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Original Article

Bone mineral density and vitamin D levels in parkinson's disease: A retrospective controlled study

Parkinson hastalığında kemik mineral yoğunluğu ve D vitamini düzeyleri: Retrospektif kontrollü çalışma

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ABSTRACT

Objective: This study aimed to compare bone mineral density and vitamin D levels in patients with Parkinson's Disease (PD) and healthy controls.
Methods: Eighty-six patients aged 60-85, diagnosed with PD and receiving regular medical treatment for the disease were screened. Data for 34 participants (19 women and 15 men) meeting the inclusion criteria were entered into the retrospective analysis. The data for 31 healthy age- and sex-matched participants (18 women and 13 men) were also included. Bone mineral density (BMD) values and vitamin D levels of each participant were recorded.
Results: BMD values for the femoral neck and total hip in the PD group were statistically significantly lower than healthy controls. In addition, T-scores for the femoral neck, total hip, and trochanteric area, and Z-scores for the total hip and trochanteric area were also lower in the patients with PD than in the healthy controls. The two groups did not have significant differences regarding lumbar spinal BMD measurements and T- and Z-score values or vitamin D levels.
Discussion and Conclusion: PD's total hip and femoral neck BMD measurements are low. Further multicenter studies involving larger patient populations are now needed to understand the incidence and mechanisms of osteoporosis in PD.

Keywords: bone mineral density, parkinson's disease, vitamin D

ÖZ

Giriş ve Amaç: Bu çalışmanın amacı, Parkinson Hastalığı (PH) olan hastaların kemik mineral yoğunluğu (KMY) ve D vitamini düzeylerinin sağlıklı kontrol grubu ile karşılaştırılmasıdır.
Gereç ve Yöntem: Bu çalışma amacıyla PH tanısı alan ve hastalığa yönelik düzenli medikal tedavi alan 60-85 yaş arası, 86 hastanın verileri retrospektif olarak tarandı. Dahil edilme kriterlerini karşılayan 34 PH bulunan hasta (19 kadın ve 15 erkek) ve yaş ve cinsiyet uyumlu 31 sağlıklı katılımcının (18 kadın ve 13 erkek) verileri analize dahil edildi. Her katılımcının kemik mineral yoğunluğu (KMY) değerleri ve D vitamini düzeyleri kaydedildi.
Bulgular: PH grubunda femur boyun ve total kalça KMY değerleri sağlıklı kontrollere oranla istatistiksel olarak anlamlı derecede düşüktü. Ayrıca femur boyun, total kalça ve trokanterik bölge için T-skorları, total kalça ve trokanterik alan için Z-skorları PH'lı hastalarda sağlıklı kontrollere oranla daha düşük olarak saptandı. Lomber spinal KMY, T ve Z skor ölçümleri ve D vitamini düzeyleri açısından iki grup arasında anlamlı fark saptanmadı.
Tartışma ve Sonuç: PH'da total kalça ve femur boyun KMY ölçümlerinin daha düşük olduğu ancak lomber spinal ölçümlerin normal popülasyona oranla farklı olmadığı görülmüştür. PH'da osteoporoz insidansı ve mekanizmalarının anlaşılabilmesi için daha geniş çapta ve daha büyük hasta popülasyonlarını içeren, çok merkezli çalışmalara ihtiyaç vardır.

Anahtar kelimeler: kemik mineral yoğunluğu, parkinson hastalığı, D vitamini

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INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive, degenerative movement disorder (1). It was first described in an original paper by James Parkinson titled "An Essay on the Shaking Palsy" in 1817 (2). PD is the second most frequent neurodegenerative disease, increasing with age. Age at onset is generally at 65-70 years, and a prevalence of 1% has been reported among individuals over 60 (3, 4). The progression of PD varies between individuals, but it exerts physical, psychological, and socioeconomic effects over time.

The basic neuropathological finding in PD is degeneration of the dopaminergic neurons in the pars compacta region of the substantia nigra and the presence of Lewy bodies characterized by the aggregation of intracellular α-synuclein in neurons in other parts of the brain. Striatal dopamine loss decreases control over voluntary movements and motor deficits (5). Motor findings such as rigidity, postural instability, gait disorder, and bradykinesia are present throughout the disease and cause a decrease in physical activity and restrictions in daily life activities (6, 7).

