

Parkinson's disease and the bones

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Summary

PRINCIPLES: Bone and joint problems in Parkinson's disease (PD) are manifold: decreased mobility, abnormal posture, as well as the risk of falling may cause both acute and chronic damage to the musculoskeletal system. In patients with Parkinson's disease, postural instability and falls are frequently observed. The aim of the study was to review the literature with respect to the bone health and risk of fractures in these patients.

METHODS: We conducted a review on bone health in patients with Parkinson's disease.

RESULTS: There is evidence that patients with PD have an increased risk of fractures, especially of the hip, due to the elevated risk of falling. While rigidity, bradykinesia and postural instability (but not tremor) predict falls, fractures also correlate with bone mineral density, which is generally lowered in this group of patients as compared to

age- and sex-matched controls. Typically PD patients have "high turnover osteoporosis" due to several causes.

CONCLUSIONS: Any newly diagnosed patient with PD should be evaluated for the risk of falling and osteoporosis and routinely be supplemented with vitamin D. In the case of osteoporosis, blood samples for detecting underlying and treatable conditions should be taken and bisphosphonates administered to the patient.

It is unclear whether drugs typically used for PD provoke or worsen osteoporosis. Nevertheless, every long-term medication should undergo safety studies to demonstrate lack of negative interference with bone metabolism. Drug admission authorities should demand these data when registering new substances or when renewing old admissions.

Key words: Parkinson's disease; accidental falls; bone fractures; bone density; osteoporosis; levodopa; homocysteine; vitamin D

Background

Almost two centuries have passed since James Parkinson introduced his "shaking palsy" to the scientific community [1] and Charcot coined the term "Parkinson's Disease" (PD). In the meantime many things have changed. People are getting older and many patients will suffer from this disease whose incidence is related to advanced age [2]. Efficacious drug treatments have only been available since the 70's, with amantadine and L-dopa plus dopadecarboxylase-inhibitors. Other drugs followed later such as dopamine agonists, monoamino-oxidase (MAO) B- and catechol-O-methyltransferase (COMT)-inhibitors. While placement of lesions stereotactically has turned out to be a "blind alley" and has been largely abandoned, so-called "deep brain stimulation" electrodes have been successfully implanted for 20 years and are now a standard therapeutic option [3]. Yet we are still awaiting curative treatment. The present therapeutic armamentarium offers a better quality of life for patients affected by this chronic-progressive neurodegenerative disease. However, a better and possibly longer life also means more long-term health problems [4], both neurological (e.g., dementia) and non-neurological (e.g., musculoskeletal). Bone and joint problems in PD are manifold: decreased mobility, abnormal

List of abbreviations

BMD	Bone mineral density
CI	Confidence interval
COMT	Catechol-O-methyltransferase
DXA	Dual energy X-ray absorptiometry
DPD-CL	Desoxypyridinoline crosslinks
GH	Growth hormone
HR	Hazard rate
Hcy	Homocysteine
IGF-1	Insulin-like growth factor 1
MAO	Monoamino-oxidase
OR	Odds ratio
PD	Parkinson's disease
PPAR-γ	Peroxisome proliferator-activated receptor gamma
PTH	Parathyroid hormone
RANKL	Receptor Activator for Nuclear Factor κ B Ligand
RR	Risk ratio
SMR	Standardised mortality rate

posture, as well as the risk of falling may cause both acute and chronic damage to the musculoskeletal system [5]. Additionally, drug therapy itself might also have an influence on the musculoskeletal system. Hence we will focus on the factors affecting bone metabolism and fractures in PD. Thus, the aim of the study was to review the literature with respect to the risk of falling and fractures in these patients.

Methods

For this review, we searched Embase and Medline (table 1). In terms of falls, fractures, mortality and bone mineral density (BMD), we selected papers comparing PD patients with normal controls. We also included studies carried out among PD patients distinguishing “fallers” from “non-fallers”. For BMD, we selected studies measuring lumbar spine and femur with dual energy X-ray absorptiometry (DXA).

We completed our database by asking pharmaceutical companies which manufacture the above-mentioned (table 1, “search E”) drugs for PD about a) systematic safety studies for bone integrity and b) incidental data referring to effects of their antiparkinson drugs on bone metabolism.

