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Research paper

Correlation between 25-hydroxy-vitamin D and Parkinson's disease

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ABSTRACT

Background: Previous cross-sectional studies have shown that Parkinson's disease (PD) patients have lower serum 25-hydroxyvitamin D (25(OH)D) concentrations than controls. Other studies have not yet tested whether research findings from other regions are generalizable to Chinese populations. In this case-control study, we examined the correlation between 25-hydroxyvitamin D and Parkinson's disease.

Methods: We established an association between 25-hydroxyvitamin D deficiency and PD in a case-control study of 100 PD patients and 100 control subjects free of neurological disease at the First Affiliated Hospital of Xinjiang Medical University.

Results: Total 25-hydroxyvitamin D levels were deficient in 21 % of patients with PD compared with 4 % of controls. In univariate analyses, plasma levels of 25-hydroxyvitamin D were associated with PD ($p < 0.001$). In multivariate analyses, vitamin D deficiency (25(OH)D < 20 ng/mL) was significantly associated with PD ($p = 0.008$, Odds Ratio =17.13, 95 % CI= 2.082–141.075). Individuals with 25(OH)D levels in the lowest quartile had the highest prevalence of PD ($p = 0.026$, OR=11.786, 95 % CI =1.342–103.51 compared to individuals with values in the highest quartile).

Conclusions: Our study reveals an association between 25-hydroxyvitamin D and PD. Patients with incident PD had significantly lower serum 25(OH)D concentrations than age-matched controls. High-risk PD patients with vitamin D deficiency who have not yet developed exercise impairment should undergo vitamin D measurement and any necessary treatment as soon as possible. Limitations of the study: the study needs further assessment of populations with low vitamin D levels in other regions of China; further assessment of the effect of different sources of vitamin D on PD; further study of longitudinal cohorts at different time points.

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder, and its incidence and disability are continually increasing as the population ages (Olanow, 2009). Although both genetic and environmental factors have been implicated, the etiological factors that drive PD are mostly unknown (de Lau and Breteler, 2006). Recently, among the many pathogeneses of Parkinson's disease, researchers identified a commonality {25-hydroxyvitamin D [25(OH)D] deficiency}, which suggests that there is a correlation between 25(OH)D levels and Parkinson's disease. A retrospective cross-sectional cohort study by Evatt et al (Evatt et al., 2008). found a significantly higher prevalence of hypovitaminosis in PD patients than in healthy controls or patients with AD. Ding et al (Ding et al., 2013). observed vitamin D deficiency in 17.6 % of PD cases (68/388) compared with 9.3 % of healthy controls (26/283; $p = 0.002$), and plasma levels of 25-hydroxyvitamin D_3 were associated with the prevalence of PD in both univariate and multivariate analyses ($P = 0.0034$, $P = 0.047$). In the Mini-Finland Health Survey, people in the lowest quartile of vitamin D status at baseline had approximately a threefold increase in the risk of developing PD compared with people in the highest quartile (Knekt et al., 2010).

Sunlight exposure is the major source of vitamin D (Holick, 2007a). The production of vitamin D depends not only on the intensity of ultraviolet rays but also on the duration of ultraviolet irradiation (Bogh et al., 2011), and there are differences between different regions and races. A case-control study by Wang (Wang et al., 2016) et al. found a significant positive correlation between serum 25(OH)D and sunlight exposure. Reduced levels of serum 25(OH)D and sunlight exposure are significantly associated with an increased risk of PD. A few case-control studies in Finland, Iran, Japan and the United States have reported lower 25(OH)D levels in PD patients than in age-matched controls (Peterson et al., 2013; Meamar et al., 2013; Sato et al., 2005).

Abbreviations: PD, Parkinson disease; 25OH D, 25-hydroxy-vitamin D; HY, Hoehn and Yahr; OR, Odd ratio; CI, confidence interval.

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As a result of geographical factors, China's annual average sunshine exposure is not identical to that of any other country. Existing studies have yet to test whether research findings from other regions are generalizable to Chinese populations. To address these limitations of previous investigations, we performed the current study, in which we used immunoassay-based vitamin D quantification techniques to investigate the association between 25(OH)D deficiency and PD in the First Affiliated Hospital of Xinjiang Medical University from March 2019 to October 2019. Total 25(OH)D was analyzed as a categorical variable using the established clinical criteria for vitamin D deficiency (25(OH)D< 20 ng/mL), vitamin D insufficiency (25(OH)D 20–29 ng/mL), and vitamin D sufficiency (25(OH)D ≥ 30 ng/mL); the last of these categories was used as the reference.

