

# Osteoporosis and Parkinson's disease

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## Summary

**Parkinson's disease (PD) and osteoporosis are two conditions with a quite high prevalence in older people. From the literature we learn that in parkinsonian people there is a major reduction of Bone Mass Density (BMD) compared to age-matched controls. A low BMD is one of the factors related to fracture's frequency in PD patients besides an increased risk of falls. From the standpoint pathophysiology, various factors are involved in osteoporosis: immobilization, endocrine factors like hypovitaminosis D, nutritional and iatrogenic factors.**

**Considering morbidity and mortality related to fractures in old people and in particular in PD patients it is reasonable that these patients would undergo to vitamin and BMD measuring, to fall risk assessment and that all preventive measure are implemented to reduce the risk of fractures. Possible interventions are essentially based on fall prevention and treatment of osteoporosis. Randomized clinical studies in the literature, in which it was studied the effect of anti-osteoporotic drugs in patients with MP showed a significant reduction in the number of fractures and increase BMD.**

*KEY WORDS: Parkinson's disease; osteoporosis; fracture; fall, vitamin D.*

## Introduction

Parkinson's disease (PD) and osteoporosis are two conditions affecting a substantial portion of the elderly population; they have a significant socioeconomic impact, caused by increased hospitalization and drug utilization (1). PD is a chronic, progressive neurodegenerative disorder characterized by tremor, muscular rigidity, slowness of movement, and postural imbalance (2). Osteoporosis is a pathology with multi-factorial etiopathogenesis, characterized by an abnormal reduction of the bone mass, as well as micro-architectural alterations of the bone which becomes fragile and more exposed to the risk of fractures (3).

## Fractures and osteoporosis among Parkinson's disease: epidemiology and risk factors

Recent advances in diagnosis and treatment have prolonged survival in elderly patients with Parkinson's disease with consequently increasing prevalence with age, rising from 0.6% in those aged 65–69 years to nearly 3% in those older than 80 (4).

In elderly population predictors of fall-related hip fracture are slower gait speed, reduced visual acuity, small calf circumference, neuromuscular and visual impairments, as well as femoral-neck bone mineral density (BMD) (5,6). According to literature, factors increasing the risk of falls in PD patients are older age, longer disease duration, worse Hoehn and Yahr stage, bradykinesia, rigidity, gait disturbances, postural instability (7), atypical parkinsonism and dementia (8). Falls increase fracture risk (5, 6, 9) and are the most common reason for emergency hospital admissions in PD patients (10).

From the literature it emerges an association between PD and lower bone mineral density (BMD), which, if present, could affect PD patients' fracture risk independent of the risk attributable to falls. Several studies found low BMD values in patients with PD, even if not all studies have used the same method of assessment or the World Health Organization (WHO) definitions (4).

In a prospective study, Yamada et al. found that among the women, lumbar spine BMD was significantly lower in the patients than in the controls, and the decrease was greater in the subgroup with more advanced disease (11).

Taggart and Crawford reported that BMD at the femoral neck was decreased by 12% in the group with PD as compared to the control group. BMD decreases more severely in women, at femoral neck and lumbar spine (12).

Kao et al. measured lumbar spine BMD in PD patients divided into subgroups based on the Hoehn and Yahr stage and on disease duration: they found that PD patients had lower BMD than controls and that bone loss was related to higher Hoehn and Yahr stage. Longer disease duration (>10 years) was not associated with lower BMD (13).

Ishizaki et al. found osteopenia in 59% of the women and 19% of the men with PD as compared to only 24% and 9% in the control group. Among women with PD, osteopenia was associated with a more severe Hoehn and Yahr stage (14). However, neither the BMD cut-off used to define osteopenia nor the BMD measurement site are specified in the study report.

Sato et al. found that the strongest risk factors for femoral fractures were low Body Mass Index (BMI), low 25-OH-vitamin D (with high PTH), and low BMD. Both disease duration and Hoehn and Yahr stage were significantly associated with low BMD only when the variables correlated with BMD were taken into account (15).

