to have a neuroprotective effect on dopaminergic pathways in the central nervous system. Animals which were pretreated with vitamin D for 1 week maintained dopaminergic functions after administration of 6-hydroxydopamine (a selective dopamine agonist (DA) toxin) [13]. Vitamin D was also found to preserve serotonin and dopamine systems in the brains of animals repeatedly administered neurotoxic doses of methamphetamine [14]. Accumulating studies reported that the distribution of vitamin D receptors (VDR) in the substantia nigra is altered in patients with Parkinson's disease [15]. It has been demonstrated that vitamin D plays a role in dopamine synthesis through regulation of tyrosine hydroxylase gene expression [16]. VDR is also highly expressed in putamen and caudate [14]. Kim and colleagues reported in their study a significant relationship between VDR gene polymorphism and Parkinson's disease [17].

Vitamin D receptors were demonstrated in the promoter regions of ret, GDNFR-α, and neurturin genes which are strongly linked to PD [18]. Furthermore, adult rats born to vitamin D-deficient mothers showed a permanent downregulation of Park 7 expression in the hippocampus [19].

Despite the accumulating biological and epidemiological data which revealed that vitamin D deficiency contributes in the development of Parkinson's disease [20], it is a debate if this relation is a direct effect or that patients suffering from Parkinson's disease mostly have decreased ambulation and sun exposure and, as a sequence, higher prevalence of vitamin D deficiency [15, 21].

Aim of the work

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 both motor and cognitive symptoms in Parkinson's disease.

Methods

The present study is a case-control study which included 25 PD patients and 25 normal healthy controls. The patients were enrolled from the Neurology outpatient clinic of Beni-Suef University Hospital. The study was approved by the ethical committee in the Faculty of Medicine, Beni-Suef University (FWA00015574 in the ninth of October 2018), and all participants in this study signed a written informed consent.

All the included patients fulfilled the criteria for diagnosis of idiopathic PD based on the British Brain Bank criteria [22] and had the ability to read, write, and do simple calculations.

Exclusion criteria were as follows: patients with visual impairment or hearing loss affecting their ability to complete the tests, patients with stroke temporally related to the onset of the disease, patients with a history of alcohol intake or drug abuse, patients with any medical disease which affects cognition or the serum level of vitamin D or calcium, patients with major psychiatric disorders, patients with structural brain lesions in an MRI study, and patients on vitamin D supplements or medications that affect the vitamin D level.

Participants of this study were subjected to the following battery of assessment

Evaluation and staging of Parkinson's disease

Evaluation and staging of Parkinson's disease were done for all PD patients (during on state) using the Modified Hoehn and Yahr staging scale (H&Y staging) [23] and Unified Parkinson's Disease Rating Scale (UPDRS) [24].

Modified H&Y staging scale was used for staging of PD patients based on clinical features and functional disability. The first stage is the mildest stage of the disease and stage 5 is the worst stage.

UPDRS includes five parts: part I: assessment of mentation, behavior, and mood; part II: evaluation of daily living activities including speech, swallowing, salivation, turning in bed, cutting food, handwriting, hygiene, dressing, freezing, walking, falling, tremor, and sensory complaints; part III: clinician-scored motor evaluation; part IV: complication of therapy; and part V: other complications.

Cognitive assessment

Cognitive assessment was done for all PD patients (on medications) using the Parkinson's Disease - Cognitive Rating Scale (PD-CRS) [25]. The following cognitive domains were included in the test: sustained attention, working memory, immediate and delayed free recall verbal memory, confrontation naming, visuoconstructional and visuoperceptual skills, and alternating and action verbal fluency. The total score for the test is 134.

Laboratory assessment

Serum level of 25(OH) vitamin D was measured for all patients and controls using Stat Fax 303Plus equipment. Fasting early morning venous blood samples were collected from resting subjects in 6-ml plain tubes then centrifuged. The processed serum was stored at − 80 °C prior to analysis. In a first step, 25(OH) vitamin D contained in

the sample has to be released from its vitamin D-binding protein. The undiluted sample is placed in a test tube and mixed with sample buffer containing a 25(OH) vitamin D tracer reagent and then with a vitamin D release reagent. Then 25(OH) vitamin D can be determined with the 25(OH) vitamin D ELISA assay. Calculation of results was done using data reduction software; a 4-Parameter-Fit with lin-log coordinates for optical density and concentration is the data reduction method of choice. Measuring range was 5–120 ng/ml. Patients were considered to have vitamin D deficiency if they had a vitamin D level below 30 ng/ml.