Values are reported as given in the original articles, i.e., mean \pm SD or mean (lower-upper CI 95%) if not stated otherwise. Statistical inference testing is reported as cited from the original papers.

Results

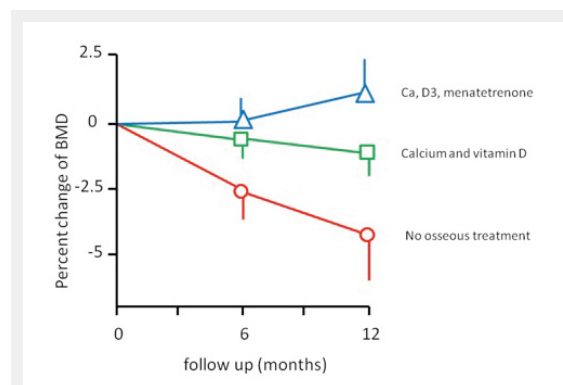


Figure 1

Metacarpal bone mineral density changes (mean \pm SEM) in patients with Parkinson's disease, treated with menatetrenone, calcium and vitamin D, compared with calcium and vitamin D alone or without bone treatment (n = 56, 60 or 54 respectively). ANCOVA: p < 0.001 for both groups treated with calcium and vitamin D vs untreated, and p = 0.05 for menatetrenone, calcium and vitamin D vs calcium and vitamin D alone [60, with permission of the editor].

Falls

Falls are frequent in PD. Most studies investigated risk factors for falling *within* PD patients. Two studies compared fall risk in PD with controls. Bloem et al. published a 6-month study [6]: 51% of PD patients fell at least once compared to 15% in the control group, corresponding to a risk ratio (RR) of 3.4. Because many PD patients had more than one fall, there were 3.5 falls per patient compared to 0.2 in the control group. Camicioli et al. also found an increased risk of falling (RR 1.4) [7]. The risk for repeatedly falling was increased by 2.6. During periods ranging from two to twelve months, in patients with PD, the proportion falling ranged from 25% to 78% (mean value 50%) [8–13]. In their meta-analysis, Deandra et al. found an odds ratio (OR) of 2.71 (1.08–6.84) for falling in PD [14]. Fall frequency seems to correlate with PD symptom severity [6, 9, 11], time since disease onset [13, 15], female gender or autonomic dysfunction [16], urinary incontinence [13] and dementia [15]. A simple battery of clinical tests can predict fall risk in PD patients with 78% sensitivity and 84% specificity [17]. Finally, besides previous falls, the most prominent predictors of falls seem to be gait disturbances and postural instability, known to be more frequent in advanced stages of the disease [10, 11, 16]. The latter can be detected by clinical tests [18], but also be objectively measured with electronic walkways such as the GAITRite system, with movement analysis such as the Vicon system, with force platforms and with accelerometers [19] or with computerised dynamic posturography [20]. Gait disturbances and postural instability can be partially mitigated by physiotherapeutic exercises [8, 21–24]. Even in the absence of a complete clinical Parkinson syndrome, single clinical signs associated with PD may increase the risk of falls [25]. Postural instability may be the only clinical sign of patients with repetitive falls and may improve after dopaminergic treatment such as amantadine or L-dopa [26]. This medication will not be generally very effective although in some patients clinical conditions may dramatically improve. Cholinergic treatment with donepezil was recently described to prevent falls in non-demented PD patients [27]. We did not find published information whether these drugs also prevent fractures. Overall, falls are a typical sign of late stages of PD, explaining why they are often associated with dementia or autonomic dysfunction, conditions themselves associated with falls independently of PD [7]. Preliminary data suggest that pedunculopontine “deep brain stimulation” may improve axial symptoms and gait [28]. Current literature on falls in PD has been reviewed by Grimbergen et al. [29].

Table 1: Search strategy.

