Observational Study

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2024, Vol. 52(3) 1–9

DOI: 10.1177/03000605241237880
journals.sagepub.com/home/imr

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Bone involvement in the early stages of Parkinson's disease: a case–control study

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Abstract

Objective: To evaluate the qualitative and quantitative alterations of bone tissue in patients with early-stage Parkinson's disease (PD) and to measure the associations between bone mineral density (BMD), trabecular bone score (TBS) and physical performance.

Methods: This case–control study enrolled patients with early-stage PD and age-matched controls. BMDs for the left femoral neck (L-FN) and lumbar spine (LS) were measured. Bone microarchitecture for the LS was determined using TBS. Muscle performance was assessed using the short physical performance battery (SPPB). Patients and controls were stratified in two groups based on the SPPB score: a poor performance group (SPPB score ≤ 8) and high performance group (SPPB > 8).

Results: This study included 26 patients: 13 in the PD group and 13 age-matched controls. The mean $\pm$ SD BMD results in the PD group were: L1–L4 BMD $= 0.935 \pm 0.183$ g/cm^2; L-FN BMD $= 0.825 \pm 0.037$ g/cm^2; with bone microarchitecture degraded in four patients and partially degraded in three patients. TBS was significantly different in the patients with PD stratified according to SPPB. Among the controls, there was a significant difference in body mass index between the two SPPB groups.

Conclusion: TBS might identify bone involvement earlier than BMD in the initial stages of PD.

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Keywords
Bone mineral density, bone quality, Parkinson disease, trabecular bone score, physical performance

Date received: 27 June 2023; accepted: 21 February 2024

Introduction

Parkinson's disease (PD) is a common neurodegenerative movement disorder that results from the progressive loss of dopaminergic neurons in the basal ganglia.[1] PD has an overall estimated prevalence of 0.3%.[2] It is clinically characterized by both motor, such as rest tremor, bradykinesia, rigidity and postural instability; and non-motor symptoms such as depression, sleep disorders and autonomic disturbances, which increase disability and decrease quality-of-life in this population.[3] Among the non-motor complications in patients with PD, low bone mineral density (BMD) frequently occurs, with a 2.2-fold increased risk of fractures, compared with age- and sex-matched controls.[4] Moreover, in this population, postural instability and gait impairment strongly contribute to a high risk of falling;[5] and both low BMD and falls are predictive factors for fracture risk in this population.[6,7] Currently, the gold standard for the diagnosis of osteoporosis and fracture risk assessment is BMD measurement using dual-energy X-ray absorptiometry (DXA), which provides quantitative bone parameters only, without any information about bone quality and architecture. However, the trabecular bone score (TBS), an instrumental tool that reflects bone microarchitecture, improves fracture risk prediction in post-menopausal women, older men and in patients with secondary osteoporosis, such as those with type 2 diabetes mellitus.[8–10] Considering the high risk of fracture in people with PD, an assessment of bone health is mandatory, although specific guidelines fail to properly address this issue.[11,12] Despite the well-known skeletal fragility in people with PD at advanced stages, bone involvement in the early stages of PD has been poorly investigated.

Therefore, the aim of this study was to evaluate the qualitative and quantitative alterations of bone tissue in patients with early-stage PD and to measure the associations between BMD, TBS and physical performance in the same population.

Patients and methods

Patient population

This cross-sectional case–control study enrolled consecutive patients with PD in the Department of Medical and Surgical Specialties and Dentistry, University of Campania 'Luigi Vanvitelli', Naples, Italy between January 2019 and March 2019. The inclusion criteria for the case group were as follows: (i) a modified Hoehn & Yahr score ≤ 2 (early stages of PD);[13] (ii) absence of a history of fragility fracture. The exclusion criteria for the case group were as follows: (i) significant comorbidities (i.e. cardiovascular or cerebrovascular disease, renal or hepatic insufficiency); (ii) individuals unable to understand and sign informed consent. The control group consisted of age-matched patients referred to the outpatient rehabilitation service of the University of Campania 'Luigi Vanvitelli', Naples, Italy for a bone health screening through DXA examination for primary prevention of osteoporosis who were recruited during the same time period.