Methods

Study design and population

In our study, we collected data from 100 PD patients and 100 neurologically healthy control subjects who received care at the First Affiliated Hospital of Xinjiang Medical University from January 2019 to December 2019. The inclusion criteria for PD cases conformed to the new standard for the clinical diagnosis of Parkinson's disease in China (Li et al., 2017). The exclusion criteria for PD cases were diagnosis of endocrine system diseases such as hyperparathyroidism and other diseases of abnormal calcium and phosphorus metabolism, recent fractures or bone tumors (≤6 months prior), known active ulcers, and active colitis. The inclusion criterion for healthy controls was the absence of any past or present diagnosis of neurological disease. The exclusion criteria were the same for controls as for PD patients. The controls were comparable to the PD cases in that they were drawn from the same source population and could be identified as cases if they had PD.

This study protocol was approved by the institutional review boards of the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University. This study is a retrospective study; thus, we did not need to obtain informed consent from eligible patients.

Collection of clinical and demographic information

The baseline characteristics of cases and controls were examined (Table 1), including factors known to affect vitamin D status such as age, sex, race, smoking status, uric acid, blood calcium, fasting blood glucose, and glycated hemoglobin.

Table 1
Presents baseline characteristics of the study populations.

	PD (100)	Control (100)	P-Value
Age, y	65.86 ± 10.00	52.88 ± 9.39	<0.001[a]
Males	54(54)	45(45)	0.203
Race (Han)	73(73)	65(65)	0.221
Hypertension	47(47)	49(49)	0.777
blood calcium	2.26 ± 0.12	2.27 ± 0.10	0.523
fasting blood glucose	5.27 ± 1.31	5.15 ± 1.61	0.571
LDL-C	2.48 ± 0.82	2.62 ± 0.86	0.221
Cystatin C	0.83 ± 0.21	0.77 ± 0.20	0.057
Clinical criteria			
Age at onset, y	62.15 ± 1.06		
Duration, y	4.09 ± 0.48		
Hoehn and Yahr stage	2.25 ± 0.07		
1	11(11)		
1.5	17(17)		
2	25(25)		
2.5	15(15)		
3	27(27)		
4	5(5)		
25(OH)D	32.39 ± 13.91	42.54 ± 17.72	<0.001[a]
<20 ng/mL	21(21)	4(4)	0.007[a]
20–29 ng/mL	27(27)	20(20)	0.234
≥30 ng/mL	52(52)	76(76)	0.033[a]

Abbreviations: 25(OH) D= 25-hydroxy-vitamin D; LDL-C=low-density lipoprotein-cholesterol; PD = Parkinson disease;
[a] Statistically significant.

25 (OH)D detection

25-OH D2 and D3 were routinely determined in the central laboratory of the First Affiliated Hospital of Xinjiang Medical University using isotope dilution liquid chromatography-tandem mass spectrometry (ID-LC-MS/MS) with stable isotope-labelled internal standards (IS), similar to the method described in reference (Maunsell et al., 2005).

Statistical analysis

Student's t-test and the chi-square test were used to compare continuous variables and categorical variables, respectively. Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated for each quartile individually, using the highest quartile as the reference. OR: Reflects the magnitude of the likelihood of a particular event occurring in one group for another in terms of the occurrence ratio. Logistic regression analysis was used to evaluate the association of vitamin D concentrations with PD status (present or absent), Hoehn and Yahr (HY) stage, and PD duration, adjusted for age at the time of sampling. General linear regression models were also used to test the association between vitamin D and the duration of PD. All analyses were performed using the statistical software SPSS 26.0 for Mac and statistical significance was defined as $p < 0.05$.

Results

Several key demographic characteristics of the subjects are shown in Table 1. The PD patients were, on average, older than the controls (65.86 ± 10.00 years for cases vs 52.88 ± 9.39 years for controls). However, no significant differences in sex, race, hypertension, blood calcium, fasting blood glucose, low-density lipoprotein cholesterol (LDL-C), or cystatin C were found between cases and controls. Therefore sex, race, hypertension, blood calcium, fasting blood glucose, low-density lipoprotein cholesterol (LDL-C), and cystatin C does not affect the results in both groups. Regarding clinical status, the PD cases had mean Hoehn and Yahr stage of 2.25 ± 0.07. The duration of PD averaged 4.09 ± 0.48 years among cases. Compared with the control group, the PD group had a reduced total plasma 25(OH)D level (32.39 ± 13.91 ng/mL for cases vs 42.54 ± 17.72 ng/mL for controls, $p < 0.001$).

