Vitamin D status in idiopathic Parkinson’s disease: an Egyptian study

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Abstract

Background: Vitamin D is suggested to play an important role in neurodegenerative disorders.
Objective: To examine the association between serum 25 vitamin D3 and Parkinson’s disease (PD).
Materials and methods: Fifty patients suffering from PD and fifty age- and sex-matched healthy control subjects were included in the study. Patients were subjected to complete clinical assessment, and Unified Parkinson Disease Rating Scale (UPDRS) was done to evaluate severity of PD. Measurement of serum 25 vitamin D3 using enzyme-linked immuno sorbent assay (ELISA) was done for both patients and controls.
Results: Serum 25 vitamin D3 was significantly lower in PD patients compared to healthy controls. Twenty-five vitamin D3 serum level was significantly negatively correlated with age and age at onset of disease but not significantly correlated with disease duration and severity of Parkinson’s disease. Multiple regression analysis showed that serum 25 vitamin D3 was not found to be predictor for severity of PD.
Conclusion: There is an association between low vitamin D levels and PD. Therefore, vitamin D may have a role in the pathophysiology of PD.

Keywords: Serum 25 vitamin D3, Parkinson’s disease (PD)

Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disorder after Alzheimer’s disease in the elderly. Pathologically, there is a slow and progressive degeneration of dopaminergic neurons in the substantia nigra, although its etiology is not fully understood [1].

Vitamin D is an environmentally modifiable factor as it is largely determined by diet and sunlight exposure. The enzyme 1-alpha hydroxylase converts the stored 25 hydroxyvitamin D form to the biologically active vitamin D form 1,25-dihydroxyvitamin D3 which then binds to vitamin D receptor (VDR) [2].

Vitamin D was proposed to alter cholinergic, dopaminergic, and noradrenergic neurotransmitter pathways in the central nervous system (CNS). It has been demonstrated that vitamin D plays a role in dopamine synthesis through regulation of tyrosine hydroxylase gene [3].

Vitamin D has been implicated in PD through its effects on L-type voltage-sensitive calcium channels (L-VSCC), nerve growth factor (NGF), matrix metalloproteinases (MMPs), prostaglandins (PGs) and cyclooxygenase-2 (COX-2), reactive oxygen species (ROS), and nitric oxide synthase (NOS) [4].

Previous studies have reported an association between PD and serum vitamin D, but the results are controversial [5]. The present study aimed to assess serum 25 vitamin D3 status in PD patients and its relation to clinical parameters and disease severity.

Materials and methods

This case control study was carried on hundred subjects (50 patients diagnosed as PD and 50 age and gender healthy matched subjects).
Patients were selected from the Neurology outpatient clinic and Neurology department of Cairo University Hospitals. Control subjects were recruited from relatives of hospitalized patients in the Neurology department. The aim and procedures of the study were explained to every participant, and an informed consent was obtained before being enrolled in the study. The study was approved by the ethical committee of department of Neurology, Faculty of medicine, Cairo University Hospitals.

Included in this study are patients (of both sexes) fulfilling the criteria for diagnosis of idiopathic Parkinson’s disease according to the British Brain Bank criteria [6]. Their age ranged from 45–70 (to minimize the effect of aging on vitamin D level).

Excluded from this study are patients with concomitant medical illness (Diabetes Mellitus, hepatic and renal diseases); patients with MRI brain showing structural lesions; patients having bone diseases or receiving drugs that may affect bone health as corticosteroids, antidepressants, anxiolytics, proton pump inhibitors, H2 receptor blockers or chemotherapeutic agents, and patients taking vitamin D supplements; and patients receiving drugs that may interact with serum vitamin D level as antiepileptic drugs, diuretics, and anticoagulants.

Methods
Patients were submitted to thorough neurological examination and assessment and staging of PD using Unified Parkinson Disease Rating Scale (UPDRS). Serum level of 25 vitamin D was measured for patients and controls using enzyme-linked immuno sorbent assay (ELISA) technique. Venous blood samples were collected then centrifuged to get serum. The KIA kit was used for the quantitative measurement of total 25-OH vitamin D3 in serum using the competitive immunoassay technique.

Statistical methods
Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data was summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparing categorical data, Chi-square test was performed. Exact test was used when the expected frequency is less than 5. Correlations between quantitative variables were done using Spearman’s correlation coefficient. Linear regression analysis was done to predict total severity scores using vitamin D. Logistic regression was done to detect independent predictors of severity. P values less than 0.05 were considered as statistically significant.

Results
The age of patients ranged from 47–70 years with a mean age 60.78 ± 5.10 years. The age of control subjects ranged from 45–70 years with a mean age 61.30 ± 5.61 years. The patients group included 32 male (64%) and 18 female (36%). The control group included 30 male (60%) and 20 female (40%). Patients and controls were matched regarding mean age and sex distribution (p = 0.545 and 0.680 respectively).

