Bone mass and vitamin D levels in Parkinson’s disease: is there any difference between genders?

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Abstract. [Purpose] The aim of this study was to determine the bone mineral density, vitamin D level, and frequencies of osteopenia and osteoporosis in patients with Parkinson’s disease and to compare male and female patients with the controls separately. [Subjects and Methods] One hundred fifteen Parkinson’s disease patients (47 males, 68 females; age range: 55–85 years) and 117 age- and gender-matched controls (47 males, 70 females) were enrolled in the study. Bone mineral density measured by dual-energy X-ray absorptiometry and serum D vitamin levels of each participant were recorded. [Results] The mean lumbar spine, femur neck, and total femur bone mineral density levels, T-scores, and vitamin D levels were found to be significantly lower in Parkinson’s disease patients in both genders. Furthermore, osteoporosis rates were found be significantly higher only in female Parkinson’s disease patients compared with female controls. [Conclusion] Data from the present study revealed that while osteoporosis was significantly higher only in female Parkinson’s disease patients, all Parkinson’s disease patients had lower bone mineral density scores and vitamin D levels compared with the controls regardless of gender, suggesting that clinicians should pay attention to the osteoporosis risk in Parkinson’s disease and that adequate preventive measures should be taken in order to limit the future risk due to osteoporotic fractures.

Key words: Parkinson’s disease, Gender, Bone mass

INTRODUCTION

Osteoporosis and Parkinson’s disease (PD) are two chronic diseases among many that can lead to a downward spiral in a patient’s quality of life, and they particularly affect elderly people. Osteoporosis is a systemic and metabolic skeletal disease characterized by increased risk of bone fragility due to a reduction in bone mass and microarchitectural deterioration of bone tissue1–3). PD is a chronic, slowly progressive neurodegenerative disease characterized by symptoms of rigidity, akinesia/bradykinesia, resting tremor, postural instability, and gait disorders. PD affects approximately 2% of the population over 60 years of age4). Recognized as the second most common neurodegenerative disorder after Alzheimer’s disease, PD has a great impact on quality of life, as it significantly affects the ability to carry out daily living activities due to both motor and non-motor symptoms and complications of medical treatment5). PD patients are at increased risk of falling compared with the general population, since they exhibit progressive symptoms such as reduced arm swing and balance and walking problems, especially at later stages of the disease6, 7). As the risk of fall steps up, falls more frequently occur, and the rates of complications from falls such as fracture increase. Indeed, many studies have revealed that fracture risk, hip fracture being the most

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common, is increased in patients with PD\textsuperscript{8–11}. Osteoporosis-related fractures, especially hip fractures, impair quality of life as the independent mobility level worsens, and ultimately, the patient becomes bed-ridden. These fractures can lead to death by the end-stage of the disease\textsuperscript{10, 12}.

Considering these potential negative effects, the importance of osteoporosis and lower bone mineral density (BMD) levels of PD patients are well understood. However, to our knowledge, no studies to date have investigated the BMD, vitamin D levels, and osteoporosis frequency of a PD population by comparing male and female patients with controls separately.

The aim of this study was to compare BMD, vitamin D levels, and osteopenia and osteoporosis rates among male and female patients with PD and controls.

**SUBJECTS AND METHODS**

Patients aged 55–85 years who consecutively admitted to the Movement Disorders Outpatient Clinic of our institute between April 2014 and October 2014 were allocated to the study if their medical treatments were optimized, they were diagnosed with PD according to the UK Parkinson’s Disease Society Brain Bank diagnostic criteria\textsuperscript{13}, and their PD stages were stage 4 or below; that is, they were still able to walk or stand unassisted or benefited from use of only one mobility aid, as per Hoehn and Yahr (H&Y) staging. Stage 5 requires confinement to a bed or wheelchair unless aided. Patients were excluded if they had a history of any chronic diseases that could affect bone metabolism, had a history of lumbar spine and/or proximal femur fractures, had had an arthroplasty, or had been treated with corticosteroids, antiepileptics, bisphosphonates, hormone replacement therapy or vitamin D replacement therapy in the last year.

The participants' body mass indices (kg/cm\textsuperscript{2}) were determined based on demographic data collected from them including their age, gender, height, and weight. Following this, the properties of PD for each patient, such as disease duration and daily levodopa dosages, were recorded. In addition, the PD severity scale was determined for each participant based on the H&Y classification\textsuperscript{14}. Unified Parkinson’s Disease Rating Scale (UPDRS) part III was utilized to assess the severity of the motor symptoms of PD\textsuperscript{15}. If the patients had fluctuations, they were assessed as being in the “ON” state, namely “medicine active”.

