

The Relationship of Vitamin D Levels with Disease Severity, Balance, and Falls in Parkinson's Disease

Parkinson Hastalığında D Vitamini Düzeyinin Hastalık Şiddeti, Denge ve Düşme ile İlişkisi

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ÖZ

Amaç: Parkinson hastalığında serum D vitamini düzeyleri ile hastalık şiddeti, denge sorunları, düşme ve düşme korkusu arasındaki ilişkiyi değerlendirmektir.

Araçlar ve Yöntem: Bu çalışma retrospektif, kesitsel olarak tasarlandı. Çalışmaya 45-80 yaş arası Parkinson hastaları ile sağlıklı kontroller dahil edildi. Çalışmanın sonuç ölçütleri, serum 25(OH) D vitamini seviyeleri, Hoehn&Yahr Ölçeği (HY), Birleşik Parkinson Hastalığı Derecelendirme Ölçeği-III (BPHDÖ-III), Berg denge ölçeği (BDÖ), Tinetti testi (TT) ve Uluslararası Düşme Etkinliği Ölçeği (DEÖ-U) idi.

Bulgular: Çalışmaya Parkinson hastalığı (PH) olan yetmiş iki katılımcı ve altmış sağlıklı kontrol dahil edildi. Ortalama 25(OH) D vitamini düzeyi PH grubunda 17.8 ± 8.2 ng/ml, kontrol grubunda ise 22.2 ± 9.7 ng/ml idi. Gruplar arasında 25(OH) D vitamini düzeyleri açısından istatistiksel olarak anlamlı fark vardı ($p=0.005$). PH grubundaki katılımcılar, HY ölçeğine göre iki gruba ayrıldı (Erken evre grubu: Evre 1-2; İleri Evre grubu: Evre 3-4). Ortalama 25(OH) D vitamini düzeyi erken evre grupta 18.6 ± 7.8 ng/ml iken ileri evre grupta 16.5 ± 8.8 ng/ml idi. Her iki grupta da istatistiksel olarak anlamlı fark saptanmadı ($p=0.299$). Pearson analiz sonuçlarına göre PH grubunda, 25(OH) D vitamini düzeyleri, HY evreleri, BDÖ, TT, DEÖ-U ve BPHDÖ-III arasında korelasyon yoktu ($p>0.05$).

Sonuç: PH'da serum D vitamini düzeyleri sağlıklı kontrollere göre daha düşüktü. Ancak PH'da serum D vitamini düzeyleri ile hastalık şiddeti, denge sorunu ve düşme korkusu arasında anlamlı bir ilişki bulunamadı.

Anahtar Kelimeler: düşme korkusu; nörodejenerasyon; postüral instabilite; vitamin D eksikliği

ABSTRACT

Purpose: To evaluate the relationship between serum vitamin D levels with disease severity, balance problems and fear of falling in Parkinson's disease.

Materials and Methods: This was a retrospective, cross-sectional study. Participants with Parkinson's disease and healthy controls aged 45-80 years were included in the study. The outcomes of the study were serum 25(OH) vitamin D levels, Hoehn&Yahr Scale, Unified Parkinson's Disease Rating Scale-III, Berg balance scale, Tinetti test, and International Falls Efficacy Scale scores.

Results: Seventy-two participants with Parkinson's disease and sixty healthy controls were included in the study. The mean 25(OH) vitamin D level was 17.8 ± 8.2 ng/ml in the PD group, while it was 22.2 ± 9.7 ng/ml in the control group. There was a statistically significant difference in terms of 25(OH) vitamin D levels between the groups ($p=0.005$). The participants in the PD group were divided into two groups according to the HY scale scores (Early-stage group: Stage 1-2; Advanced-Stage group: Stage 3-4). The mean 25(OH) vitamin D level was 18.6 ± 7.8 ng/ml in the early-stage group, it was 16.5 ± 8.8 ng/ml in the advanced-stage group. No statistically significant differences were identified in both groups ($p=0.299$). There was no correlation between 25(OH) vitamin D levels, HY stages, BBS, TT, FES-I, and UPDRS-III in PD group ($p>0.05$).