Statistical methods

The data were coded and entered using the Statistical Package for the Social Sciences (SPSS), version 15.0, released 2006, Chicago, USA. The demographic data, clinical characteristics, and serum vitamin D level for included PD patients and controls were reported as mean ± SD and number (%) for categorical variables. The Student *t* test was used for comparison between PD patients and controls in vitamin D serum level. Chi-square test was used for comparison between PD patients and controls in the frequency of vitamin D deficiency. The Pearson correlation coefficient (*r*) was used to describe the relationship between serum vitamin D level and Modified Hoehn and Yahr staging, score of UPDRS, and score of PD-CRS. *P* value equal to or less than 0.05 was considered significant.

Results

The demographic data for included PD patients and controls were demonstrated in Table 1. There was no statistically significant difference between patients and controls in age (*P* value = 0.553) or sex (*P* value = 1).

Regarding clinical characteristics of PD patients, the disease duration ranged from 0.5–5 years with a mean value of 1.77 ± 1.27 years. The total score for Modified Hoehn and Yahr staging ranged from 1.5 to 4 with a mean value 2.7 ± 0.707. The total UPDRS score ranged from 12 to 76 with a mean value 33.92 ± 15.16 (Table 2). The total PD-CRS ranged from 52 to 122 with a mean value 93.12 ± 24.45 (Table 3).

Regarding the incidence of vitamin D deficiency, 84% (*n* = 21) of PD patients were found to have vitamin D deficiency and 16% (*n* = 4) were found to have normal vitamin D. As for controls, 24% (*n* = 6) were found to have vitamin D deficiency and 76% (*n* = 19) have normal vitamin D. There was a statistically significant difference between patients and controls (*P* value < 0.001). There was also a statistically significant difference between patients and controls in the mean value for serum 25 hydroxy vitamin D level (*P* value = 0.001) (Table 4).

There was a statistically significant negative correlation between serum vitamin D level and Modified Hoehn and Yahr staging, scores of motor, mentation, activities of daily living, medication complication, other complications, and the total score of UPDRS (Table 5).

There was a highly statistically significant positive correlation between the serum level of vitamin D and the scores of attention, working memory, immediate

Table 1 Demographics of PD patients and controls

	Patients (*n* = 25)	Controls (*n* = 25)	*P* value
Age [mean (SD)]	62.84 (6.63)	61.80 (6.63)	0.553
Sex			
Male [*n* (%)]	22 (88%)	22 (88%)	1
Female [*n* (%)]	3 (12%)	3 (12%)	

P value ≥ 0.05 (non-significant)

Table 2 Modified Hoehn and Yahr staging and UPDRS score for PD patients

	PD patients (*n* = 25)	
	Range (minimum–maximum)	Mean (SD)
Modified Hoehn and Yahr staging	1.5–4	2.7 (0.707)
UPDRS		
Motor score		
Tremor	1–13	3.8 (2.36)
Rigidity	0–14	2.36 (2.93)
Postural instability	0–4	1.36 (1.35)
Bradykinesia	1–19	5.08 (3.62)
Total score	7–36	18.08 (7.71)
Mentation score	0–7	3.00 (2.25)
Activities	5–25	12.44 (5.79)
Medication complication	0–1	0.16 (0.37)
Other complication	0–2	0.24 (0.59)
Total-UPDRS	12–75	33.92 (15.16)

PD: Parkinson's disease, *UPDRS*: Unified Parkinson's Disease Rating Scale

Table 3 CRS-PD score for PD patients

PD-CRS	PD patients (*n* = 25)	
	Range (minimum–maximum)	Mean (SD)
Attention	3–10	7.20 (2.29)
Working memory	2–9	5.88 (2.50)
Immediate recall	3–10	6.40 (2.29)
Delayed recall	1–8	4.76 (2.27)
Confrontation naming	15–20	17.84 (2.13)
Visuoconstructional	4–10	8.44 (1.89)
Visuoperceptual	5–10	8.92 (1.44)
Alternating verbal fluency	3–20	13.64 (5.63)
The action verbal fluency	6–28	20.04 (6.64)
Total PD-CRS	52–122	93.12 (24.45)

