REVIEW

Parkinson’s disease and osteoporosis

FREDERIK VAN DEN BOS1,2, ARLENE D. SPEELMAN3, MONIQUE SAMSON1, MARTEN MUNNEKE4,5, BASTIAAN R. BLOEM6, HARALD J. J. VERHAAR1

1Internal Medicine, Haga Hospital, Leyweg 275, The Hague 2545 CH, The Netherlands
2Department of Geriatric Medicine, University Medical Centre Utrecht, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands
3Department of Neurology, Centre for Evidence Based Practice, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
4Radboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice, Department of Neurology, Nijmegen, The Netherlands
5Radboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice, Scientific Institute for Quality of Healthcare, Nijmegen, The Netherlands
6Department of Neurology, Donders Centre for Brain, Cognition and Behavior, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Address of the correspondence to: F. van den Bos. Email: f.vandenbos@hagaziekenhuis.nl

Abstract

Background: patients with Parkinson’s disease (PD) have a high risk of sustaining osteoporotic fractures as a result of falls and reduced bone mass.

Objective: to summarise the underlying pathophysiological mechanisms of bone loss in PD by reviewing the available literature.


Results: PD patients have a lower bone mineral density (BMD) than age-matched controls. Bone loss in PD is multifactorial, resulting from immobility, decreased muscle strength, and low body weight. Vitamin D deficiency is also important, not only because it reduces BMD, but also because cell function in the substantia nigra depends on vitamin D. Lastly, hyperhomocysteinaemia, an independent risk factor for osteoporosis, is common in PD, due to levodopa use, as well as vitamin B12 and folic acid deficiency. A few studies have demonstrated that treatment with bisphosphonates, vitamin D and calcium can increase BMD and reduce fractures in PD patients.

Conclusion: bone loss in PD is multifactorial. It is clinically important because of the concomitant risk of fractures. Screening for osteoporosis should be considered more often, and therapeutic interventions should be initiated.

Keywords: Parkinson’s disease, bone loss, osteoporosis, older people

Introduction

Parkinson’s disease (PD) is a common neurodegenerative disease characterised by both motor and non-motor symptoms. As a result, many PD patients are limited in their daily activities [1]. Compared with age-matched controls, PD patients have a significantly increased risk of fractures, mainly of the hip [2–7]. The consequences of such hip fractures in PD can be devastating, including decreased functionality, length of hospital stay, risk of nursing home admission and high mortality rates [8–11]. One explanation for the increased fracture risk in people with PD is falls, due to postural instability and gait disturbances. However, not all fractures in PD—and especially vertebral fractures—are related to falls [3, 7, 10]. The bone mineral density (BMD) of patients with PD is...
lower compared with healthy controls, thus worsening the fracture risk [3, 5, 7, 12].

However, it is unclear how many patients with PD experience bone loss. Published estimates of the prevalence of osteoporosis in PD vary considerably, and the causes of bone loss, in particular, are not well described in the literature. The aim of this study was to systematically review studies reporting bone loss in PD. In this review, we focus specifically on the pathophysiological mechanisms of bone loss, and treatment in patients with PD.

**Literature search**

A Medline search was performed for articles published between January 1975 and January 2011, using the keywords ‘bone mineral density’, ‘bone loss’, ‘BMD’, ‘bone metabolism’, ‘fractures’, ‘Parkinson’s disease’, and ‘parkinsonism’. Moreover, reference lists from the included studies were checked and author’s names were searched for additional studies. All the articles were screened on the basis of their title and abstract. Studies were included if participants had PD and the study evaluated risk factors for, or interventions to prevent, bone loss. Only studies in which dual energy X-ray absorptiometry of the hip and/or spine was used to measure BMD were included. Articles written in languages other than English, expert opinions, case reports and articles of which the full-text was not available were excluded.

**Search results**

This search yielded 403 studies. Twelve papers were considered eligible, using the above mentioned criteria (Figure 1).