25(OH)D is the vitamin D metabolite that is measured to assess a patient's vitamin D status. Vitamin D deficiency is diagnosed when 25(OH)D< 20 ng/mL (Holick et al., 2011; Holick, 2007b); vitamin D insufficiency is defined as a 25(OH)D level of 21–29 ng/mL, and a level of > 30 ng/mL is considered sufficient (Wacker and Holick, 2013a). Regarding clinical severity, the average HY stage of the cases was 2.25 ± 0.07. In univariate analysis, the total 25(OH)D level of the patient group was lower than that of the control group (32.39 ± 13.91 vs 42.54 ± 17.72 ng/mL, $p < 0.001$). There was vitamin D deficiency in 21 % of cases (21/100) compared with 4 % of controls (4/100; $p = 0.007$)). Furthermore, 27 % of cases (27/100) were vitamin D insufficient compared with 20 % of controls (20/100; $p = 0.234$) (Table 1).

Multivariate analysis (Table 2) with adjustment for baseline age showed that vitamin D deficiency (25(OH)D < 20 ng/mL) was significantly associated with PD. The probability of vitamin D deficiency was 17.13 times (OR= 17.13) as high in PD patients as in the control group ($p = 0.008$, 95 % CI, 2.082–141.075). The disease duration of vitamin D deficiency in PD patients at the enrollment visit was significantly different from that of the control group ($p < 0.001$, $\beta = -20.844$).

Low levels of 25(OH)D were associated with increased disease prevalence. Individuals with 25(OH)D levels in the lowest quartile observed in our population had the highest prevalence of PD, with OR = 11.786 and $p = 0.026$ (95 % CI, 1.342–103.51) compared to

Table 2
Presents multivariate analysis between total 25(OH) D with PD, HY stage and disease duration at the enrollment visit.

	PD		HY		Duration	
	OR (95 % CI)	P-Value	β	P-Value	β	P-Value
Clinical cutoff analysis						
<20 ng/mL	17.13 (2.082–141.075)	0.008[a]	-1.238	0.522	-20.844	<0.001[a]
20–29 ng/mL	0.719 (0.230–2.245)	0.570	0.042	0.979	-1.362	0.357
≥30 ng/mL	Ref	Ref	Ref	Ref	Ref	Ref
Quartile analysis						
Total 25(OH) D						
Q1(7.5–19.31 ng/mL)	11.786 (1.342–103.51)	0.026[a]	27.849	<0.001[a]	23.223	<0.001[a]
Q2(19.31–30.43 ng/mL)	0.974 (0.316–2.998)	0.963	4.195	0.012[a]	2.413	0.087
Q3(30.43–40 ng/mL)	0.459 (0.138–1.528)	0.204	0.983	0.281	-0.345	0.733
Q4(>40 ng/mL)	Ref	Ref	Ref	Ref	Ref	Ref

Abbreviation Bs: CI =confidence interval; HY = Hoehn and Yahr; 25(OH) D = 25-hydroxy-vitamin D; OR = odds ratio; PD = Parkinson disease; Ref. =reference
All relations are statistically adjusted for age.
β indicates regression coefficient. [a] Statistically significant.

individuals with values in the highest quartile (Table 2). Individuals with levels in the lowest quartile of 25(OH)D values had the highest disease severity (HY) and the longest disease duration (both $p < 0.001$ compared to individuals with values in the highest quartile). Subjects with the median 25(OH)D value also had greater disease severity (HY) than individuals with values in the highest quartile ($p = 0.012$). Compared to subjects in the highest quartile of 25(OH)D levels, those in the next highest quartile showed no significant difference in disease severity (HY) or disease duration ($p = 0.281$ and $p = 0.733$, respectively) (Table 2). After adjusting for these covariates, total 25(OH)D deficiency remained more frequent in PD patients than in controls, with $p = 0.016$ (Fig. 1A). The relationship of vitamin D levels with HY stage. The data showed that the total 25(OH)D concentration was related to disease severity (R^2 =0.663, $P < 0.001$). (Fig. 1B). For a subgroup analysis, HY stages were categorized (<3 or ≥3) according to whether there was motor dysfunction; scores below 3 were further categorized according to the presence or absence of postural impairment (<2 or 2 ≤HY <3). The results confirmed that there was a close and significant correlation between total 25(OH)D levels and HY stages. Significant differences were found between the HY stage <3 and ≥3 subgroups and between the <2 and 2 ≤HY< 3 subgroups (both $p < 0.0001$) (Fig. 1C, D).