A Falls: Parkinson's disease AND accidental falls (530, 16, 7)
B Fractures: Parkinson's disease AND bone fracture (338, 5, 4)
C Mortality: Parkinson's disease AND mortality (1028, 10, 3)
D Bone density and metabolism: Parkinson's disease AND (osteoporosis OR osteopenia OR bone mineral density OR NTx OR hydroxyproline OR undercarboxylated osteocalcin OR ICTP OR desoxyypyridinoline) (356, 14, 1)
E Iatrogenic effects: (L-dopa OR benserazide OR carbidopa OR bromocriptine OR cabergoline OR pergolide OR pramipexole OR ropinirol OR rotigotine OR lisuride OR quinagolide OR entacapone OR tolcapone OR amantadine OR selegiline OR rasagiline) AND (osteoporosis OR osteopenia OR bone mineral density OR NTx OR hydroxyproline OR undercarboxylated osteocalcin OR ICTP OR desoxyypyridinoline) (411, 5, 13)
Legend: The first number represents the hits found within Embase or Medline in November 2010, the second the papers included, the third number the papers found by other strategies like manual searches in citations of other papers. No wildcards were used for searching.

Fractures

Patients in the late stages of PD seem to fall sideways or backwards with disproportionate frequency [30], probably because of slowed postural reflexes. This leads to a typical pattern of fractures with an excess of hip fractures compared to other locations. Studies investigating hip fractures in PD as compared with controls are summarised in table 2. In the Olmsted County cohort study by Johnell et al. [30], 138 patients with PD were retrospectively compared with age- and sex-matched controls. The mean observational period was 6.8 years in PD and 8.6 years in controls. During this interval, 20 patients with PD suffered from hip fractures, compared with one person in the control group (RR 20.0); fractures of other locations were more evenly distributed: 68 in PD and 38 in controls (RR 1.8). In a retrospective cohort study done by Genever et al. [31] during a mean interval of 5.9 years, 200 patients with PD and controls were analysed. Eleven hip fractures occurred in the PD group compared to four in controls (RR 2.8). There were 27 fractures in other locations in PD and twelve in controls (RR 2.3). In 2008 Schneider et al. published the “Study of Osteoporotic Fractures (SOF) Research” in female patients [32]. During a prospective nine-year follow-up, 11 hip fractures occurred in 73 PD patients (15%), while 839 of 7760 controls had hip fractures (11%, RR 1.4). There were 11 other fractures (excluding vertebral) in 73 PD (15%) and 1589 in 6349 controls (25%, RR 0.6). Adjusted for age, RR for hip fractures in PD was 2.6 (95% CI 1.4–4.6), but when controlling for weight, RR fell to 1.7 (0.8–3.9). Obviously fractures were correlated to poor nutritional status; during the study period, PD patients lost on average 4.6 ± 7.2 percent of their body weight, as compared to $0.6 \pm 6.6\%$ in controls. In a shorter study on males done by Fink et al., lasting on average 4.1 (PD) to 5.1 (controls) years, 7 of 46 patients with PD (15%) were registered with fractures, as compared to 424 out of 5891 control subjects (7%) [33]. In this study the hazard ratio for non-vertebral fractures was 2.4 (95% CI, 1.1–5.0). In an older study with female patients, the RR was 9.4 (1.2–76.1) [34]. In a study done by Taylor et al. in women, PD was the strongest single predictor of fractures [35], but this was not independent of BMD. In another study by Nguyen et al., body sway and BMD best explained the fractures that were observed [36]. In a large Danish case-control study, RR for any fracture in PD was 2.2 (95% CI 2.0–2.5) [37]; yet, this ratio fell to 1.5 (1.3–1.8) when adjusting for use of antiparkinson drugs and further to 1.2 (1.0–1.4) when various anamnestic factors were included. Large prospective observational as well as intervention studies on fractures in PD are lacking. Considering that 90% of non-vertebral

fractures result from falls [38], fall prevention remains the most effective measure to prevent fractures.

