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- Gökşen GÖKŞENOĞLU[1]
- Kürşat TOPAL[2]
- Nurdan PAKER[1]
- Derya BUĞDAYCI[1]
- Nur KESİKTAŞ[1]

RESEARCH

# VITAMIN D DEFICIENCY AND RELATED FACTORS IN AMBULATORY PATIENTS WITH MILD TO MODERATE PARKINSON'S DISEASE

## Abstract

***Introduction:*** Vitamin D deficiency is a common problem in Parkinson's disease (PD). We investigated 25-hydroxyvitamin D [25(OH)D] values and related factors in ambulatory patients with PD.

***Materials and Method:*** This descriptive study included 48 (25 women, 23 men) patients with idiopathic PD. Serum 25(OH)D and parathormone levels as well as falls within the previous six months were recorded. Disease severity was evaluated by Hoehn and Yahr Scale. Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry at the L1-L4 spine and femoral neck.

***Results:*** Mean age was 64.4±10.2 years. Mean disease duration was 5.5±3.0 years. Median Hoehn and Yahr stage was 2 (Min-max: 1-3). Mean serum 25(OH)D level was 27.35±9.83 ng/mL. 54.1% of the patients with PD had vitamin D deficiency or insufficiency. The falling rate in the last six months was 41.7%. Median number of falls was 1.5 (Min-max: 1-5). There was a statistically significantly negative correlation between serum 25(OH)D level and disease duration, disease severity, number of falls, and serum parathormone level, whereas a significant positive correlation was found between serum 25(OH)D level and femoral neck BMD. Multiple linear regression analysis revealed that disease duration and number of falls were the predictors of the serum 25(OH)D level (Adjusted $R^2$=0.54, F=28.6, p<0.0001).

***Conclusion:*** This study suggests that disease duration and number of falls are main predictors for low serum vitamin D level, and that serum parathormone level and femoral neck bone density may be affected by low serum vitamin D level in patients with PD.

***Key Words:*** Parkinson disease; Bone density; Avitaminosis; 25-hydroxyvitamin D2; Osteoporosis

Correspondance

Göksen GÖKŞENOĞLU
İstanbul Physical Rehabilitation and Therapy Training and Research Hospital
İSTANBUL

Phone: 02124965000
e-mail: goksengoksenoglu@hotmail.com

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[1] İstanbul Physical Rehabilitation and Therapy Training and Research Hospital
İSTANBUL
[2] Fizyotem Medical Center
TRABZON

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ARAŞTIRMA

# HAFİF-ORTA DÜZEYDEKİ AMBULATUAR PARKİNSON HASTALARINDA D VİTAMİNİ EKSİKLİĞİ VE İLİŞKİLİ FAKTÖRLER

## Öz

***Giriş:*** Parkinson hastalığında (PH) D vitamini eksikliği sık görülen bir problemdir. Biz, ambulatuvar PH olan hastalarda 25-hidroksivitamin D [25(OH)D] düzeylerini ve ilişkili faktörleri araştırdık.

***Gereç ve Yöntem:*** Bu tanımlayıcı çalışmaya idiyopatik PH olan 48 hasta (25 kadın, 23 erkek) dahil edildi. Serum 25(OH)D ve parathormon seviyelerine ek olarak son altı aydaki düşmeler kaydedildi. Hastalık şiddeti Hoehn Yahr skalası ile değerlendirildi. Kemik mineral yoğunluğu (KMY) L1-4 vertebra ve femur boyun bölgelerinden Dual-enerji X-ray absorbsiyometri ile ölçüldü.

***Bulgular:*** Ortalama yaş 64.4±10.2 yıldı. Ortalama hastalık süresi 5.5±3 yıldı. Hoehn Yahr evresi medyan 2 (min-mak: 2-3) idi. Ortalama serum 25(OH)D seviyesi 27,35±9,83 ng/mL idi. Hastaların %54.1'inde D vitamini eksikliği veya yetersizliği vardı. Son 6 aydaki düşme oranı ise %41.7 idi. Düşmeler için medyan değer 1.5 (min-maks: 1-5) idi. Serum 25(OH)D seviyesi ile hastalık süresi, hastalık şiddeti, düşme sayısı ve serum parathormon düzeyi arasında istatistiksel olarak anlamlı negatif korelasyon varken serum 25(OH)D seviyesi ile femur boyun KMY değeri arasında istatistiksel olarak anlamlı pozitif korelasyon bulundu. Çoklu doğrusal regresyon analizi, hastalık süresi ve düşme sayısının serum 25(OH)D düzeyinin önemli belirleyicisi olduğunu ortaya koymuştur. (Düzeltilmiş R2 = 0.54, F = 28.6, p<0,0001).

