Age and Ageing 2015; **44:** 34–41
doi: 10.1093/ageing/afu122
Published electronically 18 September 2014

REVIEW

Assessment and management of fracture risk in patients with Parkinson's disease

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Abstract

Parkinson's disease (PD) is associated with substantially increased fracture risk, particularly hip fracture, which can occur relatively early in the course of PD. Despite this, current national clinical guidelines for PD fail to adequately address fracture risk assessment or the management of bone health. We appraise the evidence supporting bone health management in PD and propose a PD-specific algorithm for the fracture risk assessment and the management of bone health in patients with PD and related movement disorders. The algorithm considers (i) calcium and vitamin D replacement and maintenance, (ii) quantification of prior falls and fractures, (iii) calculation of 10-year major osteoporotic and hip fracture risks using Qfracture, (iv) application of fracture risk thresholds, which if fracture risk is high (v) prompts anti-resorptive treatment, with or without dual X-ray absorptiometry, and if low (vi) prompts re-assessment with FRAX and application of National Osteoporosis Guidelines Group (NOGG) guidance. A range of anti-resorptive agents are now available to treat osteoporosis; we review their use from the specific perspective of a clinician managing a patient population with PD. In conclusion, our current evidence base supports updating of guidelines globally concerning the management of PD, which presently fail to adequately address bone health.

Keywords: *movement disorder, fracture, Qfracture, FRAX, osteoporosis, older people*

Introduction

Parkinson's disease (PD), affecting almost 127,000 UK adults, is the second most common neurodegenerative condition after Alzheimer's disease. Prevalence is increasing within our ageing population, affecting an estimated 1% aged >60 years [1]. PD is primarily a motor disorder but at least doubles fracture risk; the hip being particularly vulnerable [2, 3]. Even within the general population, 30 days following hip fracture 8.2% have died and fewer than half will have returned to their own home [4]; comorbid PD further challenges these outcomes.

Globally, PD guidelines currently lack detail regarding assessment and management of bone health. Despite the 2004 US Surgeon General's report highlighting the importance of PD as a fracture risk [5], the American Academy of Neurology clinical guidelines for PD (and falls) omit to mention fracture/osteoporosis risk assessment [6, 7], as do the 2012 Canadian PD guidelines [8] and 2010 Scottish SIGN guidelines [9]. Although in England, the National Institute for Health and Care Excellence (NICE) acknowledges fracture as a potential complication of PD, it only includes an appendix mentioning optional osteoporosis risk assessment, without providing details [10, 11].

Despite the substantial fracture risk associated with PD, development of clear clinical guidelines has been difficult given the limited evidence base specific to PD. This, combined with heterogeneity in general bone health management, precludes a full systematic review. We aim to appraise the limited evidence supporting bone health management in PD, and interpret the broader bone health literature within the context of PD. We then propose a PD-specific algorithm for primary and secondary care assessment and management of fracture risk in patients with PD and related movement disorders.

Increased fracture risk in PD

Within the general population, osteoporosis is common, often asymptomatic and therefore insidious. The consequences, pri-

marily fractures, represent a significant societal burden, both through direct medical costs (UK > £2 billion/annum) and important social sequelae [12]. Approximately 1 in 2 women and 1 in 5 men aged >50 years will go on to sustain a fracture during their lifetime [13]. In England and Wales, an estimated 76,000 older adults fracture their hip each year [4].

Several retrospective studies have identified an increased fracture risk in PD patients [14, 15, 16, 17], particularly of the hip [18]. Recent findings from the UK Clinical Practice Research Datalink (CPRD) demonstrated a doubling of overall osteoporotic fracture risk and tripling of hip fracture risk in PD patients compared with controls [3]. Further UK analyses of over 3 million primary care patients identified a 2-fold [95% confidence interval 1.8, 2.4] hazard of hip fracture for women with PD and 3-fold [2.4, 3.8] for men, even after accounting for multiple independent risk factors [2]. Across North America, Europe and Australasia, women reporting PD have an unadjusted 3.9-fold [2.8, 5.4] increased hazard of fracture over 3 years [19]. Hip fractures occur relatively early in PD, with median duration from PD diagnosis to first hip fracture being 4 years [inter-quartile range: 1.0, 7.3], such that almost three-quarters of hip fractures occur in mild–moderate disease (Hoehn & Yahr stages I–III) [20, 21]. As most anti-resorptive agents only take effect after 1 year, early fracture risk assessment is strongly indicated.