Finally, we examined the relationship of vitamin D levels with symptom duration. Our data showed that the total 25(OH)D concentration was related to disease duration ($R^2 = 0.266$, $P = 0.001$) (Fig. 1E).

Discussion

This case-control study of 100 cases and 100 controls at The First Affiliated Hospital of Xinjiang Medical University from January 2019 to December 2019 provides compelling evidence that vitamin D deficiency is 17.13 times as prevalent in PD patients as in similarly aged controls without PD. Individuals with 25(OH)D levels in the lowest quartile had the highest prevalence of PD ($p = 0.026$, OR=11.786, 95 % CI 1.342–103.51 compared to individuals with values in the highest quartile). Serum 25(OH)D was negatively correlated with PD disease duration and disease severity (HY stage) ($\beta = -1.238$ and $\beta = -20.844$, respectively). To the best of our knowledge, this is the first study to investigate the relationship between 25(OH)D deficiency and PD in Xinjiang, China.

Several studies have reported an association between PD and reduced plasma 25(OH)D concentrations (Sato et al., 1997, 2002; Suzuki et al., 2012). A study by Wang et al (Wang et al., 2015). showed that vitamin D deficiency was significantly correlated with PD. Subjects in the lowest quartile of 25(OH)D values had the highest prevalence of PD, with an OR = 2.66 and $P < 0.0001$ (95 % CI 1.746–4.03) compared to individuals in the highest quartile. A study by Fullard et al (Fullard and Duda, 2020). showed an inverse association between serum vitamin D levels and motor symptom severity in cross-sectional studies. Our study also draws results consistent with the above studies. In our case-control study, cases were 11.786 times as likely as controls to be in the lowest quartile compared with the highest quartile ($P = 0.026$, 95 % CI 1.342–103.51). PD patients with vitamin D deficiency have more obvious symptoms, higher HY scores and shorter the enrollment visit time than PD patients without vitamin D deficiency ($\beta = -1.238$, $\beta = -20.844$).

Suzuki et al (Suzuki et al., 2013). conducted a randomized, double-blind, placebo-controlled vitamin D intervention trial showing that vitamin D, compared with a placebo, significantly inhibited the deterioration of Hoehn-Yahr staging scores in PD patients Vitamin D appeared to delay PD progression and was not found to cause adverse reactions such as hypercalcemia. Our study confirms that there is a correlation between vitamin D status and HY classification (Fig. 1B), especially for patients who do not yet have motor dysfunction (HY stage <3) or postural impairment (<2 or 2 ≤HY <3) (all $p < 0.0001$). Moreover, from the first to the fourth quartile of 25(OH)D, the HY classification gradually decreases, indicating a reduction in the severity of the disease. Individuals with 25(OH)D levels in the lowest quartile had the highest disease severity (HY) ($p < 0.001$). There was a significant negative correlation between serum vitamin D concentration and HY stage. Therefore, it can be inferred that vitamin D can be used as an index to predict the severity of PD before the onset of exercise impairment. The lower the serum vitamin D concentration in PD patients, the more likely they are to become exercise impaired.

Sleemana et al (Sleeman et al., 2017a). showed that mean serum 25 (OH)D concentrations were lower in PD patients than in control participants at baseline and 18 months later. There was a small but significant association between vitamin D status at baseline and the severity of motor symptoms at 36 months. Our results are consistent with previous studies, showing a correlation between vitamin D and disease course. From the first to the fourth quartile of 25(OH)D, the duration of the disease increases. Individuals in the lowest quartile of 25(OH)D had the shortest duration of disease ($p < 0.001$). The duration of disease had a significant negative correlation with serum vitamin D concentration; in other words, the concentration of vitamin D in the serum of PD patients decreased over the course of the disease (Fig. 1E).