***Sonuç:*** Bu çalışma, PH olan hastalarda hastalık süresi ve düşme sayısının düşük serum vitamin D düzeyi için temel belirleyiciler olduğunu , serum parathormon seviyesinin ve femur boyun kemik yoğunluğunun düşük serum D vitamini düzeyinden etkilenebileceğini düşündürmektedir.

***Anahtar Sözcükler:*** Parkinson hastalığı; Kemik yoğunluğu; vitamin eksikliği; 25-hidroksivitamin D2; Osteoporoz

## INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease, characterized mainly by tremor, rigidity, decreased mobility, and postural instability, and affected individuals may have physical activity levels lower than 29% (1). The lifelong incidence of PD is 1.3% and 2% in women and men, respectively (2). Prevalence increases with age, with the highest incidence in women aged 75–84 years (3).

In the last few decades serum vitamin D became important for the people with neurological diseases. Relation between PD and low serum vitamin D level is an interesting issue like the chicken or the egg causality. Lv et al. concluded that patients who had vitamin D deficiency had a two fold increased PD risk (4). Conversely, it is thought that high vitamin D values may protect against PD (5).

Serum 25-hydroxyvitamin D (25(OH)D) level and bone mineral density (BMD) are usually decreased in subjects with PD (6-11). Low BMD together with high fall risk frequently causes hip fractures in PD (11-14). Decreased muscle strength and physical activity, dietary factors, low body weight, vitamin D deficiency, and hyperhomocysteinaemia due to the drugs contain levodopa are the factors those responsible from the bone loss in PD (15,16 ). The aim of this study was to investigate the frequency and the factors related with the vitamin D deficiency in ambulatory PD patients.

## MATERIALS AND METHOD

This descriptive study is performed compatible with the rules in "Helsinki Declaration" and approved by the hospital Ethics Committee. Forty-eight (25 women, 23 men) patients with idiopathic PD who were admitted to the outpatient clinic of the Istanbul Physical Medicine and Rehabilitation Training Hospital between 1 November 2008 and 31 May 2009 were included in this study. Inclusion criteria were being ambulatory, >18 years, and Hoehn and Yahr Stage I–III.

Patients on corticosteroid treatment; those with a rheumatic disease with possible secondary osteoporosis, kidney disease, cardiac disease, thyroid disease, Paget's disease, diseases of the endocrine system such as primary hyperparathyroidism or diabetes mellitus, disorders of the gonads or ovaries, or cancer; and those with a previous diagnosis of osteoporosis or who had been previously treated for osteoporosis were excluded from the study.

Disease severity was evaluated by Hoehn and Yahr Scale in the present study. The Hoehn and Yahr scale is a widely used clinical staging scale, which defines categories of motor function in PD. A decrease in the functional capacity is seen as Hoehn-Yahr Stages increase (17). Hoehn and Yahr Scale contains five stages of disease severity. Stage 1 shows unilateral involvement without functional impairment or with minimal functional decline. Stage II indicates midline or bilateral involvement without balance problem. In stage III righting reflexes are impaired associated with balance problem. Stage IV shows higher disease severity in which hard to walk, whereas in stage V the patient becomes bedridden.

BMD measurements of the lumbar spine (L1–L4) and femoral neck region were performed with a dual-energy x-ray absorptiometry (DXA) (GE/Lunar DPX Pro, Madison, WI) device. According to the World Health Organization criteria, the BMD T-score is derived from comparison of the BMD values of young adults of the same gender, and osteopenia is defined as a lumbar spine or femoral neck T-score of between -1.0 and -2.5 and osteoporosis as a T-score of -2.5 or less.

Serum 25(OH)D and intact parathormone (PTH) levels were measured using an immunoassay method. The laboratory reference range for PTH was 16–68 pg/mL. Serum 25(OH)D level of <20 ng/mL was considered as vitamin D deficiency and the values between 20-30 ng/mL was classified as vitamin D insufficiency (18).

Statistical analysis was performed using an SPSS 16 package program. All data were analyzed for normality of distribution using the Kolmogorov–Smirnov test. Continuous variables were summarized as mean±standard deviation (SD). Non-continuous variables were summarized as median (range). Spearman's test was used to analyze the correlations. A correlation coefficient (R) of more than 0.30 and a P-value<0.05 were considered statistically significant. Multiple linear regression (MLR) analysis was performed to detect independent predictors of vitamin D and to determine confounding effects between potentially independent predictors. A stepwise method was used to construct multiple linear regression models. P value <0.05 was considered statistically significant.