Even accounting for poorer pre-fracture mobility, the consequences of hip fracture for a PD patient are worse than among the general population, corresponding to higher pressure sore rates, a more than doubled hospital length of stay and a greater proportion of bed/wheelchair dependency after 30 days [20]. PD-specific mortality rates after hip fracture are unknown, but are likely greater than the general population. Women with PD underappreciate their own fracture risk; 68% considered their risk 'the same or lower than women of the same age' in one prospective study [19]. This may reflect absence of bone health assessment from PD guidelines with consequent inattention by doctors.

Increased falls risk in PD patients

Almost all hip fractures occur after a fall. Falls, a major predictor of hip fracture (hazards ratio [HR] 2.0 [1.8 to 2.3]) [22], are a common, potentially devastating complication of PD. Prospective studies estimate that 46% [12, 35] of PD patients (mean age: 69 years) will fall during just 3 months of follow-up [15]. Multiple factors increase falls risk, including motor dysfunction from loss of postural reflexes and gait freezing, and non-motor features such as fear of falling and impaired cognition [23–25]. Falls and their consequences can contribute to a vicious circle of secondary immobilisation with restricted social activities [26]; immobility lowers bone mineral density (BMD) [27]. The predisposition towards hip fractures in PD likely results from characteristic truncal stiffness during postural perturbation and absence of protective arm movements when falling [28].

Pathophysiology of osteoporosis in PD patients

Osteoporosis has a multi-factorial aetiology in PD, including general and PD-specific risk factors. Several case–control studies suggest that PD patients have lower BMD than controls [29–31, 32, 33, 34]. Underlying mechanisms likely include reduced physical activity, muscle strength and nutrition. Vitamin D deficiency (≤30 ng/ml) is common in PD patients, affecting ~55% versus 36% controls and 41% with Alzheimer's disease [34]. Nutritional status is often challenged in PD patients by impaired hand–mouth coordination, dysphagia, intestinal hypomotility, depression, cognitive deficits and medication side effects. Levodopa, associated with hyperhomocysteinaemia, may also lower BMD [35].

Fracture risk assessment in the general population

Accurate fracture risk prediction is crucial to enable appropriate targeting of preventative strategies to reduce incident fractures. Whilst a range of fracture risk assessment tools have been developed, only six have been both validated and tested in more than one study, of which two (the most widely used), FRAX and Qfracture, are endorsed by NICE [36–40].

The FRAX tool calculates 10-year probabilities of hip and major osteoporosis-related fractures (MOFs) (clinical spine/forearm/hip/proximal humerus), with or without BMD, using 11 variables: age, sex, weight, height, previous adult fracture, parental hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis, ≥3 unit alcohol intake daily and secondary osteoporosis, and it is applicable from ages 40 to 90 years [39]. PD is not listed as a cause of secondary osteoporosis and is not specified within FRAX.

By contrast, Qfracture specifically includes PD when predicting incident risk [2, 38]. Qfracture algorithms are based upon prospective data from 3.1 million UK patients, studied across 420 primary care practices and validated in a further 1.6 million patients from 207 practices; 7,809 (0.2%) had a PD diagnosis, allowing inclusion of PD as an independent predictor. However, routine primary care data are likely to be less complete than the research data underpinning FRAX. Qfracture is applicable from ages 30 to 99 years, but lacks capacity to include measured BMD. However, in clinical practice, BMD is often unavailable/unmeasured in older individuals [41, 42]. Calculated Qfracture risks can be generated for annual increments up to 10 years; this flexibility aids decision-making where life expectancy is challenged by progressive degenerative disease.

Unlike Qfracture, the FRAX tool links directly to National Osteoporosis Guidelines Group (NOGG) guidance regarding intervention thresholds [40, 43]. Because these thresholds for a given age are set at a risk equivalent to that associated with a prior fracture, the thresholds rise with age and may disadvantage older people, particularly those with PD, whose first fracture is more likely to be at the hip, and those with a life

expectancy <10 years [44–46]. A Qfracture-generated fracture risk prediction over 3–5 years may have greater clinical utility. Furthermore, in those aged >80 years, NICE caution against 10-year predictions, which may underestimate short-term fracture risk [37].