All patient data were de-identified to ensure patient privacy.[14] All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki of 1975 as revised in 2013 (Ethical Committee of the University of Campania 'Luigi Vanvitelli'; Committee's reference number: protocol number 412, approved on 30 May 2018). This study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[15]

Data collection

Data collected included demographic, anthropometric and anamnestic characteristics such as age, sex, body mass index (BMI) and disease duration. The following instrumental and functional outcomes were assessed: (i) BMD of the lumbar spine (LS) and left femoral neck (L-FN), measured using a GE Lunar iDXA system (GE Healthcare Biosciences, Piscataway, NJ, USA); (ii) TBS was determined using TBS iNsight^{TM} software (GE Healthcare Biosciences); (iii) muscle performance was determined using the short physical performance battery (SPPB) and the patients in each study group were stratified into the following performance groups: a poor performance group (SPPB score ≤ 8; group A1 in patients with PD and group A2 in control patients) and a high performance group (SPPB > 8; group B1 in patients with PD and group B2 in control patients). The primary outcome of the study was to compare the qualitative and quantitative data of patients with early stage PD and controls within the performance group.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean $\pm$ SD and categorical variables as n (%). Distribution of all variables was tested using the Shapiro–Wilk test. After applying Levene's test for variance, intergroup comparisons were made using Wilcoxon Mann–Whitney U-test for independent variables. A P-value < 0.05 was considered statistically significant.

Results

This case–control study included 26 patients: 13 in the PD group (seven males, six females) and 13 age-matched controls (three males, 10 females). There were no significant differences in the demographic and clinical characteristics between the two groups (Table 1). The DXA analysis and SPPB scores of the PD and control groups are presented in Tables 2 and 3, respectively. Four patients in the PD group already presented degraded microarchitecture (TBS < 1.200) and three patients had partially degraded microarchitecture

Table 1. Demographic and clinical characteristics of patients with Parkinson's disease (PD) ($n = 13$) and healthy control subjects ($n = 13$) that were enrolled in a case–control study to investigate the qualitative and quantitative alterations of bone tissue in patients with PD at the early stages.

Characteristic	PD group $n = 13$	Control group $n = 13$
Age, years	65.77 $\pm$ 6.11	65.38 $\pm$ 8.08
BMI, kg/m^2	27.60 $\pm$ 3.86	27.47 $\pm$ 4.97
Sex		
Male	7 (53.85%)	3 (23.08%)
Female	6 (46.15%)	10 (76.92%)
Disease duration, years	4.2 $\pm$ 1.2	NA

Data presented as mean $\pm$ SD or n of patients (%).
All variables were normally distributed. No significant between-group differences ($P \geq 0.05$); Wilcoxon Mann–Whitney U-test.
BMI, body mass index; NA, not applicable.

Table 2. Dual-energy X-ray absorptiometry (DXA), trabecular bone score (TBS) and short physical performance battery (SPPB) score of patients with Parkinson's disease (PD) ($n = 13$) that were enrolled in a case–control study to investigate the qualitative and quantitative alterations of bone tissue in patients with PD at the early stages.

Bone parameter	BMD, g/cm^2	T-score	
L1–L4	0.935 ± 0.183	-0.67 ± 0.34	
L-FN	0.825 ± 0.037	-1.62 ± 1.04	
TBS for overall PD group (1.311 ± 0.39)	TBS < 1.200	$1.200 <$ TBS > 1.350	TBS > 1.350
	4 (30.8%)	3 (23.1%)	6 (46.2%)
TBS for SPPB performance groups	TBS < 1.200	$1.200 <$ TBS > 1.350	TBS > 1.350
Group A (SPPB ≤ 8) ($n = 5$)	4 (80.0%)	0 (0.0%)	1 (20.0%)
Group B (SPPB > 8) ($n = 8$)	0 (0.0%)	3 (37.5%)	5 (62.5%)

Data presented as mean $\pm$ SD or *n* of patients (%).
BMD, bone mineral density; L-FN, left femoral neck.

Table 3. Dual-energy X-ray absorptiometry (DXA), trabecular bone score (TBS) and short physical performance battery (SPPB) score of healthy control subjects ($n = 13$) that were enrolled in a case–control study to investigate the qualitative and quantitative alterations of bone tissue.

Bone parameter	BMD, g/cm^2	T-score	
L1–L4	1.180 ± 0.165	-0.10 ± 2.54	
L-FN	1.002 ± 0.15	-0.35 ± 1.21	
TBS for overall control group (1.280 ± 0.13)	TBS < 1.200	$1.200 <$ TBS > 1.350	TBS > 1.350
	2 (15.4%)	5 (38.5%)	6 (46.2%)
TBS for SPPB performance groups	TBS < 1.200	$1.200 <$ TBS > 1.350	TBS > 1.350
Group A (SPPB ≤ 8) ($n = 9$)	1 (11.1%)	5 (55.6%)	3 (33.3%)
Group B (SPPB > 8) ($n = 4$)	1 (25.0%)	0 (0.0%)	3 (75.0%)

Data presented as mean $\pm$ SD or *n* of patients (%).
BMD, bone mineral density; L-FN, left femoral neck.