An interesting finding from this study is the decrease in sunlight exposure, 25-OH-vitamin D, and BMD in patient groups. Decreased 25-OH-D levels caused by insufficient sun exposure, even if may be an explanation for low BMD, does not cause an osteoporosis on tissue level. However, the results of previous studies tend to support the concept that vitamin D status is an important factor of skeletal integrity mainly in situation of vitamin D deficiency. Low vitamin D levels were also found in another study conducted by the same group in which low exposure to sunlight was more common in the group with advanced disease (16).

The finding of the study of Wood and Walker is that over three quarters of all the PD patients analyzed, mostly women, had abnormal bone density. No correlation was found between the severity of PD according to Hoehn and Yahr stage and BMD, while duration of disease and BMD reduction were related (17).

Fink found a higher risk fractures in PD patients compared to control group even if this value is adjusted for history of multiple falls (18).

Di Monaco et al. found a negative correlation between BMI, duration and severity of disease, and BMD. The same authors also demonstrated that lower BMD was associated with more severe osteoporosis and that in PD patients the type of hip fracture (cervical vs trochanteric) was related to BMD (19).

Bezza and coworkers showed that BMD was lower in PD patients than in controls; according to the WHO criteria, they showed that more than half of a group of relatively "young" patients with PD have low BMD (osteopenia or osteoporosis) (4).

All the published studies confirm that patients with PD are at high risk for low BMD which highly contribute to increase the risk for fractures.

A number of other risk factors for fractures have been identified: advanced disease, low BMI, limited exposure to sunlight, and low vitamin D intake (with decreased 25-OH-vitamin D levels and secondary hyperparathyroidism). Some of these factors probably also contribute to the risk of falls (20-23).

### Pathophysiology

Several factors have been proposed including direct control of the central nervous system on bone metabolism and endocrine factors.

Immobilization is a known determinant of osteopenia, however the exact pathophysiology of this phenomenon is not clear (1). Immobilization leads to hypercalcaemia due to high bone turnover and re-absorption and this increased calcaemia suppresses 1- $\alpha$ -hydroxylation of 25-(OH)D in the kidney (24). Another important factor correlated with immobilization is sunlight deprivation, which may result in 25-(OH)D deficiency (16).

About the endocrine factors, their role in PD has not been completely determined. There are some data indicating the presence of a hypothalamic disturbance in patients with idiopathic PD with lower concentrations of growth hormone (GH), adrenocorticotrophic hormone and cortisol compared to age-matched controls (1). Another important endocrine factor implied in osteoporosis in PD is vitamin D metabolism.

There is increasing evidence about the role of vitamin D in central nervous system (CNS) functions. Recently many observations indicated that this vitamin is synthesized directly by the CNS with controlling and neuro-protective effects. Vitamin D receptors (VDRs) are largely distributed in the embryonic brain and in the adult brain are mostly expressed in the temporal, orbitarian and cingulated cortex, in the thalamus, in the nucleus accumbens, in the amigdala, in the olfactive system and in the in substantia nigra. It has been demonstrated that vitamin D controls neurotrophic factors and neuronal plasticity processes and it has neuro-protective actions (25).

Vitamin D protects mesencephalic neurons from Parkinson-like injuries *in vitro* and reduces the effects of 6-OH-dopamine. Vitamin D acts in many genetic regions highly associated with Parkinson's disease, like promoter region of glial cell line-derived neurotrophic factor (GDNF) and neurturina, and regulates the expression of GDNF and tyrosine hydroxylase. It has been reported an association between VDR gene polymorphism and Parkinson's disease and vitamin D binding protein has been recently identified as a biomarkers in the cerebrospinal fluid in parkinsonian patients. In Parkinson's disease patients there is a higher prevalence of insufficiency or reduction of 25(OH)D compared to Alzheimer

disease patients or healthy controls (25). 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 (26, 27).

Poor and low dietary intake is one of the major causes of low BMI and is often associated with calcium and 25-(OH)D deficiencies. A significant number of PD patients show mild to moderate nutritional depletion, frequently caused by swallowing disorders and delayed gastric emptying. Nutritional deficits can also lead to reduced folate and vitamin B12 levels, thus increasing the plasma levels of homocysteine; hyperhomocystinaemia is associated with an increased risk of fractures through a mechanism independent of BMD, and probably related to impaired cross-linking of collagen (1).