PD-specific fracture risk assessment

Although FRAX may be slightly faster to use than Qfracture, FRAX does not specifically account for the additional fracture risk conveyed by multiple clinical risk factors including PD, nor, importantly, falls. Inclusion of falls and PD within FRAX would be ideal; however, currently a formal quantitative adjustment of FRAX probabilities has not been judged possible based upon existing evidence [47]. However, an inflation of the 10-year hip fracture probability, by 30% of its value, for each fall reported in the past year, has been proposed [47]. NOGG treatment thresholds were developed for applying to FRAX MOF probabilities, but not hip probabilities nor Qfracture risks. Therefore, when interpreting Qfracture risks and FRAX hip fracture probabilities, an intervention threshold is needed. Such an approach was a major recommendation from the U.S. National Osteoporosis Foundation in 2010 that advised treating any postmenopausal woman or man aged >50 with low BMD (*T*-score < −1.0) and a 10-year MOF probability ≥20% or hip fracture probability ≥3% [48]. This low hip fracture threshold was based upon an upper limit of US$60,000 per QALY. By comparison, NICE technology appraisals (TA160&161) used a more conservative cost-effectiveness threshold (£30,000/QALY for secondary prevention; £20,000/QALY for primary prevention) [41, 42]. Hence, 10-year MOF/hip fracture probabilities of ≥20%/≥5% have been proposed by some in the United Kingdom [49].

Although PD could be considered a 'secondary cause of osteoporosis' in an attempt to capture associated fracture risk, which FRAX might otherwise miss, no study has assessed this approach. Whilst Qfracture may better capture fracture risk in a PD population, its superiority is by no means certain.

Treatment options in bone health and PD

A full review of all osteoporosis treatment options is beyond the scope of this article; instead considerations specific to PD are outlined. As in general osteoporosis clinics, PD patients should be counselled against smoking and excessive alcohol intake, and physical activity should be encouraged, both for its effects on BMD and as part of a falls reduction programme [50, 51].

Calcium and vitamin D

A healthy diet, rich both in calcium and in vitamin D, should be encouraged; patient societies, e.g. National Osteoporosis Society, offer useful free printed resources [52]. Increasing with age and disease duration, under-nutrition is common in PD patients, with 23% at medium/high risk of malnutrition defined using the Malnutrition Universal Screening Tool in one cross-sectional study [53]. Vitamin D levels, often low in PD patients, predict balance ability measured by clinical posturography [34, 54]. Both increased sunlight exposure and vitamin D replacement have been shown to reduce incident fractures among older Japanese PD patients [55]. Recent vitamin D guidelines, applicable to a PD population, suggest that 25-hydoxyvitamin D should be measured in patients with (i) bone diseases, e.g. osteoporosis/osteomalacia, and (ii) symptoms potentially attributable to vitamin D deficiency, e.g. widespread pain, sarcopenia with muscle weakness and falls risk. Routine testing of asymptomatic individuals is not currently recommended, though targeted testing may be appropriate. The high prevalence of vitamin D deficiency and reported falls among PD patients supports consideration of vitamin D testing. The Department of Health recommends daily supplementation in those aged ≥65 years with inadequate sun exposure [56]. Vitamin D deficiency and insufficiency should prompt vitamin D replacement and then maintainence, with or without calcium supplementation according to dietary calcium intake [,57 58] (Supplementary data available in *Age and Ageing* online, Data S1).