($1.200 <$ TBS > 1.350) (Table 2), while two patients in the control group had degraded microarchitecture and five had partially degraded microarchitecture (Table 3). When comparing patients with PD according to their physical performance level (SPPB score ≤ 8 versus SPPB score > 8), there was a significant difference for TBS ($P = 0.0063$) (Table 4). In the control group, the only significant difference between the two subgroups was for BMI, with the subgroup with an SPPB score ≤ 8 having a significantly higher BMI than the subgroup with an SPPB score > 8 ($P = 0.034$) (Table 5).

Discussion

Patients with PD that have a modified Hoehn & Yahr score > 2.5, which represents a moderate-to-severe functional impairment, have a reduced BMD compared with the general population.[4] These current data show that TBS, a parameter of bone quality (microarchitecture), might be an earlier predictor of bone involvement than BMD in PD patients with a modified Hoehn & Yahr score ≤ 2 (early stages of PD). In the PD group, the BMD and T-score values were not of clinical significance, which was in contrast to the

Table 4. Comparison of bone mineral density (BMD), trabecular bone score (TBS) and demographic characteristics of patients with Parkinson's disease (PD) ($n = 13$) stratified according to their short physical performance battery (SPPB) score.

	Group A SPPB ≤ 8 $n = 5$	Group B SPPB > 8 $n = 8$
Age, years	66.78 ± 5.40	65.12 ± 6.80
BMI, kg/m^2	26.58 ± 5.01	28.24 ± 3.16
Duration of PD, years	4.09 ± 1.24	4.51 ± 1.41
L1–L4 BMD, g/cm^2	1.06 ± 0.21	1.15 ± 0.11
L-FN BMD, g/cm^2	0.82 ± 0.14	0.82 ± 0.13
TBS	1.18 ± 0.10	1.38 ± 0.10[a]

Data presented as mean $\pm$ SD.
All variables were normally distributed; [a]$P = 0.0063$ for between-group comparison; Wilcoxon Mann–Whitney *U*-test.
BMI, body mass index.

Table 5. Comparison of bone mineral density (BMD), trabecular bone score (TBS) and demographic characteristics of control subjects ($n = 13$) stratified according to their short physical performance battery (SPPB) score.

	Group A SPPB ≤ 8 $n = 9$	Group B SPPB > 8 $n = 4$
Age, years	67.01 ± 7.93	61.75 ± 8.22
BMI, kg/m^2	29.49 ± 4.02	22.92 ± 3.96[a]
Duration of PD, years	NA	NA
L1-L4 BMD, g/cm^2	1.22 ± 0.21	1.03 ± 0.13
L-FN BMD, g/cm^2	0.93 ± 0.14	0.77 ± 0.09
TBS	1.25 ± 0.15	1.29 ± 0.12

Data presented as mean $\pm$ SD.
All variables were normally distributed; [a]$P = 0.034$ for between-group comparison; Wilcoxon Mann–Whitney *U*-test.
BMI, body mass index; PD, Parkinson's disease; NA, not applicable.

deterioration in bone quality that was suggested by the degraded or partially degraded TBS results. These findings may support the importance of TBS as a crucial risk factor for bone architecture. This is in contrast to a previous study that investigated the role of TBS in osteoporosis diagnosis in men with moderate-to-severe PD, which reported a significantly higher TBS in comparison with the control group (people without PD).[16]

The pathogenesis of bone loss in people with PD remains to be clarified. These current findings might support the hypothesis that the early bone microarchitectural alteration is due to dopaminergic depletion as well as L-DOPA supplementation. Indeed, it has been recently demonstrated in a mouse model that dopaminergic neuron degeneration leads to earlier bone loss than motor dysfunction.[17] This suggests that the dopaminergic system may play a role in regulating bone metabolism through both gonadal steroid hormone-dependent and -independent mechanisms; dopaminergic depletion may lead to hyperprolactinaemia, resulting in sex steroid deficiency and secondary osteoporosis.[17] Moreover, L-DOPA administration might reduce bone formation rate and increase serum homocysteine (Hcy), leading to bone loss. Higher levels of Hcy enhance osteoclastogenesis through an oxidative mechanism and matrix metalloproteinase activation mediated by mitochondria, inducing bone matrix degradation; at the same time, Hcy plays a role in the vascular network-mediated decrease in bone blood flow, impairing normal bone growth and repair.[18]

Recent evidence shows that the autonomic nervous system, including dopaminergic signalling, plays an important role in the regulation of bone metabolism.[19] In particular, dopamine seems to inhibit osteoclast differentiation via the dopamine receptor 2 (D2R)/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/cAMP-response element binding protein (CREB) pathway.[20] Activation of D2R induces second messengers, such as cAMP, to modulate PKA activity in order to phosphorylate

the transcriptional factor CREB.[20] These events trigger a cascade of osteoclast marker gene expression resulting in the inhibition of osteoclastogenesis.[20] Nevertheless, dopamine receptors are expressed in osteoblasts with a hypothesized role in cellular proliferation and mineralization that open up future scenarios for enhancing bone regeneration in several conditions, such as bone healing and peri-implant bone loss.[21] In addition, it was documented that the administration of L-DOPA increases bone fragility, presumably depending on high serum levels of Hcy that seems to be toxic for both osteoclasts and osteoblasts causing bone damage in PD patients receiving this drug.[21] The optimization of L-DOPA treatment as well as the administration of antioxidants and vitamin B (i.e. B6, B9 and B12) might be useful to prevent bone loss in this population.[22]