Skin VitD levels are directly related to sunlight exposure (Wacker and Holick, 2013b),and UV exposure increases VitD levels in the body (Engelsen, 2010). Bone mineral density is directly related to vitamin D (VitD) concentrations, which in turn are related to postural stability (Sleeman et al., 2017b). Plasma concentrations of osteotriol (1, 25-dihydroxyvitamin D3) are much lower in patients with PD, which may be associated with bone health and fracture risk (Sunyecz, 2008). A prospective study (Shrestha et al., 2016) showed no support for the hypothesis that vitamin D may reduce the risk of PD. In other words, vitamin D supplementation before the onset of disease cannot reduce the incidence of PD. However,A recent meta-analysis showed an inverse relationship between VitD levels and the risk and severity of PD in 2866

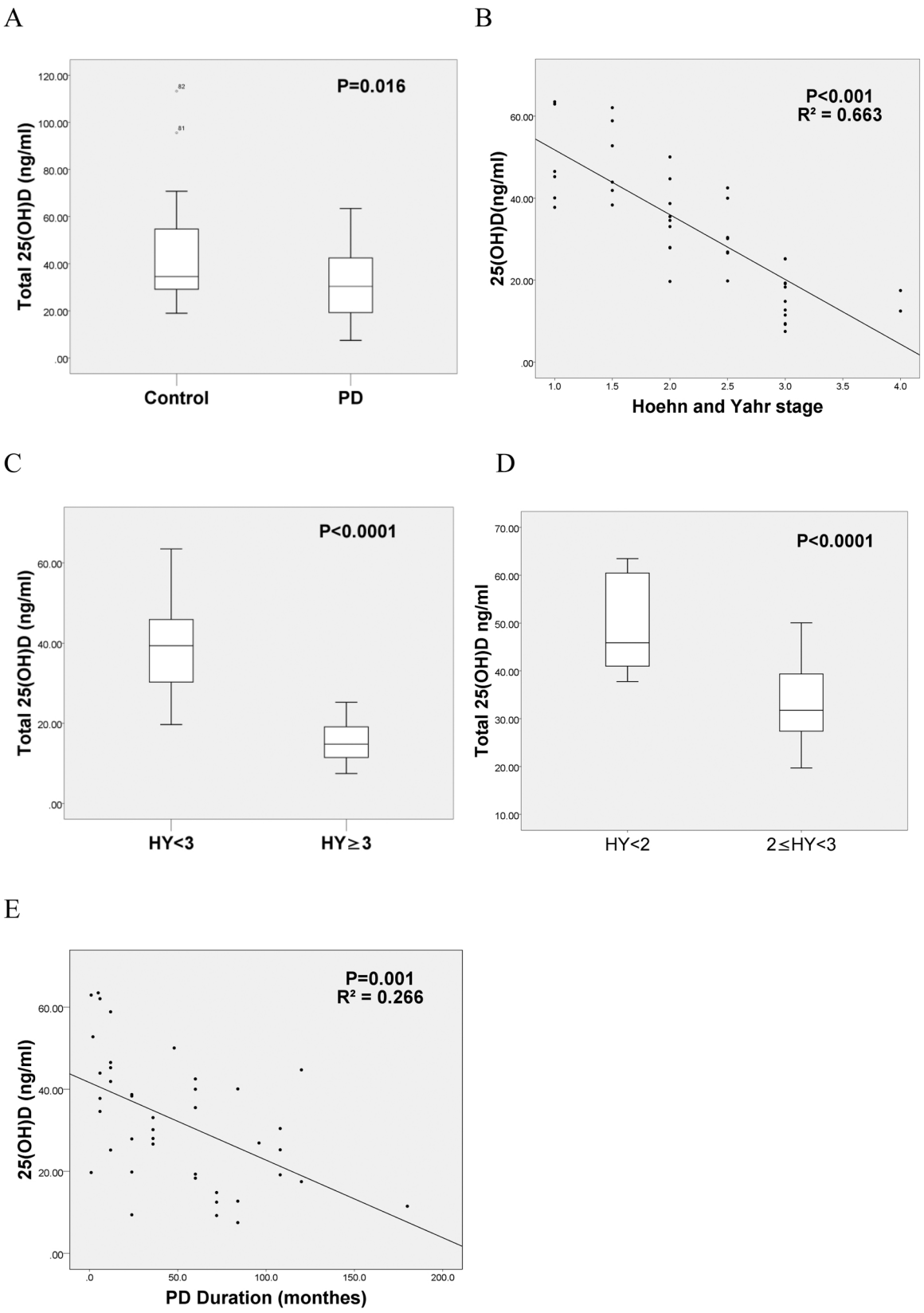

Fig. 1. A, Relations between total 25(OH) D plasma levels and PD are visualized. B-D, Relations between total 25(OH) D plasma levels and HY stage HY stage (< 3or≥3), HY stage (< 2 or 2 HY < 3) are visualized. E, Relations between 25(OH) D plasma levels and PD duration. Solid line represents fitted correlation between vitamin D levels and symptom duration, HY= Hoehn and Yahr; 25(OH) D - 25-hydroxy-vitamin D; PD= Parkinson disease.

PD patients (Rai et al., 2021). A large randomised multicentre, double-blind, placebo-controlled study of VitD supplementation (≥400 IU/day) given to patients with early PD (<5 years of PD disease) showed that patients taking VitD supplementation did not alter early disease progression, but continued supplementation with VitD still had the potential to reduce the incidence of disability associated with bone health, as osteoporosis is more common in PD and the risk of falls and risk of fracture increases with disease progression. These data may be useful in designing studies to test the effects of vitamin D supplementation over a longer time frame (Luthra et al., 2018). Therefore, more cohort studies of early and late PD patients are needed to illuminate the connection between VitD and PD further.

The high prevalence of inadequate vitamin D concentrations is also present in subjects with non-disabling and early PD (Evatt et al., 2011). Serum vitamin D2 levels are mainly from diet rather than sunlight. Gastrointestinal dysfunction, including dysphagia, delayed gastric emptying and constipation, may lead to poor digestion and absorption, which in turn reduces serum vitamin D levels in PD patients (Mrabet et al., 2016). In addition, comorbidities such as malnutrition, skin atrophy that does not produce vitamin D, and renal or liver dysfunction can also affect vitamin D concentrations (Zhen et al., 2015; Galesanu and Mocanu, 2015). In addition, the possible biological mechanisms explaining the severity of PD due to vitamin