Assessing Bone Health and Fracture Risk in Parkinson's Disease: Is Bone Mineral Density Enough?

Parkinson's disease (PD) is the fastest-growing neurodegenerative disorder worldwide. The projected number of patients with PD may cross 17 million by 2040, blaringly ringing the alarm for the "Parkinson pandemic."[1] Falls are one of the major causes of disability in these patients. PD patients tend to fall twice more often compared with their peers, ascribed to various motor and non-motor issues such as freezing, postural instability, dyskinesia, executive cognitive dysfunction, sleep disorders, autonomic impairment, psychosis, use of antidepressants and neuroleptics, lower limb sensory loss, and muscle weakness.[2,3]

Repeated falls in PD culminate in recurrent fracture and poor quality of life. Compared to the general population, patients with PD have reduced bone mineral density (BMD) resulting in osteopenia, osteoporosis, and substantial increase in fracture risk, particularly of the hip.[4] A large retrospective cohort study using the UK General Practice Research Database highlighted twice the risk of overall fractures and thrice the risk of hip fracture in PD.[5] The Gestational Weight Gain and Optimal Wellness (GLOW) study, conducted across North America, Europe, and Australasia, found PD to have the strongest association with the risk of fractures, among all other comorbidities.[6] Furthermore, the consequences of hip fracture in PD are worse in terms of prolonged hospital stay, higher incidence of pressure sores, and more wheelchair dependency at 30 days.[7] Although ongoing trials are targeting at prevention of fall risk in PD, assessment and improvement of bone health in PD to prevent osteoporosis and fracture risk are often uncared for.

The pathophysiology of osteoporosis in PD is multifactorial involving vitamin D deficiency (nutritional or related to malabsorption) and secondary hyperparathyroidism, immobilization, sarcopenia, alteration in pituitary–hypothalamic neuroendocrinal axis, levodopa-induced hyperhomocysteinemia, and altered bone remodeling through enhanced adrenergic signaling due to autonomic dysfunction or levodopa use.[8,9] *In vitro* studies have shown elevated prolactin, accelerated osteoclastogenesis, and suppressed osteoblastic bone formation in neurotoxin-induced dopaminergic degeneration.[10] Dopamine agonists themselves can inhibit osteoclast differentiation, decrease osteoblastic mineralization capacity, and alter bone remodeling by acting on the dopamine receptors present in these bone cells.[9,10]

To study such microstructural alterations of bone homeostasis and fracture risk in PD, there is an unmet need to reappraise the existing techniques. The assessment of BMD through dual-energy X-ray absorptiometry (DEXA) for calculating T-score (in comparison with young reference population) and Z-score (about age-matched controls) is commonly used in this regard. However, BMD is inadequate for measuring three-dimensional bone density, bone strength, and discriminatory ability for fractures. PD patients are often elderly and have degenerative spine changes that can depict falsely high BMD values.[11] Defining osteopenia or osteoporosis by an absolute numerical cutoff in T-scores and Z-scores is controversial as well. DEXA devices themselves have inherent problem of accuracy and linearity in calculating these scores.[12] Thus, BMD as a standalone tool to determine bone health and fracture risk prediction in PD is often fallacious. Apart from that, studies evaluating osteoporosis using BMD have mostly been done in female subjects. However, bone health analysis is equally important in male patients, more so in PD where the disease itself has male preponderance.

To obtain a more comprehensive assessment of bone microstructural alteration in Indian male PD patients, in comparison with that of age and body mass index (BMI)-matched controls, a study published in this issue of the journal has incorporated two newer parameters in addition to BMD—(1) trabecular bone score (TBS): a densitometric tool to analyze pixel gray-level variations in the lumbar spine DEXA image and (2) hip structural analysis (HSA): a tool to assess geometric parameters of proximal hip joint such as cross-sectional area (CSA), cross-sectional moment of inertia (CSMI), section modulus (Z), and buckling ratio (BR) at three sites—narrow neck, intertrochanteric region, and femoral shaft.[13] CSA, CSMI, Z, and BR indexes determine the resistance of the bone to axial forces, bending forces, and local cortical buckling. This is the first Indian study to evaluate these DEXA-derived parameters in PD patients, apart from bone biochemistry.

In accordance with the previous studies, this study noted that vitamin D deficiency was more prevalent in patients with PD compared with controls and significantly lower BMD in the subgroup of more severe parkinsonism. These emphasize the higher risk of osteoporosis in PD as discussed earlier and the importance of vitamin D supplementation in these patients to prevent fall and fracture risk.