Overall Mortality

We did not find studies, which separately analysed mortality rates resulting from fractures, yet several studies reported overall mortality in PD. Diem et al. reviewed mortality in PD [39]. In a total of 33 cohort studies, during a mean follow-up of 9.6 years, in 8081 patients, RR for mortality was 1.8 (these results are reported without the large study by Guttman, 6 yr, 15304 patients, RR 2.5). The mortality rates were higher in two pre-dopa studies (2.3) as compared to the post-dopa era (1.8). Another meta-analysis by Berger et al. on five studies reported a RR of 2.3 (1.8–3.0) [40]. He showed also a high rate of institutionalisation in 229 PD patients compared to 13 051 controls (RR 5.0; 3.3–7.4). Cohort studies are very sensitive to inequalities in the control group, e.g., non-inclusion of terminally ill patients, therefore these results could overestimate mortality. A measure to avoid this possible bias is to calculate standardised mortality rates (SMR) by comparing mortality in PD cohorts with that of the general population. This has been done by Herlofson et al. [41], Hely et al. [42] and Hobson et al. [43]. In 245, 126 or 166 PD patients, followed for 8, 15 or 4 years, SMR was reported to be 1.52 (1.29–1.79), 1.86 (1.48–2.31) or 2.1 (1.7–2.6), respectively. During her 20-year follow-up, Diem et al. [39] followed 238 PD patients. She found slightly increased overall SMR of 1.3 (1.1–1.6) for men, while women’s SMR was not significantly elevated (1.2; 0.9–1.4). She also described elevated SMR values 15 and more years after disease onset, so increased mortality may be a phenomenon of longstanding PD. Her analysis of mortality according to time after disease onset was later criticised by Rajput et al. [44]. In the PD group, no deaths could have occurred between disease onset and inclusion to the study, while in controls this was the case, so underestimation of mortality in PD was the consequence. A study by Mylne et al. described an approximate 20% decline in PD mortality over the time period from 1993–2006 [45]. Several studies reported pneumonia as a major cause of death in PD [46–50] but this observation could not be reproduced by Diem et al. [39]. Detection of causes of death from mortality registries seems difficult because of changing habits of coding over time and lack of precision. In the study by Diem et al., 23% of deaths were ascribed to PD itself, and only 7% to pneumonia [39]; perhaps some of the doctors subsumed aspiration pneumonia in patients with swallowing difficulties to PD, others to “pneumonia”. In another study, increased mortality of PD patients in winter was described [51]. Male gender, gait disorder, lack of tremor and lack of asymmetry were asso-

Table 2: Hip fractures in PD compared with normal controls.

First author [Reference Nr.]	Year of publication	Number of patients / controls	Duration, yr	Outcome	Significance	Type of study
Johnell O [30]	1992	138 / 138	6.8 / 8.6	RR 20.0 (4.0 – ∞)	<0.001	retrospective cohort
Genever RW [31]	2005	200 / 200	5.9 / 5.9	RR 2.8	= 0.07	retrospective cohort
Schneider JL [32]	2008	73 / 8032	9.0 / 9.0	adj. HR 2.6 (1.4–4.6)	not stated	prospective cohort, women only
Fink HA [33]	2008	46 / 5891	4.1 / 5.1	adj. HR 2.4 (1.1–5.0)	not stated	prospective cohort, men only, hip not separately analysed

ciated with poorer survival [39]. Fink et al. found that the presence of gait disturbances in patients with PD almost doubled the risk of dying [33].

Bone mineral density (BMD)

We found seven studies measuring BMD in g/cm^2 by DXA in PD and control subjects [52–58], they are summarised in table 3. Mean BMD (total hip) of the 365 patients (48% female, mean age 68.4 years) with PD was $0.767 \text{ g}/\text{cm}^2$, while in control subjects this value was 0.872 , a statistically ($p < 0.001$) significant and clinically important difference. In the “Osteoporotic Fractures in Men Study (MrOS)” published by Fink et al., within a cohort of community-dwelling men, 46 patients with PD were compared with 5891 participants without PD [33]. Mean total hip BMD was $0.876 \text{ g}/\text{cm}^2$ in PD vs 0.958 without PD ($P < 0.001$). Hence, PD patients were 1.8 years older than controls. Two studies investigated annual loss of BMD in PD patients: Lorefält et al. found a loss of 3.9% vs 1.2% in controls [54], while in the study done by Fink et al. on male patients the values were 1.1% vs 0.4% [33]. In two studies done by Sato et al., the groups of PD patients receiving no bone-specific treatment (control groups) had a yearly loss of 4.5% or 4.2% [59, 60] similar to the study of Lorefält et al. mentioned above. Ishizaki et al. found a slightly more decreased BMD on the preferentially affected side of PD patients [61]. In healthy perimenopausal women, yearly bone loss of approximately 2.0% was described, slowing down to 1.0 to 1.5% three to four years after menopause; thus, the 4% annual loss in PD patients will be twice that expected in perimenopausal women [38].