Three of those studies were prospective cohort studies, with a follow-up ranging from 1 to 6 years. The others were observational (mostly case–control studies). Men and women were equally distributed and their mean age varied from 60 to 78 years. Not all studies reported disease severity and duration, but when reported UPDRS varied from 25 to 33. Almost all patients had a Hoehn and Yahr stage >2, and mean disease duration varied from 2 to 6.5 years. Most studies did not take all relevant confounders (e.g. vitamin D concentration) into account. The characteristics of these studies are summarised in Table 1.

**Clinical evidence**

Data from observational and case–control studies suggested an independent association between PD and lower BMD [13–22]. These data were confirmed by three longitudinal studies [2, 3, 21]. We will discuss these three latter studies in more detail next. Two studies investigated an annual loss of BMD in PD patients. Lorefalt et al. found significant reductions in total body, total hip and femoral neck BMD (3.9 versus 1.2%) in 26 PD patients compared with 26 controls. Low body weight and low physical activity were risk factors for low BMD, whereas rigidity seemed to be protective, possibly by increasing the mechanical load on bones. BMD, however, did not correlate with the severity of PD. An important limitation of this study is the small number of patients and controls [21].

In the Osteoporotic Fractures in Men Study, Fink et al. found a significantly (\(P < 0.001\)) greater total hip bone loss of 1.1% compared with only 0.4% in community-dwelling male patients (19 patients and 4,357 controls). However,
this study had several limitations: the number of men with PD was limited; PD was self-reported and the number of patients with follow-up date was low [2]. Schneider et al. investigated a cohort of community-dwelling women with and without PD for 6 years (73 patients and 8,032 controls). The authors found no significant difference in baseline BMD and in bone loss between the two groups after correcting for confounders. Body weight accounted for 60% of the difference in BMD. Because of the small number of patients at follow-up, the authors were unable to assess the association of PD with rate of change in hip BMD. Besides the small proportion of patients, this study was also limited by the self-reporting of PD, so the duration and severity of the disease could not be taken into account [3].

**Pathophysiology**

Several factors may contribute to bone loss in PD (Figure 2). Most of these develop in the course of PD and affect or reinforce each other.

---

**Table 1. Literature about BMD and Parkinson’s disease**

<table>
<thead>
<tr>
<th>First author (reference no.)</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Number of controls</th>
<th>Outcome measures (DEXA)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam et al. [22]</td>
<td>2010</td>
<td>108</td>
<td>216</td>
<td>Hip (four subregions), lumbar spine and total body BMD</td>
<td>Female, but not male, patients with PD have lower hip BMD ($P = 0.005$). After multivariate adjustment, the result did not reach statistical significance</td>
</tr>
<tr>
<td>Abou-Raya et al. [14]</td>
<td>2009</td>
<td>82</td>
<td>68</td>
<td>Lumbar spine and femoral neck BMD</td>
<td>PD patients have significantly lower BMD at lumbar spine and femoral neck (respectively, $P = 0.005$ and $P = 0.001$)</td>
</tr>
<tr>
<td>Song et al. [16]</td>
<td>2009</td>
<td>107</td>
<td>100</td>
<td>Lumbar spine and femoral neck BMD</td>
<td>Femoral neck and lumbar spine BMD were significantly lower in PD ($P &lt; 0.00$)</td>
</tr>
<tr>
<td>Bezza et al. [17]</td>
<td>2008</td>
<td>52</td>
<td>52</td>
<td>Lumbar spine and dual femur BMD</td>
<td>BMD at lumbar spine and hip was lower in PD (respectively, $P &lt; 0.001$ and $P = 0.02$)</td>
</tr>
<tr>
<td>Fink et al. [2]</td>
<td>2008</td>
<td>46</td>
<td>5891</td>
<td>Hip BMD</td>
<td>Total hip bone loss was greater in men with PD ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>Schneider et al. [3]</td>
<td>2008</td>
<td>73</td>
<td>8032</td>
<td>Total hip and femoral neck BMD</td>
<td>Total hip BMD was lower in women with PD ($P &lt; 0.01$). After multivariate adjustment, the result did not reach statistical significance</td>
</tr>
<tr>
<td>Kamanli et al. [18]</td>
<td>2008</td>
<td>28</td>
<td>31</td>
<td>Lumbar spine, proximal femur and hand BMD</td>
<td>In female, but not male, patients hand and femoral neck BMD were significantly lower ($P &lt; 0.05$)</td>
</tr>
<tr>
<td>Lorefalt et al. [21]</td>
<td>2007</td>
<td>26</td>
<td>26</td>
<td>Hip and total body BMD.</td>
<td>The BMD was lower at all sites in PD at year 1 and 2 compared with controls ($P &lt; 0.05$) and decreased during the investigated year</td>
</tr>
<tr>
<td>Di Monaco et al. [15]</td>
<td>2006</td>
<td>28</td>
<td>28</td>
<td>Hip (five subregions) BMD</td>
<td>BMD did not differ significantly between PD patients and controls with a hip fracture</td>
</tr>
<tr>
<td>Wood et al. [20]</td>
<td>2005</td>
<td>105</td>
<td>–</td>
<td>Hip (three subregions) and lumbar spine BMD</td>
<td>41.9% of the PD patients had osteoporosis and 34.5% osteopenia</td>
</tr>
<tr>
<td>Fink et al. [13]</td>
<td>2005</td>
<td>52</td>
<td>5943</td>
<td>Hip (three subregions) and lumbar spine BMD</td>
<td>PD was associated with lower BMD at the spine ($P = 0.04$) and total hip ($P = 0.07$).</td>
</tr>
<tr>
<td>Taggart and Crawford [19]</td>
<td>1995</td>
<td>51</td>
<td>51</td>
<td>Hip and lumbar spine BMD</td>
<td>Total hip ($P = 0.014$) and femoral neck ($P &lt; 0.004$) BMD were decreased in PD patients. No significant difference was found for the lumbar spine.</td>
</tr>
</tbody>
</table>