Anti-resorptive agents

Oral bisphosphonates (e.g. alendronate) are first-line pharmacological treatments for osteoporosis [41, 42]. Poor gastrointestinal absorption is maximised by strict early morning dosing regimens; positioned upright (maintained for ≥30 min post-dose) with a full glass of water. Oesophagitis is not uncommon. Hence, (i) dysphagia (prevalence >75% in PD patients [59]), (ii) severely stooped posture (a neuromuscular feature of PD independent of osteoporotic kyphosis) or dropped head syndrome [60] (Figure 1) and (iii) cognitive dysfunction (dementia prevalence 30–40% in PD populations [61]) all challenge oral bisphosphonate use. Morning dosing before other medications may be impractical for patients on complex PD medication schedules. However, PD patients are often familiar with time-specific treatment regimens and may manage additional weekly tablets, especially earlier in the disease course prior to complex medication timetables. Ibandronate is an oral monthly alternative for postmenopausal women with vertebral fractures [62]. Bisphosphonate efficacy in PD is limited to three small studies of oral risedronate/alendronate from Southeast Asia. All showed substantial reductions in fracture risk in PD, arguably to a greater extent than expected in non-PD populations [63–65]. Oral risedronate demonstrated a relative risk reduction in hip fracture over 2 years of (i) 66% in 242 male PD patients (relative risk [RR] 0.33 [0.09, 1.20]) [64] and (ii) 80% in 272 female PD patients (RR 0.20 [0.06, 0.66]) [65]; mean age: 74 years, both reported good treatment adherence.

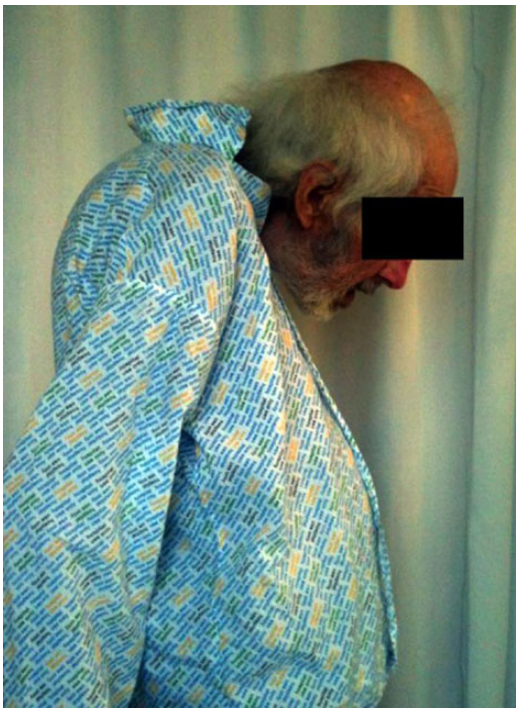

Figure 1. The dropped head syndrome, seen here in a patient after 17 years of PD, is due either to dystonia of flexor neck muscles or to weakness of extensor neck muscles [60]; a similar picture is seen with the antecollis of multisystem atrophy. Reproduced with patient consent.

When oral bisphosphonates are unsuitable or not tolerated, parenteral treatments should be considered. Annual intravenous zoledronate reduces incident hip fractures by 41% over 3 years (HR 0.59 [0.42, 0.83]) in postmenopausal women with osteoporosis [66]. A single zoledronate infusion suppresses bone turnover maintaining BMD for up to 5 years [67, 68]; this may reduce fracture risk but data are lacking. Such findings raise the potential suitability of a single infusion in more complex PD patients with limited life expectancy. Zoledronate has not been specifically trialled in a PD population; although the pivotal HORIZON trial included some PD patients, numbers were not defined and not specifically analysed (email communication, Andrew Grey [66]).

Denosumab, a human monoclonal antibody to receptor activator of nuclear factor-$\varkappa$B ligand (RANKL), blocks binding to RANK, inhibits development and activity of osteoclasts and decreases bone resorption, increasing BMD. Given by six monthly subcutaneous injection, denosumab preferentially increases cortical BMD [69], so may be especially suitable in PD where hip fractures predominate (hip strength being predominantly derived from cortical bone). In the United Kingdom, denosumab currently has an osteoporosis licence in postmenopausal women, but not in men. Trials, in non-PD populations, have included individuals with estimated glomerular filtration rate ≥15 ml/min [70].

The 2-h fast before and after evening, strontium ranelate previously limited its role in PD patients where medication schedules can impede fasting. However, recent concerns regarding vascular risk further restrict strontium use in osteoporosis [71]. The effectiveness of the provision of hip protectors in reducing incident hip fractures is not clearly established [72] although targeted use in motivated patients may have a role. Treatment costs vary by agent and administration route (Supplementary data available in *Age and Ageing* online, Data S2); parenteral treatments incur greater costs. The patent expiry for iv Zoledronate offers promise of future cost reductions.