PD: Parkinson's disease, *PD-CRS*: Parkinson's Disease - Cognitive Rating Scale

Table 4 Serum 25 hydroxy vitamin D level in patients and controls

	Patients ($n = 25$)		Controls ($n = 25$)		P value
	Range (minimum–maximum)	Mean (SD)	Range (minimum–maximum)	Mean (SD)	
25 hydroxy vitamin D	11.2–55.7	23.82 (10.35)	19.8–85	51.32 (22.50)	0.001*

*P value < 0.05 (significant)

recall, delayed recall, naming, visuoperceptual abilities, visuoconstructional abilities, action verbal fluency, alternating verbal fluency, and the total score of PD-CRS (P value < 0.001 in all parameters).

Discussion

There are accumulating evidences supporting the role of vitamin D deficiency in the pathogenesis of PD [2]. 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 [26].

In our study, PD patients were found to have a significantly lower level of serum vitamin D compared to the control group. In line with our finding, a previous cross-sectional study reported higher prevalence of vitamin D deficiency in PD patients compared to healthy controls [6].

Similarly, a cohort study carried out by Bischoff-Ferrariet and colleagues [27] showed that the risk of developing PD was higher in individuals with low serum vitamin D levels. In such study, after adjustment for the potential confounders, individuals with a serum vitamin D level equal to or more than 50 nmol/l were found to have a 65% lower risk of developing PD compared to individuals with values below 25 nmol/l.

Table 5 Correlation between Modified Hoehn and Yahr staging and UPDRS and serum vitamin D level

	Vitamin D	
	(r) coefficient	P value
Modified Hoehn and Yahr staging	− 0.573	0.003*
UPDRS		
Motor		
Tremor	− 0.383	0.059
Rigidity	− 0.446	0.025*
Postural instability	− 0.774	< 0.001*
Bradykinesia	− 0.452	0.023*
Total score	− 0.505	0.01*
Mentation	− 0.753	< 0.001*
Activities	− 0.494	0.012*
Complication of medication	− 0.474	0.017*
Other complication	− 0.416	0.039*
Total UPDRS	− 0.582	0.002*

UPDRS: Unified Parkinson's Disease Rating Scale
*P value < 0.05 (significant)

The relation between vitamin D deficiency and PD can be explained by the accumulating evidences that long-standing vitamin D deficiency results in loss of dopaminergic neurons in the substantia nigra and, as a consequence, the development of Parkinson's disease [28].

The proposed mechanisms by which vitamin D may help in protection against PD include neuronal calcium regulation, antioxidative mechanisms, detoxification mechanisms, immunomodulation, and enhancement of nerve conduction [29]. In the substantia nigra, the enzyme which controls the formation of the active form 1,25(OH)2D and vitamin D receptors was found in high levels [14].

On the other hand, a study carried out by Fullard and colleagues [30] assessed the vitamin D serum level in a population at risk for developing PD. They did not find any statistically significant difference between the high-risk group and the age- and sex-matched control group, suggesting that vitamin D deficiency is not considered a risk for developing PD.

In our study, there was a statistically significant negative correlation between serum vitamin D level and Hoehn and Yahr staging scale; the scores of motor, mentation, activities of daily living, other complication; and the total score of UPDRS. In line with our findings, Sleeman and colleagues [31] revealed a significant negative correlation between the serum level of 25(OH)D concentration and the severity of motor symptoms of PD assessed by UPDRS. Similarly, Sato and colleagues [21] reported a negative correlation between 25(OH)D with severity of PD as assessed by Hoehn and Yahr (H&Y) staging. The study revealed a higher prevalence of vitamin D deficiency in patients with advanced stage of the disease. Furthermore, Peterson and colleagues investigated the association between motor activity and serum level of 25(OH)D using five posturography tests (the sensory organization test, motor control test, sit and stand test, the unilateral stance test with eyes closed and eye opened, and the walk and turn test) in 40 PD patients. The study reported the presence of significant positive correlation between the serum level of vitamin D and the automatic postural responses [32].