Conclusion: Vitamin D levels were lower in PD than that in healthy controls. However, no significant relationship was found between vitamin D levels and disease severity, balance problem, and fear of falling in PD.

Keywords: fear of falling; neurodegeneration; postural instability; vitamin D deficiency

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized by bradykinesia, resting tremor, rigidity, and postural instability. These motor symptoms are thought to be caused by the loss of dopaminergic cells in the basal ganglia.¹

Vitamin D is a secosteroid that is associated with calcium homeostasis, bone health, and also muscular, endocrine, immune, and central nervous systems.^{1,2} It is known that the enzyme that converts vitamin D to the active form and the vitamin D receptors are present in the human brain.³ Recent studies demonstrated the role of vitamin D in neurodegenerative diseases. Neuroprotective factors regulate nerve growth or protect the nerves against cytotoxicity.⁴ According to several studies, 1.25(OH)₂D₃ regulates the synthesis of Neurotrophin-3 (NT3) and glial cell line-derived growth factor (GDF).^{5,6} Additionally, 1.25(OH)₂D₃ has a direct effect on neural stem cells which differentiate into neurons, oligodendrocytes, and astrocytes.⁶

The relationship between PD and low serum vitamin D level is contradictory. Considering the aforementioned mechanisms, vitamin D may slow down the progression of PD.⁷ Lv et al. reported that PD patients had lower mean serum 25 (OH) vitamin D levels than healthy controls, and vitamin D deficiency increased the risk of PD.⁸ Contrary, in a Mendelian randomization study, it was found that there was no clear relationship between low 25 (OH) vitamin D concentration with risk of PD.⁹

Impairment of the balance and falls cause morbidity and mortality in PD.¹⁰ It is a fact that vitamin D has a positive effect on balance and gait in older adults.^{11,12} However, there are limited studies that demonstrate the correlation between fear of falling and balance problems with low serum vitamin D levels in patients with PD. In the present study, it was aimed to demonstrate the effect of serum 25 (OH) vitamin D levels on disease severity, balance and fear of falling in PD.

MATERIALS and METHODS

Study Design and Participants

A retrospective, cross-sectional study was conducted in an outpatient clinic in a hospital. The study protocol was reviewed and approved by the ethics committee of the Kanuni Sultan Suleyman training and Research Hospital. (Date 26.11.2021 and No. KAEK/2021.11.287).

Participants with PD aged 45-80 years who were admitted to the Physical Medicine and Rehabilitation Outpatient Clinic were recruited for the study. Healthy controls with the same demographic characteristics were also included in the study. The inclusion criteria were determined as participants aged 45-80 years, diagnosed with PD before admission to the outpatient clinic, and not receiving vitamin D supplementation in the last 6 months. Participants who did not respond to dopaminergic treatment, had serious comorbidities, had a history of disease affected the underlying vitamin D synthesis (Paget's disease, primary hyperthyroidism, renal disease, cancer, etc.) and received vitamin D, bisphosphonate, estrogen, and calcitonin treatment in the last 6 months were excluded from the study.

Outcome Measures

All files between January 2020 and September 2021 were scanned. Participants who met the inclusion criteria were included in the study. Their demographic characteristics and treatment history were obtained.

Disease severity was evaluated by Hoehn & Yahr Scale. This scale is used for staging the motor functions in PD. According to the scale, Stage 1 shows unilateral involvement without functional impairment, Stage 2 shows bilateral involvement without balance impairment, Stage 3 is a mild-to-moderate disease with mild deterioration in balance, Stage 4 shows advanced disease and difficulty to walk, and Stage 5 shows using a wheelchair or being bedridden.¹³

The motor examination section (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS) was used for clinical staging. This is a clinical rating scale for PD that

was first created in the 1980s and is widely used. It was revised by the Movement Disorders Society in 2001.^{14,15}