Bone metabolism

Turnover of bone can be measured by markers of bone degradation. One of them is desoxypyridinoline crosslinks (DPD-CL) measured in fasting second morning urine expressed as a ratio to creatinine concentration. Sato et al. [60] found higher DPD-CL in PD compared to controls (9.0 ± 1.9 vs $4.0 \pm 1.2 \mu\text{mol}/\text{mol}$ creatinine, $p < 0.001$). The same author demonstrated that treatment with alendronate or risedronate restored DPD-CL excretion to normal values [62, 63]. What are the pathophysiological aspects for high bone turnover in PD? Patients with PD have markedly lower levels of 25-OH vitamin D3 compared to controls. In 197 patients with PD, serum level was $59.9 \pm 37.4 \text{ nmol}/\text{L}$, while in 158 controls $84.2 \pm 28.8 \text{ nmol}/\text{L}$ was measured ($p < 0.001$) [54, 60, 64]. Low levels of vitamin D3 were more

frequent in patients with PD compared to patients with Alzheimer’s disease [64]. As a consequence of low vitamin D3, low levels of active 1,25-OH vitamin D3 (calcitriol) were detected [65]. Furthermore in the same article Sato et al. mentioned elevated levels of ionised calcium in patients with PD compared to controls which was explained by the pronounced immobilisation of these patients. A study recently published by the same author demonstrated a preserved BMD, a doubling of serum vitamin D, a reduction of DPD-CL and fewer hip fractures in PD patients by the simple intervention of 15 minutes’ exposure to sunlight on sunny days [66]. Finally he described low levels of vitamin K1 in patients with PD, compromising the synthesis of carboxylated osteocalcin and contributing therefore to osteoporosis. Further bone loss was prevented after substitution with vitamin K2 (menatetrenone) [60] (fig. 1).

Pills and bone

Although musculoskeletal problems are well known in PD, bone pathology is a neglected issue in PD treatment. Pharmaceutical companies admitted upon our request that systematic safety studies for bone integrity during tests with their antiparkinsonian drugs are lacking. Our literature search did not reveal any prospective study on bone mineral density or bone metabolism during treatment with drugs typically used for symptomatic treatment of PD. Rico et al. did not find significant effects on cortical bone mass when investigating eleven PD patients receiving L-dopa for six years [67]. Thus, he could not replicate alleged favourable effects of L-dopa on bone metabolism published only as an abstract. There is no statement which dopadecarboxylase-inhibitor (benserazide or carbidopa) was taken together with L-Dopa. In a Danish study done by Vestergaard et al., fracture risk was increased with L-dopa treatment (RR 1.8) [37]. In a case-control study by Arbouw et al., the current use of dopaminergic drugs was correlated to hip fractures ($\text{OR}_{\text{adj}} 1.76$; 95%CI 1.39–2.22) [68].

When looking for indirect interactions of the drugs for PD with bone metabolism such as renal or endocrinological changes in humans or bone alterations in animals, some preclinical studies were found. Concerning the kidney, a study by Inglis et al. documented high concentrations of epinephrine in the renal cortex following administration of L-dopa in rats [69]. In studies done by Luippold et al. hyperfiltration, diuresis and natriuresis mediated by dopamine₃ and in part by dopamine₂ receptors were observed [70,

Table 3: Bone mineral density in PD compared with normal controls.

First author / Reference Nr.	Year of publication	Number of patients / controls	BMD total hip, g/cm^2 (SD)	Significance	Type of study, comments
Kao CH [52]	1994	22 / not stated	0.92 / 1.19	Not stated	Case series, historical controls
Taggart H [53]	1995	55 / 55	0.72 (0.19) / 0.80 (0.15)	= 0.02	Controls were patients sent to DXA scan
Lorefält B [54]	2007	26 / 26	0.74 (0.1) / 0.80 (0.1)	<0.05	Randomised controls
Abou-Raya S [55]	2009	82 / 68	0.72 (0.09) / 0.96 (0.05)	= 0.005	Femoral neck density.
Bezza A [56]	2008	52 / 52	0.96 (0.15) / 1.05 (0.16)	= 0.03	Provenance of controls not stated
Kamanly A [57]	2008	24 / 26	0.72 / 0.71	n.s.	Only in women significant difference.
Lam K [58]	2010	104 / 208	0.72 / 0.74	n.s.	Femoral neck density. Significant in women only.