**Figure 2.** Factors influencing BMD and bone strength in Parkinson’s disease.
Physical activity and exercise

PD patients are less active compared with healthy controls [23]. Bone tissue is sensitive to its mechanical environment and is continuously stimulated by muscle contraction and weight-bearing movements, and is responding to mechanical stress. Osteocytes and their dendritic connections are able to sense the fluid flow driven by stresses placed upon bone. In response to these stresses, osteocytes produce signalling molecules that stimulate bone remodelling by osteoclasts and osteoblasts [24, 25]. Subnormal mechanical stress as a result of immobilisation leads to bone loss, with the rate of bone loss being influenced by the duration, intensity and acuteness of immobilisation [26]. There are indications that immobility is associated with bone loss in PD, but research into this is limited. Only three studies investigated the association between physical performance/exercise and BMD in PD. The authors Lam and Fink found no association, Lorefält, on the other hand, found that the amount of BMD in PD patients was directly correlated to physical activity [13, 21, 22]. Data on the association between BMD and the severity of PD are also conflicting. Only one prospective study mentioned severity. They found no correlation between BMD and severity of PD symptoms. However, besides the small number of patients, none of the patients was severely disabled [21]. In contrast, results of most observational studies have suggested a significant association between disease severity and BMD. These studies also consisted of small number of patients. Most studies did not account for all potential confounders [14–18]. Although the evidence is scarce, it seems plausible that physical inactivity, which worsens as the disease progress, contributes to bone loss in PD.

Vitamin D deficiency

Vitamin D has a crucial role in bone metabolism, and a shortage of vitamin D is correlated with an increased risk of falls and fractures [27]. Vitamin D deficiency results in hypocalcaemia and compensatory hyperparathyroidism, and an excess of parathyroid hormone causes bone resorption by stimulating osteoclast activity [26–28]. Vitamin D deficiency is common in PD and may be related to malnutrition, immobility and sunlight deprivation. The prevalence of vitamin D insufficiency is significantly higher in patients with PD compared with healthy controls or patients with Alzheimer’s disease, which suggests that there is a specific association between PD and vitamin D deficiency [29–31].