Osteoporosis treatment duration guidance has recently been issued by NOGG [43], given concern regarding increased atypical femoral fracture risk associated with prolonged anti-resorptive use [73]. Although absolute atypical fracture risk remains very low proportionate to typical fractures, NOGG guidance suggests consideration of a 'drug holiday' in patients under age 75 years, without falls, with no prior fracture and a BMD response to treatment [43]. In general, for those with a high fracture risk (including many with PD) continued treatment is recommended, with reassessment in the case of incident fracture.

An algorithm for bone health in PD patients

Based upon the evidence outlined, we propose an algorithm to guide assessment and management of fracture risk in patients attending PD clinics (Figure 2; full annotated algorithm in Supplementary data available in *Age and Ageing* online, Data S1). Fracture risk is best assessed within the context of the multidisciplinary team, including specific falls risk management. The algorithm is applicable to most patients with Hoehn & Yahr stage I–IV disease [21]. In advanced PD (Hoehn & Yahr stage V), or where co-morbidities markedly curtail life expectancy and management is palliative, fracture risk assessment/treatment may no longer be appropriate.

Our algorithm follows six sequential steps: (i) calcium and vitamin D replacement and maintenance [57], (ii) quantification of prior falls and fractures (including occult vertebral fractures; consider lateral thoraco-lumbar radiographs for height loss, acute back pain or kyphosis disproportionate to the neuromuscular condition), (iii) calculation of 10-year MOF and hip fracture risks using Qfracture, (iv) application of fracture risk thresholds. High fracture risk (v) prompts treatment ± dual X-ray absorptiometry (DXA). Low fracture risk (vi) prompts re-assessment with FRAX, (with additional inflation of fracture probabilities for a history of falls) and application of NOGG guidance regarding DXA referral and treatment

We propose intervention based upon a Qfracture 10-year MOF risk ≥20% and/or a hip fracture risk ≥5%. In women aged ≥75 years with ≥2 clinical risk factors for fracture or low BMD (e.g. PD and prior fracture), NICE suggests that a DXA scan may not be required if impractical as judged by the clinician [41, 42]. A judgement must be made regarding DXA, considering the benefits of baseline BMD measurement to guide future re-assessment according to NOGG

