CHAPTER THIRTY

Osteoporosis: A Hidden Nonmotor Face of Parkinson's Disease

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Abstract

Osteoporosis is a "hidden nonmotor face" of Parkinson's disease and a cause of considerable morbidity in the older general population and in Parkinson's disease patients. Some regard this as a "hidden epidemic." Women are overrepresented and have considerable problems related to osteoporosis. In general osteoporosis leads to reduced mobility aggravating the motor syndrome of PD. The nonmotor aspects and impact of osteoporosis in PD have remained unexplored. Possible nonmotor consequences include a range of pain syndromes related to local pain, fractures, falls, and injuries as well as pathological fractures and radiculopathy. In addition depression, sleep dysfunction, dementia, as well as fear of falling also complicate the clinical picture. Quality of life deteriorates both for the patient and career. Pathways of care do not always include assessments for osteoporosis and needs to become obligatory particularly in older female PD patients. Active management strategies then need to be undertaken for osteoporosis in PD. Related motor and nonmotor consequences also highlight the importance of multidisciplinary treatment in PD particularly when dealing with osteoporosis.

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1. INTRODUCTION

In Parkinson's disease (PD), osteoporosis represents a hidden nonmotor symptom with motor and nonmotor consequences. Wood and Walker (2005) have referred to this as a "hidden epidemic." It is known that PD patients run a higher risk of falls because of the progression of PD (postural instability). In many such cases fractures complicate the falls and may be related to underlying osteoporosis (Wood & Walker, 2005). PD patients have lower bone mineral density (BMD) values in comparison to both age- and sex-matched individuals who do not have PD (Invernizzi, Carda, Viscontini, & Cisari, 2009; Malochet-Guinamand, Durif, & Thomas, 2015; van den Bos et al., 2013) conferring susceptibility to osteoporosis. In addition various comorbidities complicate the clinical scenario and the skeletal makeup in PD which include loss of bone mass (BM) and osteoporosis (Invernizzi et al., 2009; van den Bos et al., 2013; Wood & Walker, 2005). Falls, fractures, and also pathological fractures related to osteoporosis lead to a range of secondary nonmotor symptoms (NMS) such as pain of various types as well as depression, anxiety, and sleep disorders. These will be discussed in this chapter.

Osteoporosis is a bone disease and is defined as a bone density of 2.5 standard deviations (SD) below that of a young adult, measured by dual-energy X-ray absorptiometry (DEXA) at the hip (Table 1). A value on DEXA below the 2.5 SD is considered as osteopenia. This definition is based on World Health Organization (WHO) classification as shown in Table 1.

Vitamin D deficiency plays a key role in the pathogenesis of osteoporosis, and the role of vitamin D status is particularly important in PD because it reduces BMD (Wood & Walker, 2005). Supporting this concept is the fact that treatment with bisphosphonates, vitamin D, and calcium can increase BMD and reduce fractures in PD patients. Hypovitaminosis D has been correlated with an increased risk of falls and fractures (Broe et al., 2007). In a study by Evatt et al. (2008) vitamin D insufficiency was noted to be significantly more frequent in PD patients than in age-matched healthy controls and patients with Alzheimer's disease (AD). Vitamin D insufficiency was reported in 55% of PD, 36% of age-matched healthy controls, and 41% AD patients. The greatest decrease of BMD in patients is found in the lumbar spine as well as the femoral neck with advanced stages of the PD affliction. This is aggravated by low calcium intake and sunlight exposure (Invernizzi et al., 2009; Malochet-Guinamand et al., 2015; van den Bos

Table 1 The WHO Definition of Osteoporosis
WHO Definition of Osteoporosis Based on BMD

Classification	BMD	T-Score
Normal	Within 1 SD of the mean level for a young-adult reference population	T-score at −1.0 and above
Low bone mass (Osteopenia)	Between 1.0 and 2.5 SD below that of the mean level for a young-adult reference population	T-score between −1.0 and −2.5
Osteoporosis	2.5 SD or more below that of the mean level for a young-adult reference population	T-score at or below −2.5
Severe or established Osteoporosis	2.5 SD or more below that of the mean level for a young-adult reference population	T-score at or below −2.5 with one or more fractures

BMD, bone mineral density. T-score = measurement unit that compares a person's bone density with what is normally expected in a healthy young adult of the same sex, using standard deviations.

et al., 2013). Gender differences in reporting NMS of PD have also been shown (Wood & Walker, 2005), and studies indicate that the female gender is an independent predictor of osteoporosis in PD.