Vitamin D has an important role in the human brain. 1,25(OH)2D is synthesised in neurons and microglia by 1α-hydroxylase. Active vitamin D binds to vitamin D receptors (VDRs) and regulates several genes involved in cell differentiation, proliferation and apoptosis. VDRs are expressed throughout the brain, with the strongest expression of both 1α-hydroxylase and VDR being found in the (presumably dopaminergic) neurons of the substantia nigra [32]. Matkovits et al. showed that dopamine can induce VDR-mediated signalling in the absence of active vitamin D [33]. This supports the hypothesis that vitamin D has autocrine and paracrine functions in the nervous system. Vitamin D also seems to have neuroprotective actions, by inhibiting the synthesis of nitric oxide, by exerting direct antioxidant-like effects and anti-ischaemic actions and by modulating cytokine release [34, 35]. Vitamin D and PD are also linked at a gene level. Kim et al. found an association between PD and VDR gene polymorphisms, using genomic DNA extracted from the peripheral blood from patients with PD and controls [36]. Newmark and Newmark even hypothesised that a chronically inadequate vitamin D intake may contribute to the pathogenesis of PD. They suggested that a continuous inadequate intake of vitamin D leads to a chronic loss of dopaminergic neurons in the brain [37]. A recent longitudinal study supported this hypothesis. Knekt et al. investigated a cohort of 3,173 men and women free of PD in Finland with a follow-up of 29 years and concluded that a low-vitamin D status predicted the development of PD (50 cases and 3,123 non-cases). However, this study had some weaknesses, such as a small number of cases, the single measurement of vitamin D, and the possibility of residual confounders due to the fact that risk factors for PD are not well known [38].

Muscle strength

Both vitamin D deficiency and decreased mobility reduce muscle strength (Figure 2). Muscle strength has been negatively associated with BMD in various populations, and bone formation and remodelling may be affected by local mechanical signals generated by muscle contraction [39–41]. Environmental influences (exercise, nutrition and vitamin D) as well as genetic factors influence this bone–muscle relationship [42, 43]. The isokinetic muscle strength of patients with PD is reduced compared with age-matched controls, even in early disease stages, and declines further with disease progression. The specific cause of this weakness is not known [44]. One study reported lower extremity muscle strength (isometric hip flexion and knee extension) to be associated with hip BMD in women with PD (34 patients and 30 controls), after correcting for several confounders [42]. Another study investigated the association between lumbar spine BMD and trunk muscle strength and found trunk muscle strength to be independently associated with lumbar spine BMD (43 patients and 29 controls) [45]. Both studies were limited by small sample sizes and possible selection bias.

Low body weight

Several studies have suggested that low body weight is a risk factor for low BMD in PD [17, 19, 21]. Schneider et al. found that weight accounted for 60% of the age-adjusted difference in hip BMD in 73 women with PD compared with 8,032 controls [3]. One explanation is the decreased mechanical load. In addition, a lower body fat content is
associated with lower oestriol production in postmenopausal women, leading to a reduced BMD [46, 47]. Patients with PD are at a high risk of poor nutrition for several reasons, such as impaired hand–mouth coordination, dysphagia, intestinal hypomotility, depression, cognitive deficits and side effects of medication. At the same time, there is an increased energy requirement due to muscular rigidity and involuntary movements. In addition, malnutrition can lead to low levels of vitamin D, folic acid and vitamin B12, with negative consequences on bone formation and strength [48, 49].

Hyperhomocysteinaemia

Hyperhomocysteinaemia is an independent risk factor for osteoporotic fractures [50–52]. The catabolism of homocysteine depends on folic acid, vitamin B12 and vitamin B6, and thus folic acid and vitamin B12 deficiency can cause hyperhomocysteinaemia. Homocysteine has a direct effect on bone by binding to extracellular collagen, which interferes with the formation of collagen cross-linking [53, 54]. In addition, in vitro studies have shown that homocysteine stimulates the differentiation of osteoclasts and induces apoptosis of osteoblasts [55–57]. The first mechanism results in poor bone quality and the second reduces BMD, both contributing to an increased fracture risk.