Gait, balance and fall risk assessment of the participants were evaluated with the Berg Balance Scale (BBS) and the Tinetti Test (TT). BBS was created to assess balance and determine the fall risk in older adults. It consists of 14 items that directly evaluate performance. Each item is scored between 0-4 points. The highest score is 56 points. A score of 0-29 indicates that the balance is unstable, 21-40 indicates an acceptable balance, and 41-56 shows that the balance is at a good level.¹⁶ Sahin et al. performed the Turkish validity and reliability study of the scale.¹⁷

TT is designed to determine the fall risk. There are 13 items for the assessment of balance and 9 items for the assessment of gait. Impairment in gait and balance is seen as a decrease in the total TT score.¹⁸

Fear of falling was measured with the International Falls Efficacy Scale (FES-I). The scale assesses physical and social activities which may cause the possibility of falling. A high score reflects the increased fear of falling.¹⁹ The Turkish validation study of the scale was performed.²⁰

25 (OH) vitamin D levels were measured on the Cobas® 8000 (Roche, Basel, Switzerland) with the ECLIA method. Elecsys Vitamin D total II Kit was used. According to the Endocrine Society Clinical Practice Guideline, serum 25 (OH) vitamin D levels <20 ng/ml were considered as deficiency, the values between 21-29 ng/ml were classified as insufficiency, and 30-100 ng/ml were sufficient level.²¹ Calcium, phosphorus, alkaline phosphatase, creatinine, blood urea nitrogen, thyroid-stimulating hormone, and parathormone levels of the participants at the time of admission to the outpatient clinic were also investigated.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS software, version 23.0 (Statistics for MacOs, IBM Corp., Armonk, NY, USA). The normality of distribution was determined using histograms and the Kolmogorov-Smirnov test. Descriptive statistics of data were used to determine the mean (standard deviation values) in parametric variables and median (minimum and maximum

values) in non-parametric variables. For inter-group analysis, the independent samples t-test was used. Bivariate associations were determined using the Chi-square test for categorical variables. Spearman or Pearson analyses were used for correlation analysis depending on the distribution of the variables. For the sample size, the confidence interval was 95%, and p-values of <0.05 were considered statistically significant.

RESULTS

One hundred and two participants with PD who presented to the outpatient clinic were evaluated for eligibility. Seventy-two participants with PD met the inclusion criteria, and sixty healthy controls were included in the study. In PD group, thirty-four participants (47.2%) were female and thirty-eight (52.8%) were male. In the control group (C), thirty-two participants (53.3%) were female, and twenty-eight (46.7%) were male. Demographic data and clinical characteristics of the participants in PD and C groups are shown in Table 1.

Table 1. Demographic data and clinical characteristics of the participants.

Variables	PD group (n=72)	C group (n=60)	p
Age			
Mean (SD)	67.4 (8.3)	61.1 (8.5)	0.552
Gender n(%)			
Female	34 (47.2%)	32 (53.3%)	0.899
Male	38 (52.8%)	28 (46.7%)	
BMI			
Mean (SD)	29.0 (4.5)	29.9 (3.7)	0.135
25 (OH) Vitamin D (ng/mL)			
Mean (SD)	17.8 (8.2)	22.2 (9.7)	0.129
HY Scale n(%)			
Stage 1	12 (16.7%)	-	
Stage 2	33 (45.8%)		
Stage 3	16 (22.3%)		
Stage 4	11 (15.2%)		
Stage 5	-		
UPDRS-III			
Mean (SD)	23.3 (9.3)	-	
BBS			
Mean (SD)	38.6 (12.5)	-	
TT			
Mean (SD)	18.7 (6.4)	-	
FES-I			
Mean (SD)	28.1 (13.9)	-	

PD: Parkinson's disease, C: control, SD: standard deviation, BMI: Body-mass index, HY: Hoehn & Yahr, UPDRS-III: Unified Parkinson's Disease Rating Scale-III, BBS: Berg balance scale, TT: Tinetti test, FES-I: International falls efficacy scale; p<0.05 is considered as significant for homogeneity test (Levene test).