Vitamin D has been shown to have effects on mesencephalic neurons and protects these from insults causing neurodegeneration in vitro and reduces the effects of 6-OH-dopamine (Raglione, Sorbi, & Nacmias, 2011). In addition, vitamin D is involved in genetic regions closely associated with PD such as the promoter region of glial cell line-derived neurotrophic factor (GDNF) and neurturina regulating the expression of GDNF and tyrosine hydroxylase. An association between VDR gene polymorphism, PD, and vitamin D-binding protein has been recently identified and has been suggested as a potential biomarker (Raglione et al., 2011).

In PD patients there is a higher prevalence of insufficiency or reduction of 25(OH)D compared to AD patients or healthy controls (Evatt et al., 2008). Inadequate sun exposure and inadequate dietary intake could explain this condition, but it is not clearly understood whether hypovitaminosis D is a factor influencing the genesis of Parkinsonism or if PD itself leads to hypovitaminosis D.

Studies suggest numbers of mechanisms could contribute to loss of BD occurring in PD patients (Malochet-Guinamand et al., 2015). There is a correlation with BM and the weight and body mass index (BMI). One study

(Malochet-Guinamand et al., 2015) reported after age adjustment of the women in their study of osteoporotic Fractures revealed a 7.3% lower BMD than other women. Analysis via a multivariate methodology revealed the PD women had a markedly lower BMD with 2.1% than the other women in the study. This was after the weight adjustment among other criteria. Also body weight explained 72% of the BMD difference between the PD group and the control group.

Osteoporosis and osteopenia related to PD is thought to be the direct and indirect result of several factors as listed below (Invernizzi et al., 2009):

- Female gender
- Vitamin D deficiency
- Reduced exposure to sunlight
- Low body weight
- Nutritional status
- Vitamin B12 and folate deficiency
- Hyperhomocysteinemia (due to reduced vitamin B12 and folate or L-Dopa treatment)
- PD duration and severity
- Immobility and reduced BM
- Decreased muscle strength
- Other neuroendocrinal status (increased serum concentration of under-carboxylated osteocalcin)

1.1 Osteoporosis and Other NMS of PD

Osteoporosis and osteopenia are common in PD particularly the older population. Increasing life expectancy in PD and prolonged survival underpin the increased prevalence of osteoporosis in older PD. The prevalence figures of osteoporosis rises from 0.6% in those aged 65–69 years to approximately 3% in those older than 80 (Bezza, Ouzzif, Naji, et al., 2008). Broadly women are more susceptible and figures suggest a rate of 91% in women and 61% in men (Invernizzi et al., 2009). Little data exist in relation to secondary NMS that may be related to osteoporosis in PD. It is known that long-term chronic conditions such as osteoarthritis and osteoporosis may act synergistically with aging-related nonmotor issues such as progressive loss of vision as well as hearing (Melton and Riggs (1985). With superimposition of impaired balance and reflexes the overall risk factor for injury following seemingly minor traumatic mechanisms in the older patient becomes more

evident. This factor may explain the high rates of falls and fractures in older PD. Many of these patients experience a rage of NMS as a result, either acutely in the hospitalized state or chronically at home (e.g., depression). Wood and Walker (2005) reported a statistically significant link with increasing age and depression as assessed by the geriatric depression score. These patients also had a higher Hoehn and Yahr score, and gait and balance abnormality. A summary of studies reporting falls and fractures is shown in Table 2 (adapted from Invernizzi et al., 2009)

A range of NMS occur in PD as a direct or indirect consequence of osteoporosis (Table 3). These depend on the severity of osteoporosis as well as the mobility status of the patient. For instance, fractures can cause local or radicular pain; however, a severe fall in an elderly PD may lead to hospitalization. Many such patients would suffer from the trauma of the fall as well as acute hospitalization-related problems which often are nonmotor in nature (neuropsychiatric and sleep dysfunction). Respiratory and urinary infections related to underlying immobility could in turn also trigger neuropsychiatric as well as sleep problems (Table 3). An additional aspect is that in female PD high doses of levodopa secondary to intrajejunal infusion therapy may precipitate nutritional deficiencies which could cause hyperhomocysteinemia. The latter is considered a risk factor for osteoporosis.

