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Recent advances in the risk assessment and treatment of osteoporosis

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Introduction

Osteoporosis is characterised by decreased bone mass and disruption of bone microarchitecture, which results in reduced bone strength and an increased risk of fracture. The resultant fractures are a major cause of morbidity and mortality in the elderly population: one-in-two women and one-in-five men aged 50 years will suffer one or more fragility fractures during their remaining lifetime. The estimated annual cost of these fractures to healthcare services in the UK exceeds £2 billion.

In recent years, significant advances have been made in assessment of the risk of fracture, with the development of risk algorithms that combine clinical risk factors and bone mineral density (BMD). In addition, a range of treatment options to reduce fracture risk is now available. This paper provides an update on the progress that has been made in these areas.

Assessment of fracture risk

The inverse relation between BMD and fracture risk has been known for many years and formed a basis for a World Health Organization (WHO) study group's proposal that the definition of osteoporosis should be based on the criterion of BMD T-score ⩽–2.5 measured by dual energy X-ray absorptiometry (DXA) in the spine, hip or radius. Use of BMD in prediction of fracture risk has high specificity but relatively low sensitivity, and a number of studies have shown that most postmenopausal women who sustain a low trauma fracture do not have osteoporosis according to this criterion.[1] The reason for this may partly lie in the contribution, partially independent of BMD, of clinical risk factors to the risk of fracture. Box 1 lists these clinical risk factors, which provide the rationale for fracture risk algorithms in which they, with or without BMD, are used to estimate fracture probability. The best known and most widely used algorithm is FRAX, which generates a 10-year fracture probability for hip fracture and major osteoporotic fracture (hip, spine, humerus or wrist).[2,5] FRAX, which is available on the internet and is also incorporated into some DXA systems, integrates seven clinical risk factors (previous fracture, family history of hip fracture, glucocorticoid therapy, tobacco use, alcohol use ⩾3 units/day, rheumatoid arthritis and other secondary causes of osteoporosis) with age, sex and BMI. FRAX can be used without or with BMD, with the estimated fracture probability providing a basis for treatment decisions according to clinically appropriate and cost-effective intervention thresholds.[4]

Box 1 Clinical risk factors for fracture.

- Age
- Female sex
- Low body mass index
- Previous fracture
- Parental history of hip fracture
- Glucocorticoid therapy
- Tobacco use
- Alcohol ⩾3 units/day
- Rheumatoid arthritis
- Secondary osteoporosis
- Falls

Information is entered into the FRAX algorithm in the form of yes and no answers and does not take account of dose response for risk factors such as previous fracture and tobacco, alcohol and glucocorticoid use. The increase in fracture risk associated with use of oral glucocorticoids is dose dependent, and thus FRAX, which assumes a medium dose (2.5–7.5 mg daily), may underestimate the risk in patients taking higher doses. Recently, an adjustment for the dose of glucocorticoids has been developed based on data from the General Practice Research Database in the UK.[5] This recommends 20% and 15% upward adjustments for the FRAX-estimated 10-year probability of hip and major osteoporotic fractures, respectively. However, greater upward adjustment may be required in patients treated with very high doses of glucocorticoids.

Obesity and fracture

Until recently, obesity was widely believed to be protective against fracture as a result of the higher BMD in obese individuals and protection against falls by soft-tissue padding. However, a number of studies have challenged this assumption. In the Global Study of Osteoporosis in Women (GLOW), a large, prospective population-based study of 60,393 postmenopausal women from the US, Europe, Canada and Australia, both prevalent and incident fractures occurred with a similar frequency in obese and non-obese women; numerically, about one-in-four postmenopausal women with an incident fracture was obese (BMI ⩾30 kg/m^2). Fractures of the ankle, lower leg and upper

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leg were more common in obese than non-obese women, whereas obese women seemed to be protected against hip, pelvis and spine fractures.[6]

The pathogenesis of fractures associated with obesity is not fully understood. Increased risk of falling may play a role, together with the heavier impact of falls and impairment of the normal protective response to falling. Osteoporosis, as defined by BMD T-score ⩽–2.5, is very uncommon in obese women with fracture; most are osteopenic (T-score –1.0 to –2.5) or have a normal BMD (T-score ⩾–1.0). However, the higher BMD in obese individuals likely reflects appropriate adaptation to greater mechanical stresses and may not confer greater strength than a lower BMD in a smaller person. In addition, obese women with fractures have significantly lower BMD than their obese counterparts without fracture, which indicates that those who fracture have inappropriately low BMD for their body weight.[7] Potential contributory factors include vitamin D insufficiency and secondary hyperparathyroidism, immobility and genetic status. In addition, visceral fat produces substances such as proresorptive cytokines and adiponectin, which have adverse effects on bone.