The 25 (OH) vitamin D levels were below 20 ng/ml in 65.3% of the participants with PD. It was observed that the 25(OH) vitamin D levels were below 10 ng/ml in 19.4% of them. The mean vitamin D level was 17.8 ±8.2 ng/ml in PD group, while it was 22.2 ±9.7 ng/ml in C group. There was a statistically significant difference in terms of 25 (OH) vitamin D levels between the groups (p=0.005).

When the disease severity in PD group was evaluated clinically according to the HY scale, 12 participants (16.7%) were at Stage 1, 33 of them (45.8%) were at Stage 2, 16 (22.3%) were at Stage 3, and 11 (15.2%) were at Stage 4.

The participants in PD group were divided into two groups according to the HY scale (Early-stage group: Stage 1-2; Advanced-Stage group: Stage 3-4). The demographic characteristics, the scores of UPDRS-III, BBS, TT, and FES-I, and the mean 25(OH) vitamin D levels were homogenously distributed between the two groups (Table 2). The mean 25(OH) vitamin D level was 18.6 ± 7.8 ng/ml in early-stage group, whereas it was 16.5 ± 8.8 ng/ml in advanced-stage group. Upon the comparison of the 25(OH) vitamin D levels according to disease severity stages, no statistically significant differences were identified in both groups (p=0.299). Additionally, when the 25 OH) vitamin D levels were categorized into three groups according to the Endocrin Society Clinical Practice Guideline, there was no significant relationship between vitamin D groups and HY stages (p>0.05) (Table 3).

Table 2. Clinical characteristics according to disease severity in PD group.

Variables	HY stage 1-2	HY stage 3-4	p ^a	p ^b
Age				
Mean (SD)	66.7 (8.7)	68.7 (7.6)	0.156	0.338
Gender (%)				
Female	23 (51.1%)	11 (40.7%)	0.393	0.401
Male	22 (48.9%)	16 (59.3%)		
BMI				
Mean (SD)	28.9 (4.2)	29.1 (5.0)	0.096	0.096
BBS				
Mean (SD)	42.1 (12.4)	32.8 (10.5)	0.390	0.002
TT				
Mean (SD)	21.3 (5.1)	14.7 (6.0)	0.575	<0.001
UPDRS-III				
Mean (SD)	18.5 (7.2)	31.3 (6.2)	0.705	<0.001
FES-I				
Mean (SD)	22.6 (11.4)	37.1 (13.3)	0.249	<0.001
25 (OH) Vitamin D				
(ng/mL)				
Mean (SD)	18.6 (7.8)	16.5 (8.8)	0.299	0.299

HY: Hoehn & Yahr, SD: standard deviation, UPDRS-III: Unified Parkinson's Disease Rating Scale-III, BBS: Berg balance scale, TT: Tinetti test, FES-I: International falls efficacy scale; p^a<0.05 is considered as significant for homogeneity of the variables (Levene test); p^b<0.05 is considered as significant for between group analysis (student's t test).

Table 3. The ranges of 25 (OH) vitamin D levels of the participants according to HY scale.

Parameters	25 (OH) Vitamin D levels			Total
	<20 ng/ml	21-30 ng/ml	31-100 ng/ml	
HY stage 1-2 n(%)	29 (64.4%)	11 (24.4%)	5 (11.1%)	45 (100%)
HY stage 3-4 n(%)	18 (66.7%)	6 (22.2%)	3 (11.1%)	27 (100%)
Total	47 (65.3%)	17 (23.6%)	8 (11.1%)	72 (100%)

Chi-square, p>0.05, HY: Hoehn & Yahr.

According to the Pearson analysis results, there was no correlation between 25 (OH) vitamin D levels, HY stages, BBS scores, TT scores, FES-I scores, and UPDRS-III scores in PD group (Table 4).

Table 4. Correlations between serum 25(OH) vitamin D levels and other variables.