Osteoporosis is a disease characterized by a decrease in bone mass and impairment of bone microarchitecture. The risk of brittle bones and fractures increases in osteoporosis (8). While the prevalence rises with age, osteoporosis is particularly seen in postmenopausal women and elderly men (9). Studies have also reported a greater age-related bone loss in PD compared to the normal population (10, 11). Decreased motor control, limitations in physical activities, cognitive and motor disturbances that develop in association with the disease, nutritional disorders, a low body mass index, and malnutrition in PD result in an increased risk of osteoporosis (12). The risk of falls also increases due to osteosarcopenia and diminution in bone mineral density (BMD) associated with PD. Gait and balance disturbances linked to decreased motor control also exacerbate the risk of falls (13, 14). In addition to motor findings, the non-motor findings of PD, including dementia, confusion, sleep disorders, neuropsychiatric disorders, and autonomic nervous system disorders, also contribute to an increased risk of falling (15, 16).

Fracture rates associated with falls are greater in PD than in the non-PD elderly population, and hip fractures resulting from these falls significantly increase mortality and morbidity rates (17). BMD evaluation in PD, the adoption of preventive measures against falls, and treatments aimed at bone mineral loss can prevent fractures and potential complications.

This study aimed to compare BMD and vitamin D levels in patients with PD and healthy controls.

MATERIAL AND METHOD

This cross-sectional, retrospective study was performed in compliance with the Helsinki Declaration. Approval was granted by the Abant Izzet Baysal University Medical Faculty Clinical Research Ethical Committee, Turkey (No. 2021/302).

Participants

The data for patients presenting to the Abant Izzet Baysal University Medical Faculty, Physical Medicine and Rehabilitation Clinic between January 2018 and September 2021 were included in the study. Eighty-six patients aged 60-85, diagnosed with PD and receiving regular medical treatment for the disease were screened. Data for 34 participants (19 women and 15 men) meeting the inclusion criteria were entered into the analysis. Data for 31 healthy age- and sex-matched participants (18 women and 13 men) presenting to our clinic for routine controls and with available BMD measurements were also included.

The inclusion criteria were PD diagnosis and age 60-85. The exclusion criteria were receipt of treatment for osteoporosis or vitamin D replacement within the previous year, a history of disease or medical treatment capable of causing

secondary osteoporosis, a history of a systemic disease capable of affecting bone metabolism, a history of steroid use for longer than three months, or a history of surgery capable of preventing BMD measurement from the hip joint and lumbar region.

Demographic characteristics such as age, sex, body mass index, and occupation were recorded for all participants. Duration of disease, drugs used and clinical characteristics, and Hoehn Yahr Scale and Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) values were recorded for the participants with PD.

Evaluation methods

Hoehn and yahr scale:
The Hoehn and Yahr Scale is a widely used scale consisting of five stages for classifying PD. It permits an objective evaluation of disease progression, from Stage 0 (no disease symptom) to Stage 5 (confinement to bed or wheelchair). All participants in this study were evaluated based on the Hoehn and Yahr Scale (18).

The movement disorder society unified parkinson's disease rating scale (MDS-UPDRS)
This extensive scale is employed for the clinical assessment of the severity of PD. It consists of four sections, including non-motor findings, motor problems, motor findings, and treatment complications. Six of the motor examinations (gait, rigidity, arising from a chair, global spontaneity of movement, postural stability, and posture) in the third section of the scale (0 – normal, or normal, 4- severe) were subjected to analysis in the present study (19).

Laboratory analysis
Data were obtained from peripheral venous blood specimens in the Abant Izzet Baysal University Physical Medicine and Rehabilitation Hospital central laboratory. Vitamin D levels were obtained from biochemical analysis (Architect i1000 SR, Abbott, USA), and all assays were performed according to the manufacturers' instructions.

Bone mineral density measurements
BMD (kg/cm^2) values were retrieved by scanning dual-energy X-ray densitometry (Lunar, Madison, WI USA) measurements performed by an experienced technician. The dual-energy X-ray absorptiometry device was calibrated daily and weekly using appropriate methods. Lumbar spine (L1-L4), neck of the femur, trochanter of the femur, total hip BMD (kg/cm^2) values, T-scores, and Z-scores, were recorded. The T-score is a parameter determined by the bone densitometry system and used to diagnose osteoporosis and in therapeutic decisions. The T-score is obtained by dividing the difference between BMD and measurements from healthy young adult subjects by the population's standard deviation (20). According to the World Health Organization (WHO), T-scores exceeding -1 standard deviation as bone measurement within normal margins, standard deviation between –1.0 and –2.5 as osteopenia, and standard deviation –2.5 or lower as osteoporosis, while the standard deviation of –2.5 or less plus one or more fragility fracture is regarded as severe osteoporosis (21). Z-scores express the mean BMD difference of a measured BMD result from matched controls for the same age, sex, and ethnicity, in the form of standard deviation (22).