The control group was formed from individuals who were admitted to the Musculoskeletal Disorders Outpatient Clinic of our institute during the study interval. Individuals were excluded if they had a history of metabolic bone disease, had a history of lumbar spine and/or proximal femur fractures, had had an arthroplasty, or had been treated with corticosteroids, antiepileptic, bisphosphonates, hormone replacement therapy or vitamin D replacement therapy in the last year.

The institutional ethics committee of our institute approved the study, and signed informed consent forms were obtained from all participants.

The BMD (kg/cm\textsuperscript{2}) of the skeletal sites was measured by a trained X-ray technician using a Hologic QDR-4500A dual-energy X-ray densitometer (Hologic, Bedford, MA, USA). The dual-energy X-ray absorptiometry (DXA) device was calibrated daily and weekly using the appropriated phantom methods. Measurements were made at the following sites: lumbar spine (L1–4), femoral neck, and total hip. The T-scores were calculated. The T-score is defined as the number of standard deviations above or below the mean for the 20- to 40-year-old healthy adult reference population of the same sex and ethnicity. According to World Health Organization (WHO) criteria, osteopenia is diagnosed when a patient’s T-score is between −1.0 and −2.5 standard deviations, and osteoporosis is diagnosed when the T-score is less than or equal to −2.5 standard deviations. The T-scores were calculated using the reference population data.

Fasting (at 8.00–10.00 A.M.) 10 cm\textsuperscript{2} peripheral venous blood samples were collected from the participants, placed in gel-containing tubes, and then centrifuged at 1200 G for 10 min to analyze the serum for 25(OH)D level. A commercial ELISA kit (Immuno-Biological Laboratories, Minneapolis, MN, USA) was used to measure the serum 25(OH)D level, with the normal range being 11.1–42.9 ng/ml. A 25(OH)D level below 20 ng/ml was considered to indicate vitamin D deficiency, one between 20 and 30 ng/ml was considered to indicate vitamin D insufficiency, and one higher than 30 ng/ml was considered to be normal.

Data were presented as means ± standard deviation (SD) or counts (percentages). Group differences of categorical data were analyzed using the $\chi^2$ test. Means were compared using independent t-tests for two groups. Statistical significance was based on a 5% level. Statistical analyses were performed using MedCalc for Windows, version 15.6 (MedCalc Software, Ostend, Belgium).

**RESULTS**

One hundred fifty-two PD patients were assessed for allocation to the study at the Movement Disorders Clinic over the course of seven months. A total of 37 patients were excluded from the study (previously had lumbar surgery and/or total hip replacement surgery (n=14), previously received a medical treatment on account of osteoporosis diagnosis (n=19), or previously had deep brain stimulation surgery (n=4)). The study was performed with the remaining 115 PD patients in the PD group and with 117 age- and gender-matched individuals in the control group. No difference was observed between the PD group and controls according to demographic characteristics (Table 1).

The mean age of PD onset was 67.2 ± 10.2 years for men and 67.1 ± 10.0 years for women. The mean duration of PD was 85.1 ± 62.6 months for men and 58.5 ± 59.9 months for women. The mean levodopa dose was 450.5 ± 214.5 mg/day for men
and 327.9 ± 326.8 mg/day for women. The mean UPDRS part III score was 16.2 ± 8.4 for men and 17.0 ± 9.6 for women.

Table 2 shows the mean BMD, T-scores, and vitamin D levels of the PD patients and controls. The mean BMD was significantly lower in the lumbar spine (p=0.003 for male, p<0.001 for female), femoral neck (p<0.001 for both), and total femur (p=0.004 for male, p<0.001 for female) in both male and female PD patients compared with the controls. Male PD patients’ femoral neck and total hip T-scores were found to be lower than male controls (p=0.012 and p=0.005, respectively). Female PD patients also had lower mean T-scores in the lumbar spine, femoral neck, and total femur (p<0.001 for all). The mean vitamin D levels were significantly lower in both male and female PD patients compared with the controls (p<0.001 for both).

The rates of osteopenia and osteoporosis in the lumbar spine, femoral neck, and total hip of male participants were not statistically different compared with the male controls. However, the osteopenia and osteoporosis rates in female PD patients in the lumbar spine, femoral neck, and total femur were found to be higher compared with the female controls (Table 3). In addition, vitamin D deficiency and insufficiency were identified in 89.4% and 4.3% of the male PD patients and 92.6% and 5.9% of the female PD patients, respectively, which were significantly higher rates than those of their control counterparts (p=0.008 for male, p=0.004 for female) (Table 3).