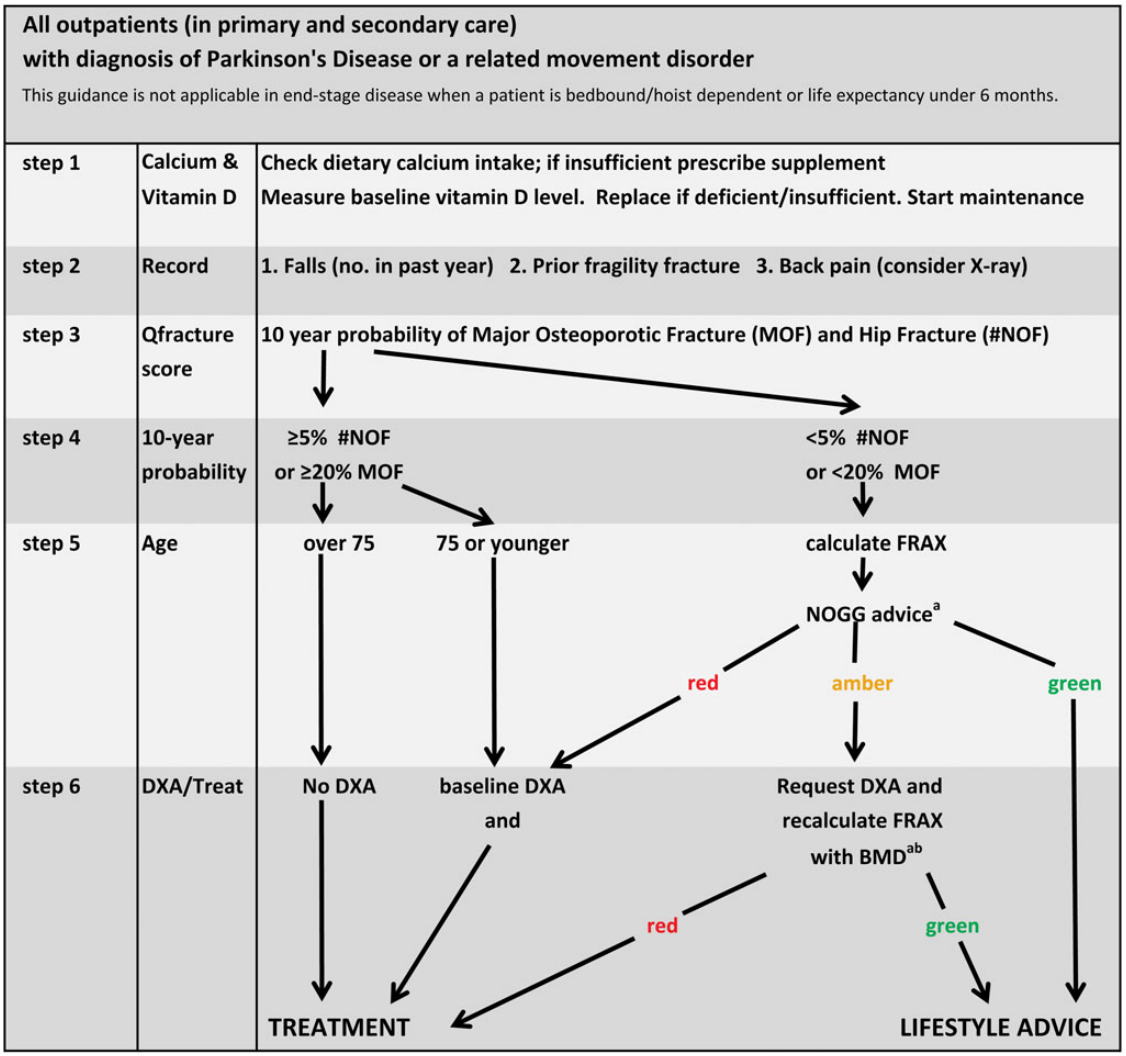

Figure 2. Work through steps 1–6 to determine treatment/lifestyle options. (a) If falls in the last year, inflate FRAX calculated MOF risk by 30% per fall (maximum five). (b) If BMD is known, calculate FRAX by including hip BMD value. Minimum 2-year duration between DXA. DXA, dual X-ray absorptiometry. See Supplementary data available in *Age and Ageing* online, Data S1 for full annotated algorithm.

guidance [43], and physiological rather than chronological age. We recommend that the algorithm is applied yearly, sooner for incident fractures, with treatment adherence checked at each clinic encounter.

Application of an algorithm for bone health in PD patients

We applied our algorithm to two hypothetical ageing individuals with PD, one female, one male, both of white European origin for a fixed BMI of 25 kg/m^2 (the median BMI in a UK PD population [53]). We used both FRAX (UK) and Qfracture to calculate 10-year MOF and hip fracture probabilities/risks, for increasing ages between 55 and 90 years with, and without, a single fall in the previous year (30% FRAX probability inflation per fall) and no additional osteoporosis risk factors (Figure 3).

Applying a ≥20% MOF treatment threshold, all women with PD aged 84+ and men aged 90+ without falls would be eligible for treatment based on Qfracture calculations, reported falls drop these ages to 75+ and 84+, respectively. Alternative use of FRAX produces similar predictions in women, but substantially lowers risk in men. Applying a ≥5% hip fracture threshold prompts intervention at much younger ages in both men and women: all women with PD aged 70+ and men aged 75+ without falls would be eligible for treatment based on Qfracture calculations, reported falls lower these ages to 67+ and 70+, respectively (Figure 3). Adding further clinical risk factors further lowers the age for intervention (Supplementary data available in *Age and Ageing* online, Data S3).