D status are complex.First and foremost, it is important to understand that only active vitamin D can maintain all normal physiological functions in our bodies. The process of vitamin D activity is regulated by the enzyme 1α-hydroxylase in the kidney, which converts 25(OH)D to 1,25(OH)2D3. secondly, vitamin D plays an important role in neuroprotection by promoting the release of glial cell-derived neurotrophic factor (GDNF) and other trophic factors.

Our study has several limitations. First, this study was conducted on patients and controls from the First Affiliated Hospital of Xinjiang Medical University, not the general Chinese population. China has a large population with diverse ethnicities and lifestyles. Thus, it is necessary to evaluate the population with low vitamin D levels in other regions of China. Second, because of the relationship between detection methods, our study failed to separate vitamin D by source and detect the association between each source and PD; we examined only the correlation between total serum vitamin D concentrations and PD disease progression. The differential effects of different vitamin D sources need further exploration in future research. Third, our study was a case-control study and did not involve longitudinal clinical evaluation with multiple vitamin D measurements over time; thus, we could not assess the relationship of vitamin D status (and its changes over time) with disease progression. In order to provide clinically valuable information, it is essential to identify the time window in which adequate exposure to vitamin D can prevent or delay the onset of PD. It is necessary to study a longitudinal cohort at different points in time to provide this valuable information.

Conclusion

In our study, a high prevalence of vitamin D deficiency was found in PD patients. High-risk PD patients with vitamin D deficiency who have not yet developed exercise impairment should undergo vitamin D measurement and any needed supplementation as soon as possible. Particularly in elderly patients, a low serum concentration of vitamin D is a very reliable indicator of a deficiency.

Ethics approval and consent to participate

The study protocol was approved by the institutional review boards of Ethics Committee of First Affiliated Hospital of Xinjiang Medical University.

Consent to publish

Not applicable.

CRediT authorship contribution statement

MX conceptualized the current study objectives, analyzed the data, and wrote the manuscript. QJZ had responsibility of the final content. All co-authors read and approved the final manuscript and were involved in the conception of the research plan.

Funding

Not applicable.

Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability

Please contact author for data requests.

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