Hyperhomocysteinaemia is common in PD and is associated with fracture risk and a low BMD [58–62]. In addition to vitamin B12 and folic acid deficiency, levodopa use may cause hyperhomocysteinaemia. Levodopa and dopamine are methylated by catechol O-methyltransferase (COMT), with S-adenosylhomocysteine as methyl donor, to form S-adenohomocysteine. Since S-adenohomocysteine is rapidly converted to homocysteine, levodopa therapy can lead to hyperhomocysteinaemia. Theoretically, inhibition of COMT should reduce levodopa-induced hyperhomocysteinaemia, but the literature on this is contradictory. These discrepancies in the literature might be related to the different levels of vitamin B12 and folic acid in the included patients [63–68]. Two studies have shown that supplementation of vitamin B12 and folic acid decreases homocysteine levels in levodopa-treated patients [69, 70]. Moreover, Lee et al. [71] concluded that homocysteine-lowering therapy with folic acid and vitamin B12 prevents bone loss in levodopa-treated patients. Another recent study found that not levodopa use, but decreased levels of vitamin B12 and folic acid cause hyperhomocysteinaemia in PD [62].

Management and treatment

The paragraphs above indicate that a complex interaction between various factors can contribute to bone loss in patients with PD. Optimal management calls for careful assessment of all these factors, followed by tailored treatment where possible. Because scientific evidence concerning the treatment of osteoporosis in PD is scarce, we would like to recommend clinicians to treat PD patients according to the same principles that apply to non-parkinsonian patients. Specific recommendations for treatment include: (i) lifestyle factors and exercise; (ii) dietary supplementation and (iii) anti-osteoporotic medication.

The WHO developed the calculation tool FRAX to evaluate fracture risk of patients based on individual patient models that integrate clinical risk factors as well as BMD at the femoral neck. The risk factors of having ‘PD’ or ‘falls related to PD’ have however, not been quantified (sufficiently) in FRAX to give an accurate 10-year probability of fracture in these patient categories. The FRAX calculation tool can therefore not be recommended in calculating fracture risk in PD patients [72].

Lifestyle factors/exercise

Smoking and alcohol are well-known risk factors for osteoporosis, so patients should be advised to stop smoking and reduce alcohol consumption. Exercise is recognised as key modifiable lifestyle factor that is essential to the prevention and management of osteoporosis. Physical activity programmes for maintaining BMD are based on a site-specific modifying effect, in addition to strengthening muscles and improving balance, thus reducing the overall risk of falls and fractures. The influence of exercise on BMD in PD is not well studied. The ParkFit study is currently being conducted. It researches whether a physical activity promotion programme can increase physical activity levels in sedentary patients with PD [23].

Dietary supplementation

Sato et al. performed a randomised, double-blind, placebo-controlled trial of 1α-hydroxyvitamin D3 supplementation (1 µg/day) for 18 months in patients with PD (43 patients in both groups). After 18 months the treatment group showed a smaller decrease in BMD (1.2 versus 6.7%; \(P < 0.00\)) and a lower risk of non-vertebral fractures (18.6 versus 2.3%; OR 9.8, \(P = 0.003\)) [73].

Lee et al. studied the effect of homocysteine-lowering therapy on preventing bone loss in patients with PD taking levodopa. Patients were randomly assigned to treatment (\(n = 14\)) (folate 5 mg daily, mecobalamin 500 µg three times daily) or no treatment (\(n = 13\)). Both groups took daily oral supplements of calcium (500 mg) and cholecalciferol (1000 IU). Follow-up was 12 months. The authors found that homocysteine-lowering therapy resulted in significantly greater improvements in BMD at the lumbar spine (4.4%), total femur (2.8%) and femur shaft (2.8%). Although this was a small trial and fracture reduction was not taken into account, it is an easy therapy with minor side effects [71].

Anti-osteoporotic medication

Only three studies focused on pharmacological treatment of osteoporosis in PD, all considering bisphosphonates.
The role for selective oestrogen receptor modulators and strontium ranelate has not been evaluated in PD patients with PD.