## RESULTS

The mean age of patients was 64.15±10.28 years. The mean body mass index (BMI) was 29.45±4.21 kg/m². The mean disease duration was 5.54±3.01 (range 1-14) years. Clinical distribution according to disease severity was as follows: 17 patients with Hoehn Yahr stage I, 22 stage II, and nine stage III patients. Median Hoehn Yahr score was 2 (range 1 to 3).

**Table 1.** Bone mineral density and laboratory findings.

| | |
|---|---|
| L1–L4 BMD (g/cm²) | 1.015±0.170 |
| Femoral neck BMD (g/cm²) | 0.814±0.124 |
| Serum 25(OH)D (ng/mL) | 27.35±9.83 |
| Serum PTH (pg/mL) | 66.73±19.43 |
| Serum calcium (mg/dL) | 9.6±0.984 |
| Serum phosphorus (mg/dL) | 3.02±0.421 |

Data were given as arithmetic mean±standard deviation

Mean BMD values, T-scores, and laboratory data are shown in Table 1. Osteopenia was present in 30 (62%) and osteoporosis in six patients (12%). 25(OH) D deficiency was found in 18 patients (37.5%), whereas 8 (16.6%) had vitamin D insufficiency. Mean serum calcium and phosphorus levels were in the normal range. On the other hand, mean serum PTH level was in the upper limit. There was hyperparathyroidism in 22 patients (45.8%). Falls in the previous six months were reported in 20 patients (41.7%). Median number of falls was 1.5 (range 1-5).

Spearman correlation test revealed a statistically negative correlation between serum 25(OH)D level and disease duration, disease severity, number of falls and serum PTH level. On the other hand, a significant positive correlation was found between serum 25(OH)D and femoral neck BMD. There was no significant correlation between serum 25(OH)D and lumbar BMD (Table 2). Multiple liner regression analysis revealed that disease duration and number of falls, were important predictors of the serum 25(OH)D level (Adjusted $R^2$=0.54, F=28.6, p<0.0001).

However, age, gender, disease severity, and BMI were not significant predictors. The disease duration and number of falls explain only 54% of the variance in serum 25(OH)D level. The negative standardized regression coefficient (Beta) showed an inverse correlation between serum 25(OH)D level and disease duration and number of falls (Table 3).

**Table 2.** Significant correlations between Serum 25(OH)D and other variables.

| | | Disease duration | Disease severity | Number of Falls | PTH | Neck BMD |
|---|---|---|---|---|---|---|
| Serum 25(OH)D | R | -0.575 | -0.421 | -0.700 | -0.816 | 0.402 |
| | *P* | 0.0001 | 0.004 | 0.0001 | 0.0001 | 0.005 |

Spearman correlation test, R: correlation coefficient

**Table 3.** Multiple linear regression analysis for low serum vitamin D level.

| | Standardized Coefficients | t | P | Collinearity Statistics | Autocorrelation Statistics |
|---|---|---|---|---|---|
| | Beta | | | VIF | Durbin - Watson |
| (Constant) | | 18.3 | <0.001 | | |
| Number of falls | -0.506 | -4.5 | <0.001 | 1.252 | 1.93 |
| Disease duration | -0.369 | -3.3 | 0.002 | 1.252 | |

VIF: variation inflation factor

## DISCUSSION

In this study, 54.1% of the patients with PD had vitamin D deficiency or insufficiency. Serum vitamin D levels are usually decreased in PD (4,7,16,19). Patients with PD were suggested to prone as much as two fold increased vitamin D deficiency risk in a previous study (OR: 2.2, 95 % CI: 1.5-3.4) (4). The mean 25(OH)D value in this study was 27.35±9.83 ng/mL, and this result was compatible with that of the previous study in which serum 25(OH)D value was reported as 20.6±6.5 ng/mL (16).

The important finding of the present study was the inverse relation between serum vitamin D level and disease duration, disease severity, number of falls, serum PTH level. A significant positive correlation was also found between serum vitamin D level and femoral neck BMD. Correlation is a bivariate analysis that measures the strengths of association between two variables and the direction of the relationship but not provide which factor is cause or effect (20). Therefore, vitamin D deficiency and related factors in ambulatory patients with PD can be evaluated in two different perspective. One of them is to define predictive factors for low vitamin D level. Another of them is to define factors affected by low vitamin D level.