To date, it remains unclear whether pharmacological treatments for osteoporosis effectively reduce risk of fractures in patients with PD.[23] However, among the available antiresorptive treatments, zoledronic acid, an ammino-bisphosphonate, shows more promising results, particularly in terms of treatment adherence in this population, as reported by the TOPAZ study.[24] Regarding other therapeutic strategies, including denosumab, a monoclonal antibody that inhibits osteoclast maturation by binding to receptor activator of nuclear factor κ B ligand (RANKL), anabolic agents such as parathyroid hormone-related protein analogues (teriparatide and abaloparatide) and dual-action drugs such as romosozumab, a monoclonal antibody sclerostin inhibitor, these have demonstrated efficacy in improving bone density and in reducing risk of fragility fractures in people affected by osteoporosis.[25,26] However, it should be noted that denosumab and romosozumab seem to reduce the risk of falls by 20% in the general population, but otherwise only limited evidence is available about the effectiveness of these drugs in PD patients.[27,28]

Several studies investigated the prevalence of osteoporosis in PD, typically including patients with worse Hoehn & Yahr scores compared to the current population.[22–29] A previous study found a high prevalence of bone loss in patients with PD at the early stages based on quantitative parameters (i.e. BMD); reporting osteopenia and osteoporosis in 41.4% and 11.8% of patients, respectively.[30] However, the study did not provide any information about qualitative parameters of bone tissue. Nonetheless, it is well known that BMD is of limited use in assessing bone fragility, considering that this method does not investigate bone quality.[31] TBS is a texture parameter that provides useful information that is not captured from the standard DXA measurement of BMD. TBS is strongly supported by clinical and scientific evidence that makes it an attractive instrumental approach to enhance fracture risk stratification,[8,32,33] particularly in patients with secondary osteoporosis, such as those with PD. A previous study that investigated the role of TBS in osteoporosis diagnosis in men with moderate-to-severe PD reported a significantly higher TBS in comparison with the control group (people without PD).[16] The TBS appears to predict the risk of fractures and detrimental bone quality earlier than BMD, even in other neurodegenerative disease. A cross-sectional study investigated the bone health in a cohort of patients with amyotrophic lateral sclerosis and reported degraded and partially degraded values in over 65% of the patients despite normal BMD values.[34]

The originality of this current study was that it investigated for the first time the bone quality of patients with early stage PD. As the current results show, the TBS scores in patients with PD were significantly different according to the physical

performance status based on SPPB scores; with lower a TBS in the subgroup with a lower SPPB score despite them having a normal BMD value. This might suggest that an evaluation of bone quality might be an earlier predictor of bone alterations in patients with early stage PD. The same comparison in the control group did not result in a significant difference in TBS between the two SPPB subgroups. These findings might support the association between muscle performance and bone impairment in patients with early stage PD.[35] This correlation is commonly observed in other neurodegenerative disorders, such multiple sclerosis (MS), where individuals often experience a decrease in bone strength and muscle function.[36] However, in patients with MS, TBS does not seem to be affected when compared with a reference population, suggesting that only BMD is reduced in these patients, rather than bone microarchitecture.[36]

This current study had several limitations. First, the study included a small sample size. Secondly, possible selection bias might have resulted from poorly defined risk factors, cross-sectional study design and confounding factors such as different disease-specific therapies (e.g. L-DOPA) or physical activity levels reported at baseline.

In conclusion, the findings of this current study suggest that TBS might identify bone involvement earlier than BMD in the initial stages of PD. Despite the limitations and preliminary nature of these current findings, they suggest that a complete bone assessment including TBS should be provided since the early management of osteoporosis based on an improved estimation of bone fragility should reduce the risk of fractures in patients with PD.

Acknowledgement

The authors acknowledge Dr Matteo Bertone who contributed to the data collection.

Author contribution

A.M., S.L. and G.I. contributed to the conception and design of the paper; A.M. and F.G. contributed to the methodology; S.L., Fi.G. and M.P. performed the data analysis; S.L. and Fi.G. wrote the original draft of the manuscript; A.M., G.B. and F.G. reviewed the second draft of the manuscript; F.G. and G.I. contributed to the study supervision. All authors contributed to manuscript revision and read and approved the submitted version.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

This research received no specific grant from funding agency in the public, commercial, or not-for-profit sectors.

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