Clinical characteristics of PD patients are illustrated in Table 1.

In the patient group, the mean serum level of 25 vitamin D3 was 6.10 ± 2.55 ng/ml. Serum 25 vitamin D3 was deficient in 45 patients (90%) and insufficient in 5 patients (10%). In the control group, the mean serum level of 25 vitamin D3 was 7.46 ± 3.61 ng/ml. Serum vitamin D was optimum in 1 subject (2%), insufficient in 9 subjects (18%), and deficient in 40 subjects (80%) (Table 2).

Mean serum vitamin D3 level was significantly lower in PD patients compared to healthy controls (p = 0.029).

No significant difference was found between disease stages as regards mean age, age at onset, or serum 25 vitamin D3 level (p = 0.456, 0.189, and 0.372 respectively) (Table 3).

Serum 25 vitamin D3 level was significantly negatively correlated with age and age at onset of disease (p = 0.015, r = −0.34), (p = 0.038, r = −0.29) respectively. However, serum 25 vitamin D3 level was not significantly correlated with disease duration, UPDRS scores, and modified H and Y staging.

Linear regression analysis was done between total scores of mentation, activity of daily living, and motor examination as dependent factors and serum 25 vitamin D3 as independent factor. Logistic regression analysis was also done between modified H and Y scale as dependent factor and serum vitamin D3 as independent factor. The P value was not significant after adjustment for age, sex, age at onset of disease, and disease duration. This indicates that serum 25 vitamin D3 is not an independent predictor for both UPDRS scores and H and Y staging.

Discussion
There is a growing body of evidence for vitamin D involvement in several neurodegenerative disorders including multiple sclerosis, Alzheimer’s disease, and PD [7].

In the present study, serum 25 vitamin D3 was significantly lower in PD patients compared to controls, a finding which showed agreement with other studies conducted on a Japanese cohort [8, 9], on American cohort [10], and to an Egyptian cohort study [11]. They reported that serum vitamin D3 was significantly lower in PD patients compared to healthy controls. An epidemiological study results from
Finland have also suggested that low serum vitamin D level predicted a high risk of PD incidence [12]. Another prospective study done in the UK by Sleeman and colleagues [13] revealed that patients with early PD have lower serum concentrations of 25(OH) D than controls within months of diagnosis and at 18 months follow-up. This may support the hypothesis that vitamin D deficiency may have a role in PD progression. The association between PD and low Vitamin D can be explained on the basis that PD patients mostly have decreased ambulation and sun exposure [9].

On the contrary, Petersen and colleagues [7] found no significant difference regarding serum 25 vitamin D3 between PD patients and controls, although cases had slightly lower values than controls. They attributed their controversy with many previous studies to minimal exposure to sunlight in Europe.

The current work revealed that serum 25 vitamin D3 was also deficient in the control group. This could be attributed to the following: the process of vitamin D synthesis by ultraviolet B irradiation from sunshine that become less efficient with age. Moreover, satisfactory exposure to sunlight is infrequent with current life styles, even in fit young adults. Furthermore, loss of mobility or residential care limits solar exposure. Financial issues often add to these problems. Thus, hypovitaminosis D is common worldwide, but is more common and more severe in older people [14, 15].

The present work revealed that serum vitamin D3 level was significantly negatively correlated with and age and age at onset of disease. This was in accordance with Jamali and colleagues [16], who found that vitamin D3 levels were strongly negatively correlated with age \( p = 0.000 \).

In the present study, severity of PD assessed by UPDRS scale and H and Y staging was not significantly correlated with serum vitamin D3. Also, serum 25 vitamin D3 is not an independent predictor for both UPDRS scores and H and Y staging after adjustment for possible confounders as age, age at onset, duration of disease, and sex. This finding showed agreement with Chitaz and colleagues [17] which showed no association between serum levels of vitamin D and different stages of H and Y scale or UPDRS in a study done on an Iranian cohort. On the contrary, Sato and colleagues [8] reported that serum levels of 25 vitamin D3 had an inverse correlation with the severity of PD, and higher circulating serum 25 vitamin D3 levels were significantly related to milder forms of PD. Moreover, Suzuki and colleagues [5] found significant inverse associations between serum vitamin D and total UPDRS, and they also found significant inverse association in UPDRS part I, part II, and part III but not in part IV using linear regression analysis after adjustment of possible confounders. Furthermore, Suzuki and colleagues [5] found that as vitamin D3 became lower, H