1.2 Why PD Patients Are More at Risk of Osteoporosis?

A review by Malochet-Guinamand et al. (2015) revealed that Parkinson's patients experience a measurable reduction of BMD compared to the age-matched controls. Several variables operate to lead to reduced BMD and bone strength in PD (Fig. 1). These include metabolic and pharmacological issues such as levodopa treatment (high dose in particular), nutritional status which affects body weight and homocysteine levels and vitamin D status (exposure to sunlight is a key issue). Other variables that contribute to reduced BMD in PD are mechanical problems such as muscle strength, low physical exercise, decreased mobility and immobility in some cases. These factors are shown in Fig. 1 (taken from van den Bos et al., 2013).

Bone densities have been shown to be different between white Caucasian south Asian and black African subjects (Zengin et al., 2016). However, there are no such studies in PD particularly related to ethnic differences and bone density, antiosteoporotic medications are mainly biphospohonates.

Table 2 Studies Reporting Falls, Bone Mineral Density, and Fractures in a Series of Reports in PD

Authors	Type	Number of Subjects and Sex	Outcome Measures	Results
Stalenhoef, Diederiks, Knottnerus, Kester, and Crebolder (2002)	PCS	311, age > 70 CD	Falls, falls injuries	33% fell; 45% fall-related injuries
Dargent-Molina et al. (1996)	PCS	7575 W, age ≥ 75	BMD fem neck DEXA, self-reported physical capacity, neuromuscular function, mobility, visual function, medications	154 first hip fracture
Fink et al. (2005)	PCS	5995 CD M, age 65, 0.9% PD	BMD hip and spine DEXA and QCT	Risk of multiple future falls OR = 2.91, CI [95%] = 1.55–5.46
Taylor et al. (2004)	PCS	6.787 CD W, age 66	BMD hip DEXA number of hip fractures	602 (8.9%) hip fracture
Woodford and Walker (2005)	PCS	246 PD patients	Emergency hospital admissions of PD patients over a 4-year period	Falls and fractures were, respectively, the first and eighth cause of hospital admission
Koller, Glatt, Vetere-Overfield, and Hassanein (1989)	RCS	100 PD patients (61 M, 39 W)	Frequency, circumstances, consequences of falling	38%—falls; 17 patients—fall-related fractures (4 hip fractures)
Wielinski, Erickson-Davis, Wichmann, Walde-Douglas, and Parashos (2005)	RCS	1092 PD patients	Number of falls within the past 2 years, related injuries	55.9%—1 fall in the past 2 years; 65.0%—injury; 33.0%—fracture
Johnell, Melton, Atkinson, O'Fallon, and Kurland (1992)	RCS	138 PD patients, 138 ASMC	Record of hip fractures	59% PD vs 44% AMSC ($P < 0.002$)

Genever, Downes, and Medcalf (2005)	RCS 200	39 PD patients, 200 AMSC	Record of fracture at any body site	PD 15% vs AMSC 7.5%; $P=0.007$
Lorefalt, Toss, and Granerus (2007)	PCS	26 PD, 26 AMSC	BMD hip and total body (including head) DEXA	BMD of total body, hip, neck is decreased in PD patients ($P<0.05$)
Taggart and Crawford (1995)	PCS	51 PD, 51 AMSC	BMD spine, hip DEXA	PD hip BMD < 10% AMSC ($P=0.014$)
Kao, Chen, Wang, Chia, and Yeh (1994)	PCS	22 PD patients, 22 AMSC	Spine BMD DEXA	BMD PD < AMSC
Sato, Kaji, Tsuru, and Oizumi (2001)	PCS	115 PD patients	BMD 2nd Met CXD	Low BMD alone is an important risk factor for hip fracture in PD patients
Yamada, Kachi, and Ando (1995)	PCS	82 PD patients, 99 ASMC	Spine BMD DEXA	Spine BMD is lower in PD than in control
Ishizaki, Harada, Katayama, Abe, and Nakamura (1993)	PCS	70 PD patients, 46 ASMC	BMD MSXP	Osteopenia 26 (59%) of the 44 PD F, 5 (19%) of the 26 PD M, 6 (24%) of the 25 AMSC F, 2 (9%) of the 21 AMSC M
Wood and Walker (2005)	X-sect	105 PD patients	Hip and spine BMD DEXA	63% W osteoporotic; 28% W osteopenic; 20% M osteoporotic; 41% M osteopenic
Bezza et al. (2008)	PCS	52 PD patients, 52 ASMC	BMD hip, spine, Dexa X-ray, osteocalcin, CTX, PTH	9 PD (17.3%) osteoporotic; 28 PD (53.8%) osteopenic
Kamanli, Ardicoglu, Ozgocmen, and Yoldas (2008)	PCS	24 PD patients, 31 ASMC	BMD spine, fem neck, Ward, troch, bilat hands DXA	PD F BMD bilat hands and fem neck < BMD AMSC ($P<0.05$)