**DISCUSSION**

There are three primary outcomes of this study: (1) Lumbar spine, femoral neck, and total hip BMD values were lower in the PD patients group, irrespective of gender, than the control group. (2) Higher rates of osteoporosis and osteopenia of the lumbar spine, femoral neck, and total hip were ascertained in female PD patients by comparison with the controls, whereas a significant difference did not exist for these rates between male PD patients and the controls. (3) As weighty factors in the development of osteoporosis, lower vitamin D levels and higher rates of vitamin D insufficiency were found for both male and female PD patients in comparison with the controls.

It was also determined that the BMD levels were higher for the men than the women in both the study group and the control group. This supports the finding that women are more susceptible to lower BMD levels. It was reported that osteoporosis and osteopenia were present in 91% of female PD patients and 61% of male PD patients and that female patients had 7.3% lower BMD levels than their age-matched controls and concordantly 2.6 times the fracture risk. In women, estrogen plays an important role in maintaining BMD. It has been shown that estrogen can promote apoptosis of bone-resorbing osteoclast and can lead to inhibition of osteoclastic bone resorption. The disappearance of a premenopausal
inhibitory effect of estrogen on osteoclastic bone resorption after the postmenopausal stage is a major cause of lower BMD level and higher rates of osteoporosis in women.

Immobilization is a leading factor explaining the decreased bone density and the increased risk of osteoporosis in patients with PD. In particular, immobilization becomes more apparent as the ambulation level reduces with PD progression. Besides, restriction of daily living activities in PD patients and transpiring motor symptoms such as bradykinesia, rigidity, postural instability, and gait disturbance form a basis for immobility. Rigidity can be considered to have a positive impact on BMD. On the other hand, that comes to a deadlock since PD increases muscle weakness and reduces mobility, but decreased mobility increases muscle weakness all the more. Lumbar BMD levels are independently associated with the strength of the trunk muscles rather than trunk rigidity\(^{20}\), whereas the specific cause of muscle weakness is not known in PD\(^{21}, 22\)\(^{26}\). Bone tissue is sensitive to the mechanical environment that it belongs to; that is, bone tissue is constantly exposed to mechanical stimulation by muscle contraction and body movement that applies forces to the bone. In response to mechanical stresses on the bone tissue, osteocytes stimulate bone remodeling by producing molecular signals stimulating osteoblasts and osteoclasts\(^{23}\). Subnormal mechanical stress as a result of reduced mobility leads to bone mass loss depending on duration and dosage. Faster bone loss occurs during early acute immobilization\(^{24}, 25\). Immobilization causing increased bone resorption additively induces hypercalcemia\(^{24}\). Sato et al. analyzed the effect of immobilization-induced hypercalcemia on bone metabolism in PD patients and found that increased serum calcium levels correlated negatively with UPDRS part III, suggesting the presence of immobilization-induced bone resorption with resultant hypercalcemia in patients with PD\(^{25}\). In the present study, the BMD values for the femoral region of interest showed greater statistically significant differences than those for the lumbar spine in the PD patients compared with the controls group. The reason for this might be the decreased downward axial mechanical loading in the femoral region due to decreased mobility\(^{26}\).

Another consideration for low BMD values in PD patients may be hyperhomocysteinemia due to L-dopa treatment. It has been shown that patients with PD have higher serum homocysteine concentrations than controls, while the serum homocysteine levels were found to be independently associated with the BMD of the proximal femur\(^{27}\). Homocysteine can induce differentiation of osteoclasts and apoptosis of osteoblasts\(^{28–30}\); thus, it is rational to infer that PD patients are readily affected by osteoporosis.

Vitamin D deficiency is a major cause of lower BMD levels and a higher risk of osteoporosis and osteopenia in PD patients when compared with controls. The recent studies indicating that PD patients have lower levels of 25(OH)D relative to controls\(^{31–33}\). It has also been demonstrated that a low vitamin D concentration was associated with bone loss\(^{31}\). The prevalence of vitamin D deficiency in PD patients is higher compared with that of patients with Alzheimer’s disease\(^{22}\). This suggests that there is a specific relationship between vitamin D deficiency and PD. Vitamin D has autocrine and paracrine effects in the central nervous system. Calcitriol (1,25(OH)\(_2\)D) can be synthesized in neurons and microglia as a means of activating 1α-hydroxylase. It was suggested that sustained inadequate vitamin D intake leads to a chronic loss of dopaminergic neurons and plays an important role in the pathogenesis of PD\(^{31}\).