Regarding the effect of vitamin D supplementation on PD progression, Suzuki and colleagues [28] conducted a double-blind placebo-controlled trial on the impact of vitamin D supplementation (1200 IU/day) on progression

of motor symptoms in PD assessed by modified Hoehn and Yahr scale and UPDRS. In such trial, 104 PD patients were studied for 1 year, 56 of them received 1200 IU vitamin D per day and the remaining 58 received placebo. Surprisingly, they found that PD patients receiving placebo experienced worsening of motor symptoms, while the deterioration in motor symptoms was significantly milder in those receiving vitamin D supplementation.

Ahmad Chitsaz and colleagues [33] found that advanced stages of PD (H&Y stages 4 to 5) were associated with a lower level of 25(OH)D compared to the early stages of the disease (H&Y stages 1 to 1.5), but this difference was not statistically significant.

Several theories can explain the influence of vitamin D deficiency on automatic postural responses. The most common theory for the link between vitamin D deficiency and falls is the associated muscle weakness. It is well recognized that chronic vitamin D deficiency may lead to myopathy. The activation of vitamin D receptors in muscles enhances protein synthesis and muscle cell growth. In vitamin D-deficient individuals, it has been demonstrated that there was significant improvement in muscle power after correction of vitamin D deficiency [34].

In our study, we found a statistically significant positive correlation between serum level of vitamin D and the scores of attention, working memory, immediate recall, delayed recall, naming, visuoperceptual abilities, visuoconstructional abilities, action verbal fluency, alternating verbal fluency, and the total score of PD-CRS.

Similar to our findings, Peterson and colleagues [4] found a significant positive correlation between vitamin D levels and the scores of immediate and delayed recall and the verbal fluency in Parkinson's disease patients without dementia. In the group of PD with dementia, no statistically significant correlation was reported between the scores of any of the psychometric tests and vitamin D levels.

There are many hypotheses that explain the impact of vitamin D on cognition. The postulated mechanisms include the effect of vitamin D on the CNS through stabilization of mitochondrial function, augmentation of neurotrophic factors, and anti-ischemic and antioxidant effects [35, 36]. Vitamin D also plays a role in the regulation of cholinergic pathways and clearance of the harmful amyloid beta peptides [9, 37]. Furthermore, hypovitaminosis D may increase the risk of diabetes mellitus [38], hypertension [39], and stroke [40]. These conditions are considered precipitating factors for cognitive impairment [41].

The limitation of this work is the relatively small number of patients due to financial issues and limitation of resources.

Further studies with a larger number of patients and for a longer duration to assess the effect of correction of vitamin D deficiency on motor and cognitive symptoms in Parkinson's disease should be conducted. Further researches should be directed also towards studying the effect of VDR polymorphisms on both motor and cognitive symptoms in PD, evaluating the relationship between serum vitamin D level and psychiatric manifestations in PD and studying the relationship between different Parkinson's disease medications and serum vitamin D level.

Conclusion

Parkinson's disease patients have a significantly lower vitamin D level compared to healthy controls, and such vitamin D deficiency significantly affects both motor and cognitive functions.

Abbreviations

6OHDA: 6-Hydroxydopamine; CNS: Central nervous system; DA: Dopamine agonist; H&Y: Hoehn and Yahr; PD: Parkinson's disease; PD-CRS: Parkinson's Disease - Cognitive Rating Scale; UPDRS: Unified Parkinson's Disease Rating Scale; VDR: Vitamin D receptors

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Availability of data and materials

The datasets used and/ or analyzed during the current study are available from the corresponding author on reasonable request with permission from the Faculty of Medicine, Beni-Suef University, Egypt.

Authors' contributions

RHS participated in the study design and sequence alignment and helped to draft the manuscript. SAE participated in the study design, performed the laboratory work, and helped to draft the manuscript. MIO participated in the study design and sequence alignment and helped to draft the manuscript. MH participated in the study design and collection and analysis of data and helped to draft the manuscript. SM participated in the sequence alignment, collection of data, and data analysis and helped to draft the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

A written informed consent was obtained from each participant in this study or from one of his family members, and the study was approved by the local ethics committee in the Faculty of Medicine, Beni-Suef University (the number is FWA00015574, and the date is ninth of October 2018).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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