Optimising the management of osteoporosis

Authors: Ziad Farrah[A] and Ali SM Jawad[B]

ABSTRACT

With increasing longevity of the population globally, the prevalence of osteoporosis will rise, associated with significant morbidity, disability and increased mortality. Adequate intake of calcium, vitamin D, increasing physical activity, a strategy of avoiding falls, cessation of smoking and avoiding excessive alcohol intake are pivotal in maintaining healthy bones in all age groups. Oral bisphosphonates remain the most cost-effective first line of treatment. Better methods of identifying patients with high fracture risk is needed as there is adequate effective treatment for osteoporosis.

KEYWORDS: Osteoporosis, bisphosphonates, denosumab, teriparatide

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Introduction

The prevalence of osteoporosis increases with age. It is well documented that fragility fractures are associated with significant morbidity including pain and disability, increased mortality and a substantial societal economic burden.[1] With the increasingly ageing population, predictions suggest an ever increasing cost burden resulting from osteoporotic fractures.[2] In this review, we set out to explore some of these concepts and present the evidence relating to them.

Definitions

Osteoporosis is defined as a skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture.[3] Indeed, there are multiple factors affecting the strength of bone and, therefore, fracture risk including bone mineral density (BMD) and bone architecture.[4]

Bone mass in both men and women increases until a peak is attained at around the age of 30.[5] A slow rate of bone loss starts at around age the age of 40 years. However, the accelerated postmenopausal phase of bone loss is superimposed on top of this slow loss phase and the rate of bone loss can be as great as 5–6% per year.[6] Oestrogen deficiency is the major determinant of bone loss after the menopause due to the removal of the 'brakes' from osteoclastic activity.[7]

Authors: [A]consultant in rheumatology, Northwick Park Hospital, Harrow, UK; [B]professor of rheumatology, The Royal London Hospital, London, UK

The World Health Organization classification of BMD may be applied to perimenopausal and postmenopausal women of all ethnicities and in men aged 50 years and older. Using dual-energy X-ray absorptiometry (DXA), a T-score of −2.5 or less defines osteoporosis at the femoral neck.[8] However, most authorities accept the definition of osteoporosis using the lumbar spine or total hip but not at other sites.[9] This is because a T-score of −2.5 identifies about 30% of postmenopausal white women as having osteoporosis, which is approximately the lifetime risk of fragility fracture in this population. While this definition is widely used due to its simplicity and practicality, some suggest that the BMD definition of osteoporosis can result in significant variability, depending on site selection with a significant potential for misdiagnosis.[9,10] Moreover, the diagnosis of osteoporosis in young people remains contentious. It is suggested that in growing children and adolescents (5–19 years), osteoporosis is diagnosed if there is a BMD Z-score of less than or equal to −2.0 plus a secondary cause of osteoporosis or a fragility fracture.[11]

Impact of the disease

Osteoporotic fractures are associated with significant morbidity especially with increasing age. Cooper outlines that at 1 year after hip fracture, 60% of patients had difficulty with at least one essential activity of daily living, 40% were unable to walk independently and 30% had permanent disability.[12] In addition, there is a 20% mortality 1 year post-fracture. Osteoporosis is also a rapidly progressive disease, one in four osteoporotic women will have a fracture within 1 year of an incident vertebral fracture, and one in three patients with subsequent non-vertebral fractures will have another non-vertebral fracture within a year.[13] A study which examined the impact of all clinical fractures on mortality rate using data from the Fracture Intervention Trial (FIT) found that women who sustained any clinical fracture had a 6–9 times higher mortality rate, with the highest risk associated with hip and vertebral fractures.[14]

Fracture assessment

- **DXA:** Using DXA, a T-score of −2.5 or less defines osteoporosis at the femoral neck, total hip or the lumbar spine. But since most fractures occur in patients with T-scores better than −2.5, relying on DXA will lead to missing a large number of patients at risk of fracture.
- **Fracture Risk Assessment Tool (FRAX):** FRAX is a risk assessment tool used to predict the probability of fracture in both men and women.[15] It is recommended for use by the National Institute for Health and Care Excellence (NICE) as it

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can provide a framework to assess risk using clinical risk factors alone or in combination with BMD.[16] However, FRAX has many limitations.[17] For example, it does not incorporate all risk factors, such as fall frequency. Some risk factors are not quantified, including corticosteroid dose and smoking history. Diseases such as diabetes are not included either. FRAX is only relevant for untreated patients and those who are aged 40 years or more. FRAX, therefore, should not replace clinical judgement.