### Table 1 Characteristics of PD patients

| Characteristic                        | Range       | Mean ± SD       |
|--------------------------------------|-------------|-----------------|
| **Age at onset (years)**             | (40–69)     | 57.32 ± 6.4    |
| **Duration (years)**                 | (1–10)      | 3.42 ± 2.35    |
| **Family history of PD, n (%)**      |             | 6 (12%)        |
| **Distribution of starting motor**    |             |                |
| symptoms, n (%)                      | Bradykinesia| 10 (20%)       |
|                                     | Tremors     | 40 (80%)       |
| **The frequency of non-motor**       |             |                |
| symptoms, n (%)                      | Constipation| 28 (56%)       |
|                                     | Memory impairment | 15 (30%)   |
| **Visual problems**, n (%)            |             |                |
|                                     | REM sleep behavior disorder | 12 (24%)   |
|                                     | Depression  | 9 (18%)        |
|                                     | Erectile dysfunction | 3 (6%)     |
|                                     | Insomnia    | 3 (6%)         |
|                                     | Fatigue     | 1 (2%)         |
|                                     | Impaired olfaction | 1 (2%)     |
|                                     | Incontinence| 1 (2%)         |
| **UPDRS scores**                     |             |                |
|                                     | Mentation, behavior, and mood | (0.0–7) |
|                                     | Activities of daily living | (1–33) |
|                                     | Motor       | (12–47)        |
| **Modified Hoehn and Yahr staging, n (%)** | |                |
|                                     | Stage 1     | 20 (40%)       |
|                                     | Stage 1.5   | 11 (22%)       |
|                                     | Stage 2     | 9 (18%)        |
|                                     | Stage 2.5   | 4 (8%)         |
|                                     | Stage 3     | 4 (8%)         |
|                                     | Stage 4     | 2 (4%)         |

### Table 2 Serum 25 vitamin D3 in patients and control groups

| Serum 25 vitamin D3 level (ng/ml) | Mean ± SD | Median | Minimum | Maximum |
|-----------------------------------|-----------|--------|---------|---------|
| Patient group                     | 6.10 ± 2.55 | 6.00   | 1.00    | 12.50   |
| Control group                     | 7.46 ± 3.61 | 7.15   | 2.00    | 25.00   |

### Table 3 Comparison between patients distributed according to modified Hoehn and Yahr regarding clinical parameters and serum 25 vitamin D3 level

| Modified Hoehn and Yahr staging | P value |
|---------------------------------|---------|
| Less than stage 3               | Stage 3 or more |
| Mean ± SD | Mean ± SD |
| Age (years) | 61.05 ± 4.97 | 58.83 ± 6.05 |
| Age at onset (years) | 57.82 ± 6.05 | 53.67 ± 8.26 |
| 25 Vitamin D3 (ng/ml) | 6.17 ± 2.37 | 5.55 ± 3.85 |

*Significant
and Y stage became worsened after adjustment of possible confounders. The disagreement might be attributed to the inclusion of small sample size (50 patients) in this study compared to large number in studies conducted by Sato and colleagues [9] (142 patients) and Suzuki and colleagues [5] (137 patients). Another explanation is inclusion of small number of patients with advanced PD which may reduce the chance to find significance between H and Y staging and studied vitamin D level. Chitaz and colleagues [17] enrolled 109 PD patients with mean H and Y scale stage 1.1. Most of our patients had H and Y staging less than 3, while in Sato study [9], most patients had advanced disease with mean H and Y scale 3.3.

The limitations of this study were the small sample size. Also, most of included PD patients (88%) had H and Y staging less than 3, and only few patients with advanced stages were enrolled. For these reasons, the results are clearly exploratory and preliminary.

Conclusion

With the limitations of this study, it could be concluded that there is an association between low vitamin D levels and PD. Future studies are recommended to clarify the possible role of vitamin D in the pathogenesis, progression, and severity of the disease.

Abbreviations

COX-2: Cyclooxygenase-2; ELISA: Enzyme-linked immuno sorbent assay; H and Y: Staging Hoehn and Yahr staging; L-VSCC: L-type voltage-sensitive calcium channels; MMPs: Matrix metalloproteinases; NGF: Nerve growth factor; NOS: Nitric oxide synthase; PD: Parkinson’s disease; PGs: Prostaglandins; ROS: Reactive oxygen species; UPDRS: Unified Parkinson Disease Rating Scale; VDR: Vitamin D receptor

Acknowledgements

The authors acknowledge subjects for their participation and cooperation in this study.

Authors’ contributions

EMF: research idea, data acquisition, data analysis and interpretation, and manuscript writing and reviewing. MEE: data acquisition and data analysis and interpretation. SS: performing and reviewing the laboratory workup. RSI: data acquisition, data interpretation, and manuscript writing and reviewing. SH: data acquisition and data analysis and interpretation. All authors read and approved the final manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the current Cairo University regulations and Egyptian legislation but are available from the corresponding author on reasonable request and after institutional approval.

Ethics approval and consent to participate

An informed written consent was taken from each patient. All data obtained from every patient were confidential and were not used outside the study. The patients have rights to withdraw from the study at any time without giving any reason. All the cost of the investigations was afforded by the researcher.

Our study was approved by the ethical committee of the Department of Neurology, Faculty of Medicine, Cairo University, on 5 February 2017.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 19 July 2019 Accepted: 13 April 2020
Published online: 07 May 2020

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