Variables	HY scale	TT	BBS	UPDRS-III	FES-I
25 (OH) Vitamin D					
r	-.072	.146	.084	-.118	-.066
p	.550	.222	.480	.323	.584

HY: Hoehn & Yahr, UPDRS-III: Unified Parkinson's Disease Rating Scale-III, BBS: Berg balance scale, TT: Tinetti test, FES-I: International falls efficacy scale; r: correlation coefficient, p: probability value for correlations (Spearman correlation analysis).

DISCUSSION

The effect of 25 (OH) vitamin D levels on disease severity, balance, and fear of falling in PD were evaluated in this study.

In recent studies, vitamin D levels in PD were found to be lower than those in the normal population.^{8,22-24} Bradykinesia, fear of falling as a result of deterioration in balance and coordination, decreased muscle strength, and immobility reduce sunlight exposure and may cause vitamin D deficiency in PD.^{22,25} In the present study, similarly, vitamin D levels were significantly lower in PD compared to healthy controls. In a cross-sectional study, it was found that the prevalence of vitamin D deficiency was 54.1% in PD.²⁵ Van den Bos et al. reported that 56.2% of PD patients had vitamin D deficiency.²² In the present study, 65.3% of the participants with PD had vitamin D deficiency. Serum 25 (OH) vitamin D levels were below 10 ng/ml in 19.4% of them. This result may be related to the fact that the participants were not questioned about sunlight exposure, diet, and gastrointestinal problems. Additionally, the seasonal changes may affect the vitamin D levels.²² Vitamin D deficiency is more common in Turkish population.²⁶ Çalış et al. found vitamin D levels being below 10 ng/ml in 46% of participants with PD.²⁷ Compared to the results, the lower rate in the current study

may be associated with differences in the geographic region.

The disease severity in PD is measured with the HY scale and UPDRS.^{13,14} Several studies were reported the inverse relationship between HY scale and mean serum 25(OH) vitamin D levels.^{7,25} In the present study, although there was a decrease in vitamin D levels as the HY stage increased, no significant relationship was found between disease stages in PD and vitamin D levels.

Progressive functional limitations, such as postural instability and gait disturbance in PD, lead to impaired balance and increased fall risk.²⁸ Few studies showed that vitamin D deficiency affected muscle mass and performance, balance, and fall risk in older adults.^{29,30} In a cross-sectional study, a positive correlation was found between mean serum 25(OH) vitamin D levels and automatic postural response in PD.¹⁰ In another study, it was stated that there was an increase in the frequency of falls in PD compared to the normal population. PD patients did not go out because of the fear of falling; thus, it resulted in a further decrease in vitamin D levels.²⁵ Furthermore, vitamin D deficiency increases the fall risk and balance problems.³⁰ According to the current study, it was observed that as the disease severity increased, there was an increase in balance problems and fear of falling. However, no significant relationship was found between serum vitamin D levels and balance and fear of falling.

According to the results of the study, reporting the lower vitamin D levels in PD patients is important for considering vitamin D supplementation in these patients. Furthermore, the strength of this study is that it will inspire further studies evaluating the effect of vitamin D supplementation on balance, fear of falling, and fall risk in PD.

This study has some limitations. First of all, it was designed retrospectively. Secondly, the physical activity levels of the participants and the seasonal situation at the time they applied to the clinic are not known. Thus, the level of vitamin D synthesis may be affected by these parameters.

Serum vitamin D levels were lower in PD than those in healthy controls. However, no significant relationship was

found between vitamin D levels and disease severity, balance problem, and fear of falling in PD. Further studies with a large number of participants are needed.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

A retrospective, cross-sectional study was conducted in an outpatient clinic in a hospital. Study protocol İstanbul S. B. Ü. It was reviewed and approved by the ethics committee of Kanuni Sultan Süleyman Training and Research Hospital (Date 26.11.2021 and No. KAEK/2021.11.287).

Authors' Contributions

Concept/Design: MDK. Data Collection and/or Processing: MDK. Data analysis and interpretation: MDK. Literature Search: MDK. Drafting manuscript: MDK. Critical revision of manuscript: MDK.

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