- **Qfracture score:** Qfracture was developed to address some of the shortcomings of FRAX and also estimates the 10-year absolute risk of osteoporotic fractures and hip fractures in men and women. It is recommended in NICE and other national guidelines.[18] It has been validated in UK general practice population and it is applicable to other populations. Qfracture expands on the components of FRAX to include more detailed smoking history, falls risk, and comorbidities like diabetes and epilepsy.[19] Unlike FRAX, Qfracture does not integrate BMD in the assessment of fracture risk and relies solely on clinical risk factors. Further, the evidence for different pharmacological treatments in osteoporosis is based on patients with fractures or low BMD, and not calculated scores derived from independent risk factors. Therefore, whichever risk tool is used; clinical judgement remains central in the decision-making process.[19]
- **Garvan Fracture Risk Calculator:** This tool was developed in Australia using five key risk factors for fracture: a person's age, weight, BMD, a history of previous fractures and a history of falls. Using this information, an algorithm of risk is constructed forming the basis of the calculator tool.[20]
- **Vertebral fracture assessment:** Vertebral fractures carry a significant prognostic value in predicting future fractures in patients with osteoporosis.[13] However, these may not always be symptomatic or come to clinical attention. As such, assessing for vertebral fractures has gained popularity when establishing patients' risk of fractures and can influence choice of treatment. This can be done using simple lateral lumbar spine radiography, or by performing a vertebral fracture assessment (VFA) using the densitometer.[21] VFA by DXA provides images of the thoracic and lumbar spine for the purpose of identifying vertebral fractures.[22] The benefits of VFA are that it can be performed conveniently at the time of DXA, it uses less radiation compared to standard X-rays and it is affordable.[22] However, appropriate use of this assessment tool requires adequate training and adherence to clinical guidelines and quality standards.[23]

In our practice, we rely on DXA, FRAX and clinical judgement in assessing fracture risk.

How useful is a diagnosis of osteopenia?

It is arguable that a diagnosis of osteopenia can create a lot of anxiety for both patients and physicians. It can be challenging to know how significant the degree of osteopenia is and when would be most appropriate to re-scan for BMD. A prospective study of 4,957 postmenopausal women of at least 67 years of age sought to answer these questions.[24] All women included in the study had either normal BMD or osteopenia (T-score −1.01 to −2.49, total hip) at baseline and no history of hip or vertebral fracture and not receiving any osteoporosis treatments. They were followed-up for 15 years. The BMD testing interval was defined as the time required for 10% of women to make the transition to osteoporosis without having a hip or clinical vertebral fracture. This study found that osteoporosis would develop in less than 10% of older women during rescreening intervals of approximately 17.4 or 16.5 years for women with normal BMD or mild osteopenia (T-score −1.01 to −1.49) at baseline, respectively; 4.6 years for women with moderate osteopenia (T-score −1.50 to −1.99); and 1.0 year for women with advanced osteopenia (T-score −2.00 to −2.49).[24] In our practice, we follow the conclusions of this study. We tend to use the term 'low bone mass' for patients with a T-score between −1.00 to −1.99.

Management of osteoporosis

Clinical guidelines for the management of osteoporosis have been published by numerous groups including NICE and the National Osteoporosis Guideline Group (NOGG).[25,26] Useful information can also be found on the Royal Osteoporosis Society website.[27] These share common recommendations in managing osteoporosis and are discussed in the following sections.

Lifestyle advice

Cessation of smoking, avoidance of excessive alcohol intake, regular exercise within the limit of the person's ability and a strategy of prevention of falls are advisable to all patients and even people without osteoporosis.[1,3,5] Though weight bearing exercise helps in increasing bone density in the weight bearing bones, any exercise, such as walking and swimming, may strengthen muscles and improve wellbeing. However, the beneficial effect of exercise on BMD is small.[28]

Calcium and vitamin D

There is an increasing confusion and controversy regarding the benefits of supplementation in calcium and vitamin D without other treatments.[29]

The Institute of Medicine recommends that adults maintain a daily calcium intake of 1,000 to 1,200 mg for preventing osteoporosis and reducing fracture risk.[30] A meta-analysis of 29 randomised trials (n=63,897) found that in trials that reported fracture as an outcome (17 trials; n=52,625), calcium supplementation was associated with a 12% risk reduction in fractures of all types (risk ratio 0.88; 95% confidence interval (CI) 0.83–0.95; p=0.0004).[31] The treatment effect was better with calcium doses of 1,200 mg or more than with doses less than 1,200 mg (0.80 vs 0.94; p=0.006).