The first study, a 2-year, randomised, double-blind, placebo-controlled trial, studied the effect of risedronate in men with PD (121 patients in both groups). Risedronate (2.5 mg) and ergocalciferol (1000 IU) daily were compared with ergocalciferol (1000 IU) and placebo. BMD increased 2.2% in the risedronate group and decreased 2.9% in the placebo group, while nine patients in the placebo group and three patients in the risedronate group sustained hip fractures. So, risedronate reduced the relative risk of hip fracture by 0.33 (95% CI: 0.09–1.20) [74]. The same authors reported similar benefits in a study of elderly women with PD allocated to once weekly 17.5 mg risedronate and ergocalciferol compared with ergocalciferol and placebo (136 patients in both groups) [75]. The third study investigated the effect of alendronate in a 2-year randomised, double-blind, placebo-controlled trial of elderly women with PD (144 patients in both groups). Patients were treated daily with alendronate (5 mg) or placebo, and both groups received ergocalciferol (1000 IU). BMD increased 1.3% in the intervention group and decreased 2.8% in the control group. Alendronate reduces the relative risk of hip fractures (14 versus 4 fractures) by 0.29 (95% CI: 0.10–0.85) [76]. A shortcoming of these studies was that BMD measurements were performed at the second metacarpal using computer X-ray densitometry and not DEXA at the hip. Nevertheless, they found a decrease in the number of fractures. Altogether, bisphosphonates seem to be effective for osteoporosis in PD. No drug interaction occurs with levodopa or other medications used to treat PD and when a patient experience dysphagia bisphosphonates can be administrated intravenously.

Conclusion

Patients with PD have a lower BMD than age-matched controls. This reduced bone mass, in combination with frequent falls, explains the increased fracture risk. The BMD reduction in PD is multifactorial in origin, involving reduced mobility, vitamin D deficiency, hyperhomocysteinaemia (caused by levodopa use, or vitamin B12 or folic acid deficiency), malnutrition/low body weight, and decreased muscle strength. All these factors are common in PD and act synergistically (Figure 2). It is essential to monitor these factors in order to assess the risk of osteoporosis and, consequently, reduce fracture risk. Patients with PD are currently not routinely screened for osteoporosis [77], yet the high incidence of fractures in these patients, resulting in an increased morbidity and mortality, makes careful management necessary. An extensive risk assessment should be performed, including medication use, level of immobilisation, muscle strength and nutritional status. If a patient has several risk factors, then BMD should be measured with DEXA. If osteoporosis is present, treatment should be started with bisphosphonates and vitamin D supplementation, and an adequate intake of calcium. Osteoporosis in PD has not been extensively studied and further research is needed. Larger and more powerful studies should investigate the pathophysiology of osteoporosis in PD and ways to prevent bone loss and reduce the incidence of fractures.

Key points

- Patients with PD have a lower BMD than age-matched controls.
- This reduced bone mass, in combination with frequent falls, explains the increased fracture risk of patients with PD.
- Bone loss is multifactorial, involving immobility, vitamin D deficiency, hyperhomocysteinaemia, malnutrition and muscle weakness.
- Treatment with bisphosphonates could decrease bone loss in PD.

Conflicts of interest

None declared.

Funding

This study was primarily funded by ZonMw (The Netherlands Organization for Health Research and Development (75020012)) and The Michael J Fox Foundation for Parkinson’s research. Additional financial support was provided by VGZ (health insurance company); Glaxo Smith Kline and National Parkinson Foundation.

Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

References

The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available in Supplementary material *Age and Ageing* online.


23. van Nimwegen M, Speelman AD, Smulders K et al. Design and baseline characteristics of the ParkFit study, a randomized controlled trial evaluating the effectiveness of a multi-faceted behavioral program to increase physical activity in Parkinson patients. BMC Neuro 2010; 10: 70.
45. Pang MY, Mak MK. Trunk muscle strength, but not trunk rigidity, is independently associated with bone mineral density of the lumbar spine in patients with Parkinson’s disease. Mov Disord 2009; 24: 1176–82.
62. dos Santos EF, Busanello EN, Miglioranza A et al. Evidence that folic acid deficiency is a major determinant of hyperhomocysteinemia in Parkinson’s disease. Metab Brain Dis 2009; 24: 257–75.

Received 7 April 2012; accepted in revised form 23 August 2012