| Table 3. Osteoporosis and osteopenia in Parkinson’s disease patients and controls |
|------------------------|-----------------|-----------------|-----------------|-----------------|
| Subjects               | PD (n=47)       | Controls (n=47) | PD (n=68)       | Controls (n=70) |
| Lumbar spine (n, %)    |                 |                 |                 |                 |
| Osteoporosis           | 7 (14.9)        | 5 (10.6)        | 32 (47.1)*      | 15 (21.4)       |
| Osteopenia             | 17 (36.2)       | 17 (36.2)       | 26 (38.2)*      | 33 (47.1)       |
| Normal                 | 23 (48.9)       | 25 (53.2)       | 10 (14.7)*      | 22 (31.4)       |
| Femoral neck (n, %)    |                 |                 |                 |                 |
| Osteoporosis           | 14 (29.8)       | 7 (14.9)        | 39 (57.4)**     | 6 (8.6)         |
| Osteopenia             | 24 (51.1)       | 29 (61.7)       | 19 (27.9)**     | 43 (61.4)       |
| Normal                 | 9 (19.1)        | 11 (23.4)       | 10 (4.7)**      | 21 (30.0)       |
| Total femur (n, %)     |                 |                 |                 |                 |
| Osteoporosis           | 6 (12.8)        | 5 (10.6)        | 16 (23.5)*      | 10 (14.3)       |
| Osteopenia             | 20 (42.6)       | 25 (53.2)       | 38 (55.9)*      | 32 (45.7)       |
| Normal                 | 21 (44.7)       | 17 (36.2)       | 14 (20.6)*      | 28 (40.0)       |
| Vitamin D (n, %)       |                 |                 |                 |                 |
| Deficient              | 42 (89.4)*      | 29 (61.7)       | 63 (92.6)*      | 50 (71.4)       |
| Insufficient           | 2 (4.3)*        | 7 (14.9)        | 4 (5.9)*        | 12 (17.1)       |
| Sufficient             | 3 (6.4)*        | 11 (23.4)       | 1 (1.5)*        | 8 (11.4)        |

PD: Parkinson’s disease
*p<0.05; **p<0.001
Vitamin D status is a significant factor of skeletal integrity, and inadequate serum 25(OH)D level is correlated with weakness of muscles and increased incidences of falls and related fractures[34]. It can be concluded that vitamin D deficiency in PD patients may result in decreased BMD values and increased risk of osteoporosis. Immobilization-induced hypercalcemia can cause suppression of 1,25-(OH)2D in the kidney by partially inhibiting parathyroid hormone secretion[25]. Furthermore, sunlight deprivation due to immobilization may also lead to vitamin D deficiency in patients with PD[35]. This study showed that vitamin D levels both in male and female PD patients were lower compared with those of the controls. The study elucidates that all PD patients regardless of gender have high vitamin D deficiency and insufficiency rates.

Malnutrition is a quite common problem, specifically in patients with an advanced stage of PD. Hand-eye coordination disorders, dysphagia, intestinal hypermotility, depression, cognitive deficits, and the side effects of antiparkinsonian medications increases the risk of malnutrition. The reduction in BMI due to malnutrition may produce negative effects on BMD in the case of axial loading, although the present study could not observe any differences in BMI for either gender between PD patients and the control group. Additionally, regarding reduced BMD, a lower body fat content has also been found to be associated with lower estriol secretion in women[16]. Also, malnutrition adversely affects the stability of vitamin D, and it results in deficiency of folic acid and vitamin B12, which leads to increased homocysteine.

To the best of our knowledge, this is the first case-control study on BMD scores, vitamin D levels, and osteoporosis in PD patients that has separately compared male and female groups with controls. Nevertheless, it has several limitations. Firstly, H&Y stage 5 patients were not included in the study; that is, the negative impact of stage 5 disease on BMD was avoided. In connection with this, higher rates of osteoporosis and osteopenia might have been ruled out. Secondly, it was not a population-based study. Patients and controls were enrolled from outpatient clinics. Therefore, the osteopenia and osteoporosis rates, as well as vitamin D levels, could be different from those of the general population. Thirdly, we did not collect data about dietary habits (e.g., smoking, alcohol consumption, or receipt of a vitamin D-fortified diet), activities of daily living, and amount of sunlight exposure, which might affect vitamin D levels and BMD scores.

The main finding of this study was that all the PD patients had lower BMD levels, both in the lumbar and femoral regions, compared with the controls regardless of gender. In addition, the frequency of osteoporosis was only higher in female PD patients. Consequently, screening for osteoporosis is needed as part of evaluations of patients diagnosed with PD in order to establish preventive measures to limit the future risk due to osteoporotic fractures, which may reduce quality of life and even increase mortality.

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