In another meta-analysis of 59 randomised controlled trials (RCTs), however, increasing dietary calcium intake (by 250–3,320 mg daily) increased baseline BMD by 0.6% to 1.0% at the total hip and total body at 1 year and by 0.7% to 1.8% at the total hip, total body, femoral neck and lumbar spine at 2 years, but no changes at the forearm were observed.[32] Although statistically significant, this study concluded that these BMD increases did not translate into clinically significant reductions in fracture risk.

A systematic review analysed 58 cohort studies of dietary calcium intake and fracture risk.[33] Most of the studies (74%), showed no association between dietary calcium intake and risks for total, hip, vertebral or forearm fractures; and positive associations in the remaining studies were weak. Yet, in analyses of data from 26 randomised trials, calcium supplements (≥1,000 mg daily in most studies) lowered relative risk (RR) for total and vertebral fractures by 11% and 14%, respectively. Nevertheless, corresponding

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numbers needed to treat to prevent one fracture were found to be high (77 and 489), and calcium supplements did not lower risks for hip fracture or forearm fracture. The study concluded that untargeted increases in calcium intake through dietary sources or supplements have minimal effects on BMD and fracture risk and that evidence that calcium supplements prevent fractures is weak and inconsistent.[33]

Not only is the evidence regarding calcium supplementation conflicting, there is growing evidence of the harmful consequences of calcium.[34] These include cardiovascular disease, renal calculi, dyspepsia, constipation and malabsorption of medication such as levothyroxine.[35–37]

It is well recognised that in adults, severe vitamin D deficiency can cause osteomalacia, most likely when serum 25-hydroxyvitamin D (25(OH) vitamin D) level falls below 15 ng/mL. In this case, replacing vitamin D is advised. However, establishing clear recommendations regarding vitamin D for fracture prevention outside this context may not be straightforward. In a survey of the diet and nutrition of adults aged 19–64 years living in private households in the UK, carried out between July 2000 and June 2001, the mean daily intake of vitamin D from food sources was 3.7 µg for men and 2.8 µg for women.[38] This is significantly lower than that recommended by the Scientific Advisory Committee on Nutrition (SACN).[39] SACN reviewed previous recommendations in the light of public health advice to stay out of the sun and wear sunscreen and accumulation of new evidence on vitamin D. It has recommended a reference nutrient intake, the amount that is sufficient to meet the needs of 97.5% of the population, for vitamin D of 10 µg (400 IU) a day to protect musculoskeletal health in people aged 4 years or older.

A systematic review found in osteoporotic populations, the prevalence of 25(OH) vitamin D concentration <12 ng/mL ranged from 12.5% to 76%, while prevalence rates reached 50% to 70% of patients with a history of fracture using a cut-off of 15 ng/mL.[40] This review also found that in post-menopausal women, the prevalence of 25(OH) vitamin D concentrations ≤20 ng/mL was also very variable ranging from 1.6% to 86% for community-living and institutionalised women, respectively.[40] Vitamin D in a dose of 700–1,000 IU a day was found to reduce the risk of falls among older individuals by 19% and to a similar degree as active forms of vitamin D.[41] However, several randomised trials have reported that patients with high blood levels or taking high bolus doses of vitamin D had an unexpected increased risk of falls and fractures, suggesting that this vitamin can have unexpected toxic effects.[42,43]

Using fractures as an outcome, a meta-analysis of five trials comparing vitamin D (400 to 1,370 units/day) with placebo in over 14,500 older men and women reported that vitamin D supplementation alone did not reduce fracture risk (RR 1.03; 95% CI 0.84–1.26), with high heterogeneity between studies (I^2=60%; p=0.02).[44] In a subgroup analysis, the fracture risk reduction was larger among institutionalised older individuals than community-dwelling individuals (RR 0.71 vs 0.92).