Continued

Table 2 Studies Reporting Falls, Bone Mineral Density, and Fractures in a Series of Reports in PD—cont'd

Authors	Type	Number of Subjects and Sex	Outcome Measures	Results
Di Monaco, Vallero, Di Monaco, Tappero, and Cavanna (2006)	CCS	56 hip fracture, 28 PD, 28 ASMC	BMD tot fem, fem neck, troch, intertroch, Ward (unfractured femur) DXA	T-score did not differ significantly between PD patients and AMSC
Di Monaco, Vallero, Di Monaco, Tappero, and Cavanna (2008)	PCS	38 PD hip fracture, 38 AMSC hip fracture	BMD tot fem, fem neck, troch, intertroch DEXA	BMD lower in PD troch fractures than cervical fractures ($P=0.028$)
Schneider et al. (2008)	PCS	8105 CD W, 73 PD	Fem neck, tot fem BMD DEXA, number of fractures, BMI	Mean tot fem BMD was 7.3% lower in PD group. PD patients had a 2.6-fold higher age-adjusted risk for incident hip fracture
Yamanashi et al. (2005)	PCS	714 fractured patients	Second hip fracture, age, gender, fracture type, cognitive impairment, comorbidities, medical conditions	45 second hip fractures; no significant difference in the incidence of second hip fracture as to gender or age; increased risk of a second hip fracture was associated with senile dementia and PD

2nd Met, 2nd metacarpal bone; *ASMC*, age–sex-matched controls; *bilat hands*, bilateral hands; *BMD*, bone mineral density; *BMI*, body mass index; *CCS*, case–control study; *CD*, community-dwelling; *CTX*, C-telopeptide; *DEXA*, dual energy X-ray absorptiometry; *F*, female; *fem neck*, femoral neck; *intertroch*, intertrochanteric; *M*, male; *MSXP*, multiple scanning X-ray photodensitometry; *PCS*, prospective cohort study; *PD*, Parkinson's disease; *PTH*, parathyroid hormone; *RCS*, retrospective cohort study; *tot fem*, total femur; *troch*, trochanter; *W*, women; *X-sect*, cross-sectional.

Adapted from Invernizzi, M., Carda, S., Viscontini, G. S., & Cisari, C. (2009). Osteoporosis in Parkinson's disease. *Parkinsonism and Related Disorders, 15*(5), 339–346. doi:10.1016/j.parkreldis.2009.02.009.

Table 3 Bone Status, Osteoporosis and PD, and Consequent Direct or Indirect Nonmotor Symptoms

PD and Osteoporosis	Nonmotor Symptoms
Decreased BMD	Local and radicular pain, posture-related pain
Fractures	Local pain
Fractures with immobility (hospitalized patient)	Secondary infection (respiratory and urinary) Neuropsychiatric complications (hallucinations, delirium) Sleep dysfunction (insomnia and confusional states)
Osteoporosis in older subjects Severe pain related to osteoporosis	Depression, anxiety
Female patient on intrajejunal levodopa infusion and osteoporosis	Nutritional deficiency triggering hyperhomocysteinemia