Intriguingly, the study captured significantly lower TBS and higher BR at the narrow neck and intertrochanteric region in PD patients compared with controls, while no significant difference was noted in BMD at the femoral neck or lumbar spine. Previously, studies from China and Ukraine have also failed to reveal any significant difference in mean BMD at the lumbar spine and femoral neck in male PD patients, pointing to the need for more detailed analysis to get access to bone microstructure.[14,15] TBS is a texture index used to measure bone microarchitecture related to three-dimensional bone

characteristics such as trabecular number, trabecular separation, and connectivity density.[16] Thus, low TBS in PD patients reflects weak, fracture-prone microarchitecture. However, BR is an index of cortical instability measured by the ratio of the outer radius to cortical thickness.[17] Higher BR in these patients indicates greater instability and more susceptibility to local cortical buckling under compressive loads.

To conclude, though BMD can grossly show the severity of osteoporosis in PD, it would not be prudent to apply BMD as a sole measure for bone microstructural assessment. For an in-depth evaluation of bone quality and three-dimensional geometry, emerging tools such as TBS and HSA should be utilized more commonly in clinical practice. Early capturing of alteration in bone microstructural milieu in patients with PD will enable the clinician to take therapeutic interventions to improve bone health, and this will not only prevent the risk of fall and fracture; in the long run, it will also improve the overall quality of life.

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References

1. Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. J Parkinsons Dis 2018;8:S3-8. doi: 10.3233/JPD-181474.
2. Contreras A, Grandas F. Risk of falls in Parkinson's disease: A cross-sectional study of 160 patients. Parkinsons Dis 2012;2012:1-10. doi: 10.1155/2012/362572.
3. Schrag A, Choudhury M, Kaski D, Gallagher DA. Why do patients with Parkinson's disease fall? A cross-sectional analysis of possible causes of falls. NPJ Parkinsons Dis 2015;1:15011. doi: 10.1038/npjparkd. 2015.11.
4. Torsney KM, Noyce AJ, Doherty KM, Bestwick JP, Dobson R, Lees AJ. Bone health in Parkinson's disease: A systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2014;85:1159-66.
5. Pouwels S, Bazelier MT, de Boer A, Weber WE, Neef C, Cooper C, *et al*. Risk of fracture in patients with Parkinson's disease. Osteoporosis Int 2013;24:2283-90.
6. Dennison EM, Compston JE, Flahive J, Siris ES, Gehlbach SH, Adachi JD, *et al*. Effect of co-morbidities on fracture risk: Findings from the global longitudinal study of osteoporosis in women (GLOW). Bone 2012;50:1288-93.
7. Walker RW, Chaplin A, Hancock RL, Rutherford R, Gray WK. Hip fractures in people with idiopathic Parkinson's disease: Incidence and outcomes. Mov Disord 2013;28:334-40.
8. van den Bos F, Speelman AD, Samson M, Munneke M, Bloem BR, Verhaar HJJ. Parkinson's disease and osteoporosis. Age Ageing 2013;42:156-62.
9. Figueroa CA, Rosen CJ. Parkinson's disease and osteoporosis: Basic and clinical implications. Expert Rev Endocrinol Metab 2020;15:185-93.
10. Handa K, Kiyohara S, Yamakawa T, Rutherford R, Gray WK. Bone loss caused by dopaminergic degeneration and levodopa treatment in Parkinson's disease model mice. Sci Rep 2019;9:13768. doi: 10.1038/s41598-019-50336-4.
11. Pors Nielsen S. The fallacy of BMD: A critical review of the diagnostic use of Dual X-ray absorptiometry. Clin Rheumatol 2000;19:174-83.
12. Garg M, Kharb S. Dual energy X-ray absorptiometry: Pitfalls in measurement and interpretation of bone mineral density. Indian J Endocrinol Metab 2013;17:203. doi: 10.4103/2230-8210.109659.
13. Sooragonda BG, Sridharan K, Benjamin RN, Prabhakar AT, Sivadasan A, Kapoor N, *et al*. Do bone mineral density, trabecular bone score and hip structural analysis differ in Indian men with Parkinson's disease? A case-control pilot study from a tertiary centre in southern India. Ann Indian Acad Neurol 2023;26:496-501.
14. Lam K, Li M, Mok V, Hui A, Woo J. A case control study on bone mineral density in Chinese patients with Parkinson's disease. Parkinsonism Relat Disord 2010;16:471-4.
15. Povoroznyuk V, Bystrytska M, Grygorieva N, Karaban I, Karasevich N. Bone mineral density, TBS, and body composition indexes in Ukrainian men with Parkinson's disease. Parkinsons Dis 2019;2019:1-7.
16. Rajan R, Cherian K, Kapoor N, Paul T. Trabecular bone score—An emerging tool in the management of osteoporosis. Indian J Endocrinol Metab 2020;24:237. doi: 10.4103/ijem.IJEM_147_20.
17. Anitha D, Lee T. Assessing bone quality in terms of bone mineral density, buckling ratio and critical fracture load. J Bone Metab 2014;21:243. doi: 10.11005/jbm.2014.21.4.243.

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