Supplementary calcium and vitamin D without other pharmacologic medication is not effective as treatment for osteoporosis apart from institutionalised older individuals.[44] We do not recommend calcium and vitamin D in others except those taking pharmacologic treatments for osteoporosis like bisphosphonates or denosumab, however, should take concomitant vitamin D (and calcium) supplements to ensure adequate serum vitamin D levels, optimise the medication effect and reduce the risk of post-treatment hypocalcaemia.

Pharmacologic treatment of osteoporosis

There are multiple guidelines from professional organisations, and numerous drugs approved for the treatment of osteoporosis.[45] Systematic review of the pharmacologic treatments of osteoporosis shows high-strength evidence that bisphosphonates, denosumab and teriparatide reduce fractures compared with placebo, with relative risk reductions from 0.40 to 0.60 for vertebral fractures and 0.60 to 0.80 for non-vertebral fractures.[45] Raloxifene has been shown in placebo-controlled trials to reduce only vertebral fractures.[46] It is recommended that the use of bisphosphonates, denosumab, teriparatide and raloxifene have to be given with a total calcium intake of at least 1,000 mg per day and a total vitamin D intake of 600 to 800 IU per day.

Oral bisphosphonates, especially alendronate, is recommended as first-line therapy for postmenopausal osteoporosis. Zoledronate is preferred in patients with uncontrolled gastroesophageal symptoms, poor adherence and those on polypharmacy. Denosumab is an alternative. We recommend zoledronate in preference to alendronate in patients who smoke because we have found that smokers with osteoporosis have a significantly poorer response both in the lumbar spine and in the hip to alendronate compared to intravenous zoledronate.[47] However, our findings need to be confirmed by others. Teriparatide is best reserved for patient with severe osteoporosis and multiple fractures.

Bisphosphonates

Three key trials of the use of bisphosphonates in osteoporosis show a reduction in fracture rate as the primary end point, and increases in BMD at the lumbar spine and a reduction in markers of bone turnover as secondary end points. In the FIT trial, at 3 years, 15% of those who received placebo and 8% of those on alendronate had sustained one or more new vertebral fractures (p=0.001), and 2.1% and 1.1%, respectively, sustained new hip fractures (p=0.05) as assessed by X-ray.[48]

In the VERT trial, the rate of new vertebral fractures after 3 years was 11.3% on 5 mg of risedronate daily, as compared with 16.3% on placebo (p=0.003).[49] In a subsequent trial, risedronate was shown to be effective in reducing the rate of hip fractures as well.[50]

The HORIZON trial, at 36 months, the absolute rate of new vertebral fractures was 3.3% in the zoledronic acid group, as compared with 10.9% in the placebo group (p<0.001). There were 52 new hip fractures (1.4%) in the zoledronic acid group, as compared with 88 (2.5%) in the placebo group (p<0.001).[51]

In a 6-year, double-blind trial involving 2,000 women with osteopenia (defined by a T-score of −1.0 to −2.5 at either the total hip or the femoral neck on either side) who were aged 65 years or older, participants were randomly assigned to receive four infusions of either zoledronate at a dose of 5 mg or normal saline at 18-month intervals.[52] In comparison with the placebo group, women who received zoledronate had a lower risk of nonvertebral fragility fractures (hazard ratio (HR) 0.66; p=0.001), symptomatic fractures (HR 0.73; p=0.003), vertebral fractures (odds ratio (OR) 0.45; p=0.002) and height loss (p<0.001). The number needed to treat to prevent the occurrence of a fracture in one woman was 15.

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Black *et al* discusses the evidence regarding duration of bisphosphonate therapy.[53] The use of alendronate for 5 years and zoledronic acid for 3 years may allow residual anti-fracture benefits even after these drugs are discontinued, but this may not be applicable to risedronate because of its shorter half-life. The data presented suggest that patients with low BMD at the femoral neck (T-score <−2.5) after 3 to 5 years of treatment are at the highest risk for vertebral fractures and therefore appear to benefit most from continuation of bisphosphonates. Patients with an existing vertebral fracture who have a somewhat higher (although not >−2.0) T-score for BMD may also benefit from continued therapy. Patients with a femoral neck T-score above −2.0 have a low risk of vertebral fracture and are unlikely to benefit from continued treatment.[53] However, a recent robust study concluded that existing evidence does not support offering patients on long-term treatment with bisphosphonates a drug holiday.[54] National guidelines and NICE quality standards recommend a re-assessment of patient fracture risk against the potential adverse effects of treatment at 3 years for zoledronic acid and 5 years for other bisphosphonates.[25]