Statistical analysis
The study data were analyzed on SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) version 21.0 software. Mean values, standard deviation, median, minimum and maximum values were calculated for all parameters. The tables show descriptive values as number and % frequencies, mean, and standard deviation. Nominal variables were evaluated using the Chi-square test. The Shapiro-Wilk test was first applied to analyze the normality of distribution between the two groups. Two independent t-tests were used to compare the means between the groups for normally distributed data. The non-parametric Mann-Whitney U test was applied to investigate potential intergroup differences in non-parametric variables without normal distribution. The results were evaluated at a 95% confidence interval,

and p values <0.05 were considered statistically significant.

RESULTS

The data for 65 individuals were included in this study, 34 participants with PD and 31 healthy controls. The mean age of the participants was 71.4±6.6 years, 37 were women, and 28 were men. The mean body mass index (BMI) value was 26.4±2.4. The demographic data and clinical characteristics of the participants in the study are summarized in Table 1. No statistically significant difference was observed at the initial analysis regarding age, BMI, or gender (p>0.05).

The lumbar spine, femoral neck, trochanteric area, total hip BMD, T-score, Z-score values, and vitamin D levels of the individuals with PD and healthy individuals are shown in Table 2. Femoral neck BMD values and T-scores were significantly lower in the PD group (p<0.05). Total hip value BMD, T-score and Z-score values were significantly lower in the PD group than in the healthy control group (p<0.05). T- and Z-score values for trochanter measurements were also significantly lower in the PD group compared to the healthy control group (p<0.05). No significant differences were found between the two groups regarding lumbar spinal BMD measurements and T- and Z-score values or vitamin D levels (p>0.05).

Patients with PD were divided into groups based on their Hoehn Yahr stages - G1 (H&Y stages 1-2) and G2 (H&Y stages 3-4). The patients' clinical characteristics and demographic data by groups are shown in Table 3. The mean duration of PD was 6.0±4.1 years. The PD patients' mean MDS-UPDRS part III scores were 21.0±3.9 for G1 and 35.3±3.3 for G2. No statistically significant difference was observed at the initial analysis regarding age, BMI, or gender (p>0.05).

Lumbar spine, femoral neck, trochanteric area, total hip BMD, T- and Z-score values, and vitamin D values for the patients with PD are

Table 1. Characteristics and demographic data in the participant groups.

	PD (n:34)	CG (n:31)	Total (n:65)	p-value
Age				
Mean±SD	71.2±7.4	71.7±5.6	71.4±6.6	0.78
Min-Max	60.0/85.0	62.0/84.0	60.0/85.0	
Gender (%)				
Male	15 (44 %)	13 (42 %)	28 (43 %)	0.85
Female	19 (56 %)	18 (58 %)	37 (57 %)	
BMI				
Mean±SD	24.9±2.4	26.9±2.4	26.4±2.4	0.99
Min-Max	22.0-31.9	21.9-30.9	21.9-31.9	

PD: Parkinson's Disease; CG: Control Group; BMI: Body Mass Index; SD: Standard deviation; Min: Minimum; Max: Maximum; α=0.05

Table 2. Bone mineral density, T-scores, Z scores, and vitamin D status of the PD patients and controls.

	PD (n:34)	CG (n:31)	Total (n:65)	p-value
Lumbar Spine				
BMD	1.00±0.19	1.03±0.12	1.01±0.16	0.499
T score	-1.15±1.62	-0.95±0.90	-1.05±1.30	0.542
Z score	0.06±1.83	-0.01±1.03	0.02±1.48	0.841
Femoral Neck				
BMD	0.77±0.12	0.83±0.11	0.80±0.12	0.032*
T score	-1.82±1.11	-1.32±0.84	-1.59±0.99	0.048*
Z score	-0.15±1.18	0.27±1.01	0.06±1.09	0.116
Total Hip				
BMD	0.83±0.17	0.92±0.11	0.87±0.15	0.015*
T score	-1.70±1.34	-0.88±0.89	-1.32±1.19	0.005*
Z score	-0.54±1.38	0.14±1.01	-0.21±1.24	0.017*
Trochanter				
BMD	0.74±0.25	0.83±0.17	0.78±0.22	0.135
T score	-1.29±1.17	-0.42±0.83	-0.89±1.10	0.001*
Z score	-0.53±1.24	0.25±0.95	-0.15±1.16	0.004*
Vitamin D	16.0 ±5.1	17.7 ±9.2	17.1±8.1	0.161

PD: Parkinson's Disease; CG: Control Group; BMI: Body Mass Index; SD: Standard deviation; Min: Minimum; Max: Maximum; α=0.05

Table 3. Characteristics and demographic data in the PD patients at different stages of H&Y.