### Predictive factors for low vitamin D level

We considered that age, gender, body weight or body mass index, disease duration, disease severity, number of falls may be potential predictive factors for the low vitamin D level. The MLR analysis showed that predictors for the low serum vitamin D level were only disease duration and number of falls.

A decreased serum 25(OH)D level accompanied to the patients with higher disease severity and longer disease duration in this study. These results are in accordance with that of the previous studies' (8,21,22). However, MLR analysis showed that disease duration but not disease severity was

a predictive factor for the low vitamin D level in patients with PD. Severe, non-ambulatory patients were not included in this study. For this reason, it can be stated that effects of the disease severity on the low vitamin D level could not be determined in patients with PD.

This study revealed that the fall rate in the previous year was 41.7% in PD. Abou-Raya et al. reported a fall rate of 46% in the last year in a group of patients with PD (7). Falls are common in patients with PD, and falls in the previous year were found as the strongest predictor of future falls in a meta-analysis (23). Therefore, fear of falling may be more prominent in patients with longer disease duration. Because of fear of falling, the outdoors activities may be limited. PD is characterized by decreased mobility, and postural instability (1). Both decreased mobility and postural instability may also limit the outdoor activities. So, the fear of falling, decreased mobility and postural instability lead to decreased sunlight exposure in PD. Finally decreased conversion of vitamin D3 in the skin and decreased renal hydroxylation besides the nutritional problems as in the elderly may result in vitamin D insufficiency or deficiency in PD (24). On the other hand, vitamin D insufficiency may cause increased fall risk because of balance impairment and decreased muscle strength (25). As a result, a vicious circle may develop between vitamin D deficiency and the fear of falling, the decrease in functional capacity.

**Factors affected by low vitamin D level**

In the present study, BMD and serum PTH levels were also measured. We considered that BMD and serum PTH levels may be factors affected by low vitamin D level.

We did not considered as serum PTH level as a predictor for low serum vitamin D level because primary hyperparathyroidism was not included in this study. So, an inverse relationship between serum vitamin D and PTH levels may be explained by secondary hyperparathyroidism due to serum vitamin D level in our patients.

Low serum vitamin D level associated with the low hip BMD in PD patients in this study. Particularly lower hip BMD values were reported in patients with PD (26-29). In a previous study positive relationship was found between the femoral neck BMD and 25(OH)D values in older women whose serum 25(OH) D levels were <30 ng/mL, and it was suggested that the risk of secondary hyperparathyroidism, and consequently the risk of high bone turnover, were prominent in older women with a serum 25(OH)D level of <30 ng/mL (30). In this context, it can be expected a lumbar bone loss induced by secondary hyperparathyroidism and a correlation between 25(OH)D and lumbar BMD. However, no correlation was found between vitamin D and lumbar BMD in the present study.

How can the discrepancy of association between serum vitamin D level and different sites BMD be explained? In some studies lower BMD values for both lumbar spine and hip were declared (8, 22,31,32). It is well known, that the problems as degenerative disease of lumbar spine or abdominal aorta calcification may cause false high BMD values in lumbar region in the elder people. So hip BMD measurement is more important in the older patients with PD as in all the elder people (7,17,33).

Another explanation for discrepancy of association between serum vitamin D level and different sites BMD may be the disease severity. The disease severity was evaluated by using Hoehn and Yahr Scale in the present study. As the mobility decreases, hip BMD reduces as well. Because of the mechanical load of upper body by which the lumbar spine is exposed during sitting, the lumbar BMD may be relatively less affected by the reduction of mobility. Similar results have been noted for the spinal cord injury and multiple sclerosis patients (34-36).

Falls and low femoral neck BMD are both risk factors for the development of fractures, and particularly hip fracture risk is increased in patients with PD (8,27,32,33). Therefore, falling history and

BMD should be evaluated in patients with PD to prevent the fractures.

This study have some limitations. First, the number of subjects included in the study was

relatively small for MLR analysis. A substantial case to predictor ratio should be at least 10 to 1. Second, this is a descriptive study. A longitudinal study can more definitely reveal the predictive factors for low vitamin D level and the factors affected by low vitamin D level.

As a conclusion, more than half of the patients with PD had vitamin D deficiency or insufficiency. This study suggests that disease duration and number of falls are main predictors for low serum vitamin D level, and that serum PTH level and femoral neck BMD may be affected by low serum vitamin D level.

**Conflict of interest**

The authors declare no conflict of interest in respect to this study.

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