An important issue in PD patients is polypharmacy which could be related to fracture risk. In a study conducted by Vestergaard, investigating the associations between Parkinsonism and related therapy, Levodopa was associated with an increase overall fracture risk and an increased risk of hip fractures at high doses (28); the possible explanation of this relationship is that Levodopa can bring, as consequence of his metabolisms, hyperhomocystinaemia (29).

### Management of osteoporosis and fractures in Parkinson's disease

PD patients show an increased incidence of severe osteoporosis compared to the age-matched population, but at present no specific guidelines or recommendations are available for treatment and prevention of osteoporosis in PD patients (1).

The fracture risk reduction program consists in reducing the number and severity of falls. Because of the absence of data for PD patients, it is reasonable to use elderly fall prevention program consisting in correcting decreased visual acuity, reducing consumption of medications that alter alertness and balance, and improvement of home environment (slippery floors, obstacles, insufficient lighting, handrails) (30). However, although large trials have shown that it is possible to reduce falls (31, 32), randomized studies have not shown any significant decrease in fracture risk. In PD patients there is insufficient evidence to support or refute the value of programs of muscle strengthening and balance retraining in reducing falls (33).

In the absence of specific guidelines about the treatment of osteoporosis in PD patients, it could be reasonable to follow guidelines for postmenopausal osteoporosis and clinicians should consider that the risk profile of PD patients for hip and non-hip fractures could be different from that of non-PD patients due to the higher risk of falls, lower physical activity, lower vitamin D intake, and swallowing impairment (1).

Almost all the studies concerning the pharmacological treatment of osteoporosis in PD patients were made by Sato et al. The authors found, in randomized, double-blind, placebo-controlled trial, that 1 $\alpha$ -hydroxyvitamin D3 reduces the number of non-vertebral fractures in the treated group (OR 9.8), that riserodronate reduces the relative risk of hip fracture by 0.33 and increase the BMD by 2.2% ( $p < 0.0001$ ), and finally that alendronate reduces the relative risk for hip fractures by 0.29 and increases BMD by 3.1% (34-36).

However, BMD measurements in these studies were performed at the second metacarpal using computer X-ray densitometry, and not Dual energy X-ray Absorptiometry (DEXA) at the hip, which is considered the gold standard for BMD evaluation and furthermore, the study population consisted exclusively of Asian patients (1).

The results of a recent meta-analysis of strictly conducted randomized controlled trials (RCTs) suggest that there is efficacy against hip fracture and safety with riserodronate treatment in patients with

neurological diseases including Parkinson's disease: the relative risk (95% CI) for hip fracture with risedronate treatment was 0.25 suggesting 75% of risk reduction rate with risedronate treatment in patients with Alzheimer's disease, stroke and Parkinson's disease (37).

The absorption or metabolism of bisphosphonates are not affected by Levodopa or other medications used to treat PD, any contraindications or drug interactions seem to occur (28).

## Conclusion

Patients with Parkinson's disease have an increased incidence of osteoporosis and falls with subsequent increasing of fractures compared to age-matched healthy subjects.

All the studies presented suggest that patients with PD have lower BMD values than age- and sex-matched individuals without PD; the BMD decreases at the lumbar spine and femoral neck were greatest in patients in advanced disease and with low sunlight exposure and calcium intake.

As shown osteoporosis in PD is due to several factors and an interesting hypothesis might be an aggravation of osteoporosis in PD patients due to an aggravation of a pre-existing hypovitaminosis D state. Considering morbidity and mortality caused by fractures in elderly population and particularly in PD patients, it is reasonable to suggest that these patients should undergo to vitamin (Vitamin D, B12, Folic acid) and BMD measures and to falls risk evaluation, and that all the falls preventive measures should be applied; the possible intervention are based on fall prevention programs and on osteoporosis treatment. Bisphosphonates seem to be an effective treatment for osteoporosis in PD patients but further trials to evaluate their effectiveness are needed.

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