	H&Y I, II (n:16)	H&Y III, IV (n:18)	p-value
Age			
Mean±SD	70.1±6.2	72.2±8.4	0.408
Min-Max	61.0/80.0	60.0/85.0	
Gender (%)			
Male	7 (44 %)	8 (44 %)	0.968
Female	9 (56 %)	10 (56 %)	
BMI			
Mean±SD	26.1±2.1	25.7±2.7	0.650
Min-Max	23.3-31.9	22.1-30.1	

H&Y: Hoehn Yahr, BMI: Body Mass Index; SD: Standard deviation; Min: Minimum; Max: Maximum; α=0.05

shown in Table 4. No significant differences were determined between the two groups regarding BMD values, T- and Z-scores, or vitamin D levels ($p>0.05$).

In this study, the prevalence of osteoporosis and osteopenia among the patients with PD was 64.7%, compared to 32.2% among the healthy controls ($p<0.05$).

DISCUSSION

The basic hypothesis in the present study was that BMD measurements would be lower in patients with PD than healthy controls. In the light of that hypothesis, BMD values were compared between patients with PD and healthy controls. The results showed that BMD values for the femoral neck and total hip values in the PD group were statistically significantly lower than healthy controls. In addition, T-scores for the femoral neck, total hip, and trochanteric area, and Z-scores for the total hip and trochanteric area were also lower in the patients with PD than healthy controls.

Various previous studies have reported lower BMD in patients with PD compared to healthy controls. Zhang et al. compared a PD group and a healthy control group and reported significantly lower lumbar spine and femoral neck measurements in patients with PD compared to the control. However, they observed no relationship between Vitamin D levels and BMD measurement (23). Similarly, Öztürk et al. determined significantly lower lumbar spine and femoral neck measurements in patients with PD compared to healthy controls (11). Although the results for the lumbar spine and total hip BMD measurements in the present study are consistent with the previous literature, no significant difference was determined in this research in lumbar spine BMD measurements between the PD and healthy control groups.

Table 4. Comparisons of bone mineral density, T-scores, Z scores, and vitamin D status in PD patients at different H&Y stages.

	H&Y I, II (n:16) Mean±SD	H&Y III, IV (n:18) Mean±SD	p-value
Lumbar Spine			
BMD	0.98±0.20	1.01±0.18	0.677
T score	-1.21±1.8	-1.08±1.43	0.827
Z score	0.14±2.20	-0.01±1.49	0.833
Femoral Neck			
BMD	0.79±0.11	0.74±0.14	0.197
T score	-1.53±1.15	-2.08±0.97	0.136
Z score	0.13±1.19	-0.37±1.08	0.202
Total Hip			
BMD	0.86±0.17	0.79±0.16	0.257
T score	-1.39±1.43	-1.99±1.16	0.188
Z score	-0.26±1.42	-0.81±1.26	0.243
Trochanter			
BMD	0.78±0.28	0.70±0.22	0.413
T score	-1.06±1.27	-1.55±1.06	0.238
Z score	-0.30±1.33	-0.76±1.11	0.283
Vitamin D	16.4 ±5.3	15.1 ±5.0	0.475

H&Y: Hoehn Yahr, BMD: Bone Mineral Density; $\alpha=0.05$

Although dual-energy X-ray absorptiometry is employed as an objective method, the incidence of radiographic osteoarthritis of the lumbar spine in the elderly population may increase higher than expected BMD values. One study reported an incidence of lumbar spondylosis of approximately 76% in stage 2 and above based on the Kellgren/Lawrence (KL) radiological classification (24). Liu et al. investigated the effect on BMD measurements of lumbar spondylosis and osteoarthritis of the hip ark (25). Their findings showed that lumbar osteophytes affected a mean 17% of women and 22% of men, while hip osteophytes affected approximately 2% of women, but no men. Based on these results, the authors concluded that greater attention should be paid to BMD measurements in patients with lumbar spondylosis. Although a decrease in the femoral neck and total hip BMD values was observed in the present study, the absence of any significant difference in lumbar spinal measurements compared to the healthy control group may be attributable to potential osteoarthritis findings.