71]. Deletion of the dopamine transporter gene in mice results in deficiencies of skeletal structure and integrity [72]. Influences of L-dopa on the endocrine system have been shown: L-dopa is known to increase release of growth hormone (GH) and thus IGF-1 [73]. This effect is even used as a provocation test for measuring normal pituitary function [74]. In the study conducted by Rico mentioned above, GH stimulation was the underlying mechanism discussed to explain the supposed positive effect of L-dopa on bone. Finally, lower BMD in post-menopausal women with low IGF-1 points to an effect of GH in long-term bone mass regulation [74] and hence to a lever by which dopaminergic drugs could protect bone mass. Long-term excess of GH, in contrast, probably does affect the skeleton negatively, due to unfavourable changes in the micro architecture and matrix composition [75]. Interestingly, GH levels of treatment-naive patients with PD are lowered [76].

In the presence of dopadecarboxylase-inhibitors, L-dopa is preferentially metabolised by catechol-O-methyltransferase (COMT) to S-adenosylmethionine and rapidly converted to S-adenosylhomocysteine and later to homocysteine (Hcy) [77]. Treatment with L-dopa therefore raises Hcy levels. Elevated Hcy levels seem to be correlated with fractures independently from BMD [78–80]. Furthermore, elevated Hcy levels and a high intake of L-dopa correlate negatively with BMD values in PD patients [79]. In patients with PD treated with L-dopa, hyperhomocysteinaemia and BMD loss were prevented by substitution with vitamin B₁₂ and folate [81]. Treatment with Vitamin B₁₂ and folate also reduced hip fracture rates in patients with ischemic stroke and hyperhomocysteinaemia [82].

Benserazide, the dopadecarboxylase inhibitor included in Levopar/Madopar[®], was investigated in two studies in terms of bone changes in rats [83, 84]. Both studies show dose-dependent marked epiphyseal growth disturbance due to lost columnar organization of epiphyseal cartilaginous tissue, followed by ossifications and grotesque compression dislocations in the epiphysis. Morphologically, the changes have some similarity to rickets and to osteolathyrism (a condition linked to defective collagen cross-linking), although neither pattern fits perfectly. Ultimately, rats may not be the appropriate animal model to demonstrate bone safety of drugs aimed at use in humans, because the epiphyses remain open throughout their life spans. Thus some of the problems described could only be relevant for use of benserazide in children with a growing skeleton [84]. As for carbidopa, the dopadecarboxylase inhibitor included in Sinemet[®], we did not find any studies reflecting on bone metabolism.

Discussion

Bone health and bone disease are neglected issues in PD. We have given here an overview of the current knowledge and uncovered the blind spots. PD is a chronic disease, but some non-motor symptoms like constipation, anaemia, anxiety disorder or REM sleep irregularities are very frequent and may precede the onset of typical PD motor affections by five up to twenty years [85]. Hence, mortality of PD patients seems not to be relevantly increased, at least during the first ten years of the disease [39]. So, chronic

endogenous problems like vitamin D deficiency may have plenty of time to weaken the bones in patients with PD.

Falls are frequent in PD and seem to correlate with typical cardinal symptoms of PD, like postural instability, bradykinesia or rigidity [10]. Pathologies of both dopaminergic and non-dopaminergic systems play a role. In particular, postural instability has been linked to the degeneration of the non-dopaminergic neurotransmitter system occurring in late stages of the disease. Cholinergic mesencephalic neuron dysfunction is of major importance in understanding gait and postural disorders in PD and explains why falls are a serious medical problem mainly in patients in the late stages of PD [86, 87]. Furthermore, fear of falling seems to be associated with recurrent falls in patients with PD [88]. Independently of PD, any patient who repeatedly falls should be treated using an interdisciplinary diagnostic and therapeutic approach [89–91].