We further tested our algorithm for the BMI range of 15–30 kg/m^2 with NOGG versus ≥20/5% intervention thresholds (Supplementary data available in *Age and Ageing* online, Data S4), based upon which we can broadly

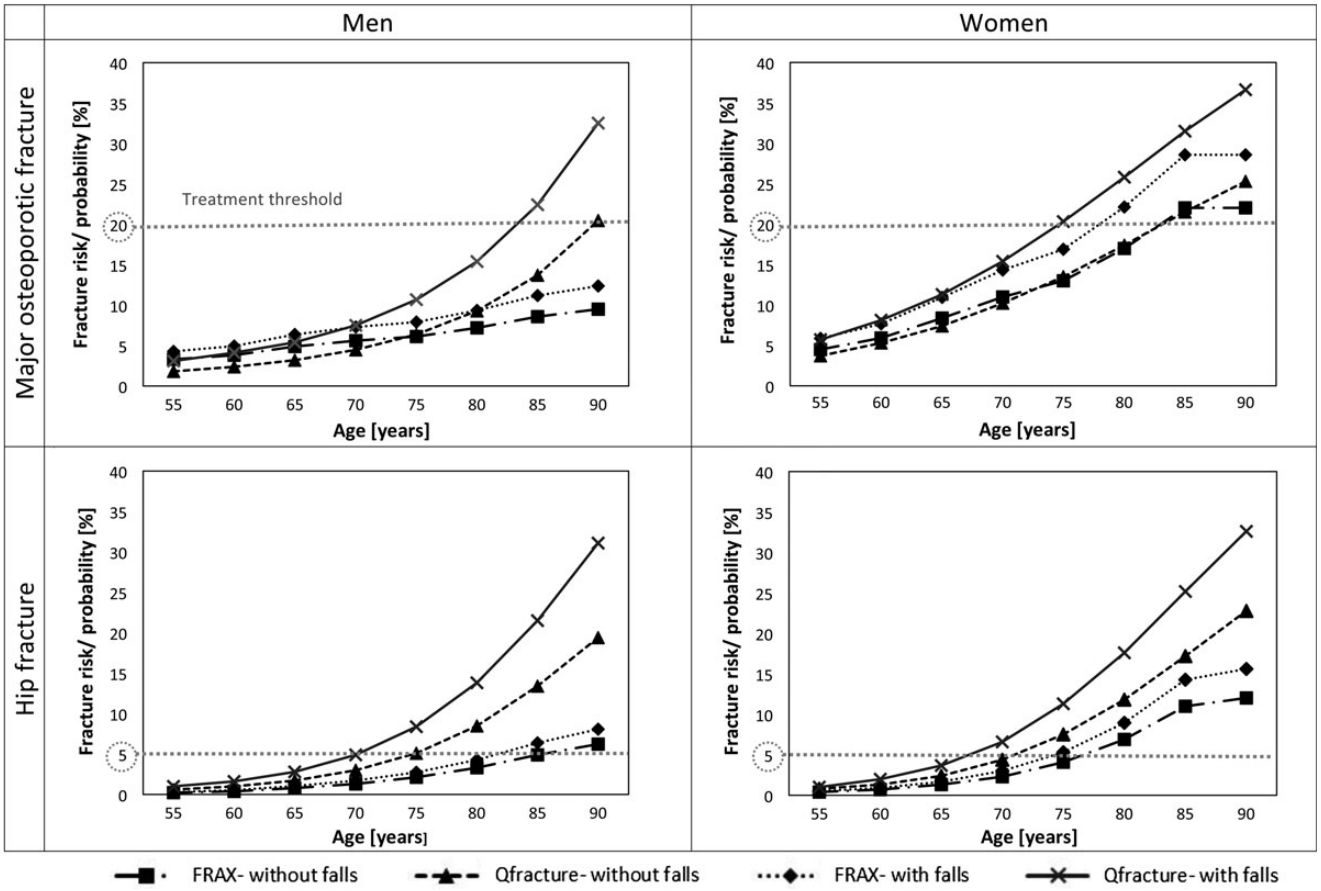

Figure 3. Ten-year probability/risk for major osteoporotic fracture and hip fracture for men and women with PD calculated using FRAX and QFracture algorithms assuming a BMI of 25 kg/m^2, for ages 55–90 years. Multiplication coefficient of 1.3 was used to inflate FRAX to reflect one fall within the preceding year. The recommended thresholds for treatment are shown.

recommend that, as a minimum, all women aged ≥75 years and men aged ≥80 years with PD should be prescribed bone protection, and in the cases of reporting falls, all women aged ≥70 and men aged ≥75. FRAX probabilities (with falls inflation) are proportionate to Qfracture risks, although FRAX judges fracture risk to be lower. We illustrate application of this algorithm with three clinical cases (Figure 4).