Kamanlı et al. compared right hand, proximal femur, and spinal BMD values between patients with PD and healthy controls (26). The authors reported lower hand and right femoral neck, but no difference in higher lumbar spine measurements in women with PD than healthy controls. Taggart

et al. compared patients with PD and a control group and observed lower femoral neck and total hip BMD measurements in patients with PD than in the control group (27). The results of these studies are consistent with those of the present research.

Song et al. determined an association between severity of immobility and BMD values compared to patients with PD and healthy controls and reported a greater variability in BMD values in the femoral neck region than the spinal region (28). That study also reported that postural instability played a role in the development of osteoporosis, particularly in the total hip region. They suggested that it may contribute to the development of osteoporosis more than in the spinal region by causing greater immobility in the hip region, which has relatively more joint movement and is employed more actively in walking.

No statistically significant difference was observed in BMD values, and T- and Z-scores in the patients divided into two groups based on disease stages in this study (G1: H&Y 1-2, G2: H&Y 3-4). Results concerning the relationship between disease stage and osteoporosis in the literature are inconsistent. Gao et al. reported significantly low lumbar and femoral measurements in the advanced stages of the disease compared to earlier stages (29). In contrast, Wood et al. determined no significant association between severity of disease in PD and osteoporosis (30). However, they did report an association between the disease duration and severity of osteoporosis. Those authors concluded that prolonged restriction on physical activity in the early stages of the disease might have a greater effect on BMD than severe but shorter duration disease. Song et al. reported that the stage of the disease had no effect on spinal BMD measurements but impacted adversely on femoral neck BMD (28). There may be several reasons for the absence of any association between the severity of disease and the presence of osteoporosis in the present study. BMI values play an important role in the relationship between PD and BMD (31). Since there was no difference in BMI values between the two groups in our study, there may have been no significant difference being detected in BMD. Additionally, lack of information concerning patients' nutrition levels due to the retrospective nature of the study design, and the fact that physical activity levels could not be determined, may have played a contributory role in this.

In addition to affecting calcium homeostasis and bone metabolism, vitamin D is a hormone with receptors in numerous tissues and organs, including the heart and immune system. It regulates vital bodily functions by activating numerous genes with autocrine functions (32, 33). Vitamin D deficiency has been reported to be linked to chronic diseases such as cancer, osteoporosis, diabetes mellitus, cardiovascular diseases, and hypertension, together with neurodegenerative diseases such as PD (34, 35). In addition, various studies have suggested that high vitamin D levels are protective against PD (36, 37).

Studies have reported a higher prevalence of vitamin D deficiency in PD compared to the normal population (10, 38). Factors such as decreased mobilization in PD, a low body mass index, and impaired nutrition affect low vitamin D levels (13). In the present study, no difference was observed in vitamin D levels between the patients with PD and the healthy controls. This may derive from the fact that the PD patients' and healthy controls' nutritional status and levels of exposure to sunlight could not be determined due to the retrospective study design. Since PD is a chronic degenerative disease that increases with age, these patients are routinely followed-up by different branches compared to healthy controls. Patients with PD having taken various multivitamin preparates or nutritional substitutes despite not having received vitamin D replacement therapy in the previous year may account for the absence of any difference between their vitamin D levels and those of the healthy controls. In addition, vitamin D levels may have differed from those expected due to potential gastrointestinal problems that may have been overlooked; if they were not presented to health institutions, they thus

remained undiagnosed. Although lower vitamin D levels have been reported in PD in the literature, some studies have determined no association between vitamin D levels and stage of the disease. Evatt et al. observed a high prevalence of vitamin D deficiency in early-stage PD but reported that no decrease in vitamin D concentrations occurred as the disease progressed (33). Based on these findings, the authors suggested that chronic deficiency may be present before the emergence of PD symptoms and that this may play a role in the pathogenesis of the disease. Further studies are therefore needed to elucidate the relationship with individual, genetic, ethnic, and sociodemographic factors capable of leading to vitamin D deficiency in PD.

The principal limitations of this study are its retrospective design, the low numbers of participants, and the fact that their nutritional status, physical activity levels, and routine habits could not be determined. In addition, the fact that potential diagnoses of osteoarthritis in the lumbar region and hip joint were not excluded may have resulted in different BMD measurements.

In conclusion, total hip and femoral neck BMD measurements and T-scores are low in PD. Further multicenter studies involving larger patient populations are now needed.

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Ethics Committee Approval: The study protocol was approved by the Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee on January 4, 2021 (Ethics committee registration number: 2021/302).

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