Two major risk factors are crucial for bone fractures: falls, and porous bones with compromised mechanical strength. Characterising bone *quality* with regard to loss of trabecular continuity in high turnover osteoporosis requires bone biopsies and is not feasible for epidemiological purposes. So studies on bone alterations in PD are usually based on measuring the *quantity* of mineralised bone. Most studies have described lowered BMD in PD. Typically “high turnover osteoporosis” is found in this group of patients. It is characterised as lowered BMD in the presence of elevated levels of bone resorption markers. Hence, lowered BMD accounts for a maximally fourfold risk increase for hip fracture, while other factors like age explain an up to tenfold risk excess [38]. One of them may be sarcopenia as found frequently in PD patients [92]. Besides the compelling assessment of classical risk factors, elderly patients should be evaluated for fracture risk in the following cases: history of falls, fainting or loss of consciousness; muscle weakness; dizziness, coordination or balance problems; difficulty standing or walking; osteoarthritis of the lower limbs; neuropathy and vision loss [38]. In particular, patients with swallowing disturbances are prone to losing weight and developing hypo-nutrition with mineral, protein and vitamin deficiencies. Lack of exposure to sunlight and its consecutive vitamin D deficiency will also be frequent in these patients. In their review published in 2009, Invernizzi et al. question whether vitamin D deficiency itself could trigger neurodegenerative progression of PD [93]. New data, recently published by Knekt et al. seem to support his hypothesis [94]. The pathophysiologic role of GH, IGF-1, PTH, leptine, osteoprotegerine, PPAR- γ and RANKL in this special type of osteoporosis in PD has still to be elucidated.

One cornerstone for fracture risk evaluation is DXA measurement of BMD. In Switzerland, health insurance companies will only reimburse DXA in the following cases: 1) manifest osteoporosis or pathological fracture in the past, 2) hypogonadism, 3) long-term treatment with corticosteroids, 4) primary hyperparathyroidism, 5) osteogenesis imperfecta, 6) malabsorptive gastrointestinal diseases, or 7) therapy control after two years. This list should be extended to A) elevated risk of falls, B) immobility by other disease, or C) long-term medication known to reduce BMD. The actual costs of approximately CHF, US\$ or € 180.–

seem moderate when compared with the potential health benefit for patients.

Until now, bone loss was mostly explained by the immobility of patients with PD. For example, Sato et al. described a similar pattern of bone mineral loss in patients after stroke [95]. Better mobility of PD patients treated with antiparkinsonian agents should therefore increase muscular strength or increase outdoor activity allowing vitamin D production. Thus, when applying Occam's razor to the question whether low BMD in PD needs other explanations than immobility and hypo-nutrition, the oracle's answer would certainly have been "there is no need!" But there are nowadays some reasons to assume that drugs typically used for PD may cause or worsen bone problems in these patients. Osteoporosis can be provoked by benserazide in a rat model. There is evidence of renal and endocrinological effects of dopaminergic drugs in animals as well as in humans. L-Dopa increases Hcy and GH levels. Hyperhomocysteinemia is associated with osteoporosis and elevated fracture risk. Even direct [96] and indirect by GH [75] or Hcy [97] effects of L-dopa inhibiting collagen biosynthesis have been described. If one corrects hypovitaminosis D and low calcium intake in patients with PD, bone loss is mitigated (fig. 1), and if one adds vitamin K₂ (menatetrenone), further bone loss will be prevented – but "high turnover osteoporosis" in terms of DPD-CL excretion will still persist [60]. Bone turnover is only restored to normal values in PD when patients are treated with bisphosphonates [62, 63].

Hyperhomocysteinaemia is correlated with osteoporosis [79, 80], dementia [98] and cardiovascular problems [99]. Supplementation with folate and vitamin B12 seems to favourably influence osteoporosis in PD patients [81], effects on PD dementia remain to be evaluated, whereas these supplements seem to not alter cardiovascular prognosis [100]. Starting dopaminergic treatment with dopamine agonists instead of L-dopa [101] and adding a COMT-inhibitor to L-dopa (Stalevo[®]) instead of increasing the dose to high or very high levels [101, 102] and liberal application of vitamin B12 and folic acid could be favourable for limiting hyperhomocysteinaemia in PD patients.