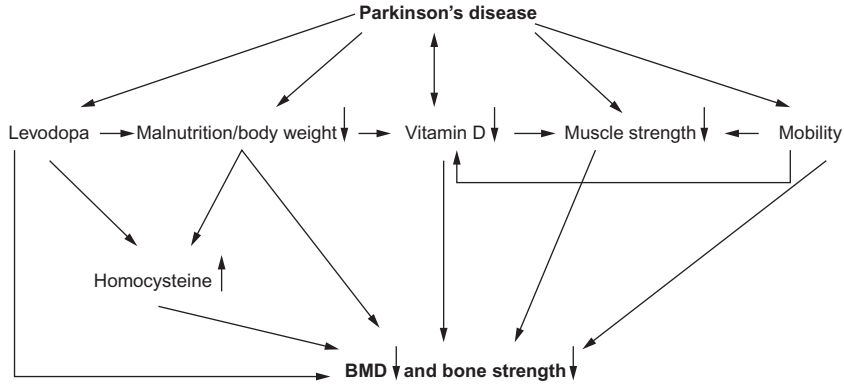

Fig. 1 Bone and Parkinson's disease. *BMD*, bone mineral density.

2. DIAGNOSIS AND TREATMENT

Screening for osteoporosis in PD should be a quality standard in clinic which would enable appropriate therapeutic interventions to be initiated (van den Bos et al., 2013). All patients with PD should be evaluated for clinical risk factors like thyroid disease, gonadal hormone deficiency, risk of falls, immobilization, inadequate activity, smoking, and alcohol intake (Fig. 2). Screening for vitamins D, B12, folic acid, calcium, thyroid function, and

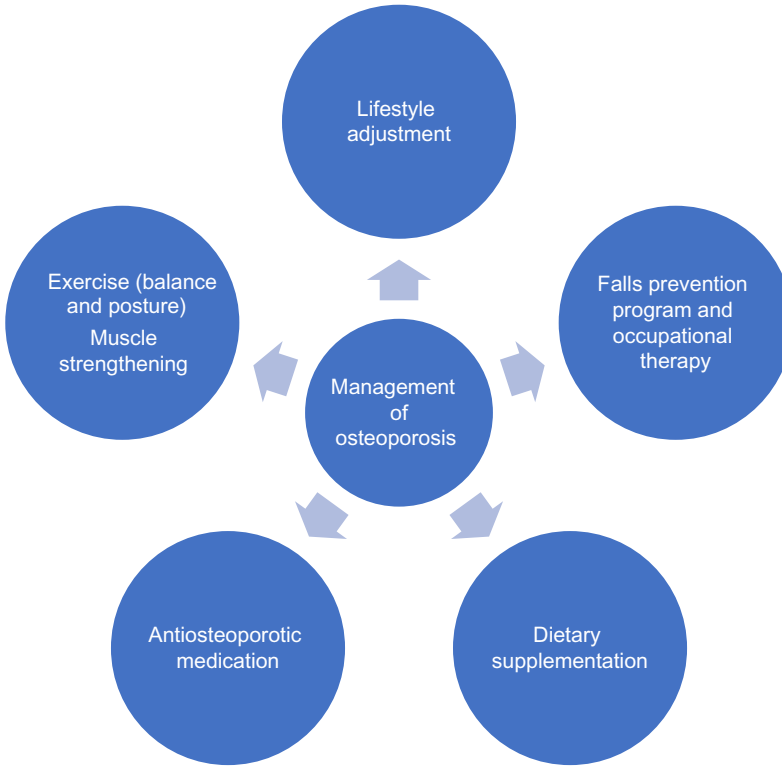

Fig. 2 A summary of the various enablers of a successful osteoporosis management programme for Parkinson's disease.

parathormone levels should be done on a regular basis (Invernizzi et al., 2009; Malochet-Guinamand et al., 2015; van den Bos et al., 2013).

Radiological diagnosis of osteoporosis is based on BMD test. BMD test measures bone density at the spine and at the hip for the PD patient. Another tool called FRAX has been recently developed to evaluate fracture risk of patients (Kanis, Johnell, Oden, Johansson, & McCloskey, 2008). FRAX is based on individual patient models that integrate the risks associated with clinical risk factors as well as BMD at the femoral neck. Whether this will be effective in PD is unknown.