Denosumab

Long-term treatment with denosumab has been shown to be associated with continued benefits for postmenopausal women with osteoporosis. The FREEDOM extension study showed reduction in bone turnover, continued increase in BMD without therapeutic plateau, and low incidence of fractures in postmenopausal women treated with denosumab 60 mg twice a year for 10 years.[55] However, it is important to balance this benefit against potential risks of denosumab. Meta-analysis of nine RCTs (10,329 patients) demonstrated increased risk of serious adverse events (OR 1.83; 95% CI 1.10–3.04; p=0.02) and serious infections (OR 4.45; 95% CI 1.15–17.14; p=0.03) related to denosumab therapy.[56] Unlike bisphosphonates, discontinuation of denosumab leads to loss of bone within a short period of time, though this can be mitigated by administering a dose of zoledronic acid or a course of an oral bisphosphonates.[57] Denosumab has to be given regularly every 6 months. Because of disruption of outpatient services as a result of SARS-Cov-2 pandemic, denosumab administration may be disrupted. We need to make sure the therapy is not interrupted either by asking their family physician to give the injection or the patient is taught how to inject themselves. Failing that, the use of an oral bisphosphonate is recommended in the interim period.

Teriparatide

Teriparatide is of particular importance as it modulates the bone architecture acting on bone formation, rather than being an anti-resorptive agent.[58] A study of 503 postmenopausal women with osteoporosis who received teriparatide for 24 months demonstrated significant increase in BMD in patients with and without previous anti-resorptive agent use.[59] It is important to consider continuing therapy with an anti-resorptive agent following cessation to teriparatide in order to avoid a rebound decline in BMD.[60,61] Teriparatide is given subcutaneously daily and is much more expensive than bisphosphonates and denosumab. However, a more cost-effective biosimilar, Terrosa, is available. Treatment with a bisphosphonate such as alendronate or zoledronate after stopping teriparatide can stop the bone loss.[62] It is contraindicated in patients with pre-existing hypercalcaemia or hyperparathyroidism, severe renal impairment and a history of metastatic cancer or skeletal malignancies given its mechanism of action.

Raloxifene

Raloxifene has been shown in placebo-controlled trials to reduce only vertebral fractures.[46] It is best avoided in patients with breast cancer, oestrogen-induced hypertriglyceridemia, risk factors for stroke and venous thromboembolism.

Serious adverse reactions

Atypical fractures are a rare but significant complication of anti-resorptive therapy. These are typically considered in long-term bisphosphonate use, but short-term use was found to confer some risk.[63] The multivariable-adjusted odds ratio with 4 to 5 years of bisphosphonate use was 100 times as high as that with non-use. For each year since the last use, the risk reduced by 70%. Nevertheless, the number needed to treat with bisphosphonate for 3 years to prevent one non-vertebral fracture is 35, or hip only is 90. Yet the hypothetical number associated with an increase in one atypical fracture in the same population may be as high as 800 or as low as 43,300.[45] Patients should be asked specifically about midthigh pain or unusual hip pain particularly if on therapy for many years.

Another significant adverse reaction is osteonecrosis of the jaw (ONJ). This is much more common following intravenous bisphosphonate therapy for patients with cancer. The risk increases with duration of treatment beyond 5 years.[64] ONJ is also well recognised in association with denosumab therapy, particularly with oncology patients in the context of dental extraction, poor oral hygiene or chemotherapy.[65] Patients should be warned about this small but significant risk, and a dental check prior to initiating therapy is recommended.

Conclusion

Adequate intake of calcium, vitamin D, increasing physical activity, a strategy of avoiding falls, cessation of smoking and avoiding excessive alcohol intake are pivotal in maintaining healthy bones in all age groups. Oral bisphosphonates remain the most cost-effective first line of treatment. Better methods of identifying patients with high fracture risk is needed as there is adequate effective treatment for osteoporosis. ■

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Address for correspondence: Prof Ali Jawad, The Royal London Hospital, Bancroft Road, London E1 4DG, UK.
Email: ali.jawad8@nhs.uk

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