Conclusion

Inevitably, the heterogeneity of a clinic population will generate a wide variety of fracture risks. Parkinsonian syndromes with high falls risk, e.g. progressive supranuclear palsy and multi-system atrophy, and patients with prominent dementia (such as PD-dementia or dementia with Lewy bodies) will convey some of the highest fracture risks. We have outlined the evidence base supporting a clinical algorithm aimed at guiding an individualised fracture risk assessment among patients with PD and associated movement disorders managed within an outpatient setting. When first implemented, we expect to increase bone health treatment within our PD population. Best use of this algorithm will occur in conjunction with multidisciplinary team assessment and falls programmes and will include systems for monitoring and auditing practice and outcomes. Whilst clinical trials specific to a PD population would permit more detailed recommendations, the current evidence base supports updating of guidelines globally concerning the management of PD, which presently fail to address bone health.

Key points

- Fracture risk is increased in PD, especially at the hip.
- The increased fracture risk occurs relatively early in the disease course.
- Qfracture calculates hip and major osteoporotic fracture risks, taking into account both PD and falls history as risk factors.
- Fracture risk assessment, with appropriate anti-resorptive treatments to reduce risk, should be part of routine PD care.
- PD guidelines should be revised to include management of fracture risk.

Case 1

- An 83-year-old white European woman, BMI 27 kg/m^2, with moderate PD (3 years from diagnosis) and a PD dementia, is largely housebound.
- She is vitamin D replete maintained on daily calcium and vitamin D supplements. Her medications are managed with a dosette box and evening carer input.
- Chronic marked kyphosis prompts a thoraco-lumbar X-ray; a vertebral fracture is identified. She has fallen once in the past year. Qfracture calculates her 5-year risks of both MOF and hip fracture as 27%; anti-resorptive treatment is indicated without the need for a DXA.
- As oesophageal dysmotility and cognitive impairment prevent oral bisphosphonate use she is prescribed **denosumab**, given twice yearly by the district nurse.

Case 2

- A 63-year-old Asian woman, BMI 25 kg/m^2 has early parkinsonism and 'red flag' symptoms suggesting possible multi-system atrophy, including frequent falls (five in last year). She is vitamin D replete and has no other co-morbidities
- Qfracture (with PD selected) calculates her 10-year MOF and hip fracture risks as 4.9% and 1.0%, respectively, well below the recommended treatment threshold of 20/5%. FRAX confirms 10-year probabilities of 4.6/1.0% (11.5/2.5% with falls inflation using 30% increase per fall). **Lifestyle advice** is provided.

Case 3

- A 72-year-old white European man, with PD for 9 years, without cognitive impairment, BMI 19 kg/m^2, takes antidepressants. He has dropped head syndrome (figure 1) which makes swallowing difficult.
- In clinic vitamin D deficiency (18 nmol/l) is treated with 300,000 units of cholecalciferol; maintenance of calcium and vitamin D is commenced.
- Despite falling 3 times/year, he has never fractured. Qfracture 10-year MOF and hip fracture risks are both 19.2%. Aged <75 years he has a DXA scan; a femoral neck T-score of –2.9 gives a FRAX 10-year probability of MOF/hip fracture 8.7/4.1%. Applying a 30% inflation for each of three falls, estimates a 7.8% hip fracture risk.
- Anti-resorptive therapy is indicated. As his dropped head syndrome precludes oral bisphosphonates, **iv zoledronate** is initiated.

Figure 4. Three clinical cases illustrating application of the bone health algorithm.

Supplementary data

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

Acknowledgements

We thank Ashok Bhalla, Tehseen Ahmed and Jackie Webb for their feedback regarding the practicalities of the algorithm.

Funding

This work was supported by Arthritis Research UK (C.G. is funded through a clinician scientist fellowship grant number 20000) and Parkinson's UK (E.H. is funded through a career development award grant number F1003). The sponsors played no role in the design or writing of the paper.

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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 data available in *Age and Ageing* online, Data S5.

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Received 3 April 2014; accepted in revised form 25 June 2014