Osteoporosis is a silent disease and bones do not complain until they break. If a condition is linked to bone problems, the individual consequences will only come to light much later. Not one of the eleven pharmaceutical companies selling drugs for symptomatic treatment of PD in Switzerland stated that they had undertaken systematic studies for bone integrity in PD. We know about several groups of drugs causing or worsening osteoporosis in men. Some less-known examples are antiepileptic drugs [103], anticoagulants [104], antidiabetics [105], antidepressants [106] and proton pump inhibitors [107], all of which are widely used. Why is systematic research for bone health in this vulnerable group of PD patients still lacking? Firstly, studies investigating symptomatic treatments of PD are designed by neurologists, not by rheumatologists or general practitioners. Therefore trials will naturally be focused on neurological changes and not on long-term side effects affecting bone quality and bone strength. Secondly, there is no compelling stimulus for pharmaceutical companies to care about bone safety. Drugs typically used for PD will also be administered to patients with "restless legs syn-

drome" – but even for this indication, bone safety studies are absent. The complete lack of studies on long-term effects of PD drugs on bone metabolism should be corrected by regulatory authorities.

Bone integrity should not be the only concern in long-term treatment: we have learnt a lot from the Vioxx[®] story [108] in terms of drug surveillance. Other topics to monitor could be of great interest such as heart attacks, loss of kidney function, liver cirrhosis, diabetes or macular degeneration. An international database for long-term drug safety could be helpful, as well as meticulous control for health problems associated with medical treatment in large cohort studies (e.g., the Australian "45 and Up Study"; www.45andUp.org.au). To put it frankly: epidemiological studies and observational trials can provide hints to possible health problems, but nothing can replace prospective safety studies.

Limitations

Our article represents an overview including the available literature addressing the problem "bone disease" in patients with PD. Although we performed a broad and unrestricted literature search, we did not find many high quality studies; if we are contending a lack of evidence, we cannot be sure of not having overlooked studies undetected by our search strategy. Some of the studies cited in this review are more than 20 years old. Since then antiparkinsonian treatments as well as life style and health services have changed – maybe our notions on fall risk and fractures cannot be translated into current health care of PD patients.

As mentioned above, prospective studies with respect to bone metabolism during a defined drug treatment for PD are completely lacking. There are observational studies on fall risk, fractures and BMD in patients with PD, but these studies are mostly retrospective and do not define exactly which drugs were given to the patients. Some small intervention studies address bone integrity but not elevated fracture risk in PD. Interventions were done with vitamin D and calcium, menatetrenone (vitamin K₂), vitamin B12, folate, bisphosphonates and sunlight exposure. Since the 2009 review of Invernizzi et al. on the same topic as ours, the data of Jung-Min Koh's Korean group have now been published, backing theories about iatrogenic influences on osteoporosis in PD patients [79, 81]. The available data cannot however definitively answer the question whether symptomatic treatment of PD will do harm to the skeleton – there is some evidence that this is a point of concern, but our opinion is that yes: L-dopa, particularly in higher doses, indeed leads to "high turnover osteoporosis" in PD patients. We still need more prospective studies of good quality bringing light into the complexity of PD, its medication and the consequences for the musculoskeletal system.

Conclusions

The skeleton of patients with PD is obviously in danger of frequent falls and bone mineral loss. Any newly diagnosed patient with PD should be clinically evaluated for fracture risk and usually undergo bone densitometry to detect osteoporosis. Hypo-nutrition should be ruled out. If it is present, the patient should be referred to a nutritional specialist for

counseling. In all patients, routine vitamin D substitution should be started. In cases of osteoporosis, blood samples should be taken to rule out other secondary causes (incl. vitamin K deficiency), and treatment with bisphosphonates started. In cases of pronounced bradykinesia, rigidity and especially postural instability, physiotherapy should be initiated and hip protector devices should be discussed with the patient, preferentially if the patient falls frequently. Irrespective of PD, each patient who newly starts falling should undergo an interdisciplinary diagnostic and therapeutic approach to characterise his risk of osteoporosis and falls.

Every medication applied for long-term treatment of a chronic disease should undergo safety studies for bone preservation. Drug admission authorities should demand these data when registering new substances or when renewing old admissions.

Authors' contributions

MG conceived the study, did the literature analysis and wrote the first draft of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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