There are no specific guidelines related to management of osteoporosis and PD. Broadly treatment needs to be started with a combination of biphosphonates combined with vitamin D and ensuring a regular intake of calcium containing food or supplements. Fig. 2 shows the other important aspects for a holistic management of osteoporosis in PD.

Treatment with medications is mainly based on DEXA (T score < -2.5) and FRAX scores (10-year risk for fracture >3% hip, >20% of any major osteoporotic fracture). Mainly two types of pharmacological treatments are available to treat patients with osteoporosis. Antiresorptive agents which prevent bone loss and preserve architecture, improve quality of bone, reduce the risk of vertebral fractures. Biphosponates have been studied for osteoporosis in PD and risedronate in men with PD was studied in 121patients in a 2-year, randomized, double-blind, placebo-controlled trial. Risedronate (2.5 mg) and ergocalciferol (1000 IU) daily were compared with ergocalciferol (1000 IU) alone as well as placebo (Sato, Honda, & Iwamoto, 2007). BMD improved in the risedronate group and overall reduced the relative risk of hip fracture by 0.33 (95% confidence interval: 0.09–1.2). In another study, benefit with 17.5 mg risedronate and ergocalciferol over ergocalciferol and placebo in elderly PD patients was reported by the same authors. Another biphosphonate, aledronate was reported to reduce the relative risk of hip fractures in a study in PD by 0.29 (95% confidence interval: 0.10–0.85) (Sato, Iwamoto, Kanoko, & Satoh, 2006). Although some have criticized these studies for the absence of use of DEXA at hip for BMD measurement, the data indicate that biphosphonates are useful for osteoporosis in PD and should be used. Zoledronic acid and denosumab (monoclonal antibody) have also been reported to reduce the risk of nonvertebral and hip fractures. Anabolic agents have also been tried, and rhPTH [1–34] (teriparatide) increases bone density and size, improves quality of bone, and reduces the risk of vertebral and nonvertebral fractures especially for advanced PD patients. When swallowing is a issue parenteral treatment options like monoclonal antibody (denosumab, 60 mg subcutaneous injection) every 6 months and the anabolic teriparatide daily subcutaneous injections have been shown to be beneficial (Neer et al., 2001).

Dietary and nutritional manipulation is important, and vitamin D, B12, and folate status need to be addressed and corrected if required. One study has shown that folate supplementation and vitamin B12 in levodopa-treated PD patients may prevent bone loss and hyperhomocysteinemia (Malochet-Guinamand et al., 2015), the latter a risk factor for osteoporosis. Vitamin K is another nutritional factor that may cause carboxylation of gamma-carboxyglutamic acid-rich residue related to types of bone proteins such as osteocalcin. Vitamin K supplementation improved metacarpal BMD of PD patients aged 65 and older in a small controlled study with a mean 5-year follow-up (Malochet-Guinamand et al., 2015).

Lifestyle-related management approach is related to addressing risk factors such as smoking and excessive alcohol consumption. Smoking needs to be stopped while alcohol intake needs moderating. Exercise is to be encouraged as it is believed this helps strengthening specific affected area of the body as well as muscle strength and balance improvement which reduced risk of falls (Fig. 2). However, this concept is not strictly evidence based. Falls prevention program is an important aspect of management of PD patients with osteoporosis, and these fracture risk reduction programs are aimed at reducing the number and severity of falls. In the elderly, falls prevention program consists of correcting decreased visual acuity, reducing alertness, and balance altering medications. Occupation therapy input is required for improvement of home environment (slippery floors, creating space and familiarization with furniture, insufficient lighting, handrails, bathroom, and kitchen adaptations). Behavioral adaptations include avoiding multitasking and taking time while attempting to stand (orthostatic hypotension may complicate).

3. CONCLUSIONS

Osteoporosis is a relatively underexplored nonmotor aspect of PD but with major functional consequence. The pathophysiology is a little unclear, and patients with PD have a lower BMD than an age-matched control population. Frequent falls complicate PD and reduced BM leads to increased fracture risk with consequent morbidity and mortality. The bone loss itself is multifactorial and is contributed to by a combination of immobility, vitamin D deficiency, hyperhomocysteinemia, poor nutritional state, and muscle weakness. Treatment with bisphosphonates, calcium, and a close input from occupational therapist is important to manage osteoporosis in PD as is an effective falls prevention program.

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