Pharmacological intervention to reduce the risk of fracture

A number of options are approved for the prevention of fractures in postmenopausal women at increased risk of fracture (Table 1). Some of these are also approved for men at increased risk of fracture (alendronate, risedronate, zoledronic acid and teriparatide) and for glucocorticoid-induced osteoporosis (alendronate, risedronate and teriparatide). No head-to-head studies of the different drugs with fracture as the primary outcome have been undertaken, so comparison of their efficacy in terms of the magnitude of fracture reduction is not possible. However, reductions of 30–70%, 15–20% and up to 40% have been reported for vertebral, non-vertebral and hip fractures, respectively, after three years of treatment.

In terms of the spectrum of efficacy across different fracture sites, the available evidence base does show some differences. Only alendronate, risedronate, zoledronic acid, denosumab and strontium ranelate have been shown to reduce vertebral, non-vertebral and hip fractures, and these are therefore generally regarded as frontline options in most patients. Alendronate is now available in generic formulations and provides the most cost-effective option because of its low price.

Denosumab, the most recently approved treatment, is a fully humanised monoclonal antibody to receptor activator of nuclear factor kappa B (NFκB) ligand (RANKL). A major regulator of osteoclast development and activity, RANKL is produced by osteocytes and osteoblastic cells and interacts with the RANK receptor on osteoclastic cells to stimulate osteoclastogenesis and inhibit osteoclast apoptosis. Administration of denosumab results in rapid and profound inhibition of osteoclastic bone resorption, with fracture reductions of 68%, 20% and 40% at the spine, non-vertebral sites and hip, respectively, after three years of treatment.[8] When used for the treatment of osteoporosis, denosumab is given in a dose of 60 mg every six months by subcutaneous injection.

A major advance in treatment has been the development of more easily tolerated formulations and dosing regimens. In common with other chronic diseases, adherence to therapy for osteoporosis is poor, and more than half of those treated with oral bisphosphonates have discontinued them by one year. The longer dosing intervals for oral formulations (once weekly for alendronate and risedronate and once monthly for ibandronate) and for parenteral formulations (once every three months for intravenous ibandronate, once every six months for subcutaneous denosumab and once a year for intravenous zoledronic acid) are generally preferred by patients and may ensure better adherence.

Table 1. Treatments approved for prevention of fractures in postmenopausal women at increased risk of fracture.

Intervention	Fracture site (risk) Vertebral (30–70% reduction)	Non-vertebral (15–20% reduction)	Hip (up to 40% reduction)
Alendronate	+	+	+
Ibandronate	+	+*	–
Risedronate	+	+	+
Zoledronic acid	+	+	+
Denosumab	+	+	+
HRT	+	+	+
Raloxifene	+	–	–
PTH (1–84)	+	–	–
Strontium ranelate	+	+	+*
Teriparatide	+	+	–

*Post-hoc analysis in high-risk group.
HRT = hormone replacement therapy; PTH = parathyroid hormone.

Duration of treatment

The optimal duration of therapy has become a highly topical issue in osteoporosis, mainly because of the emergence of rare but serious conditions that may be related to long-term suppression of bone turnover. In addition, the long half-life of bisphosphonates in the skeleton raises the possibility that their beneficial effects may persist for some time after withdrawal and that 'drug holidays' might be appropriate in some patients. Conversely, discontinuation of some treatments – for example, denosumab – is associated with rapid bone loss and increased bone turnover in the first year after withdrawal. Although the effects of these changes on fracture risk have not been documented, it is likely that maintained protection against fracture requires continued therapy.

The rate of offset of treatment effects after withdrawal of bisphosphonates has been studied for alendronate, risedronate and zoledronic acid. In postmenopausal women treated with alendronate for five years, discontinuation of treatment was followed by significant decreases in hip BMD in the first two years after withdrawal, whereas a more rapid decline in BMD is seen after withdrawal of risedronate therapy. Recently, the effects of discontinuing zoledronic acid therapy after three years of treatment have been reported: after three years off therapy, only very small decreases in BMD were seen compared to those in women who continued on treatment. Increases in femoral neck BMD over the six-year period were 4.5% and 3.1%, respectively, with only a small, albeit statistically significant, difference between the continuation and non-continuation groups at the end of the study; similar patterns were seen for spine BMD.[9] None of these studies were powered to show differences in fracture rates, but the incidence of clinical vertebral fractures in the alendronate study was significantly lower in women who continued alendronate,[10] while women who discontinued zoledronic acid had a higher rate of morphometric vertebral fractures than the group who continued treatment.[9]

These studies indicate that, in the case of alendronate and zoledronic acid, a drug holiday might be considered after 3–5 years of treatment in patients who have not sustained a fracture during the treatment period and in whom post-treatment BMD is satisfactory. However, continued treatment should be advised in those who remain at increased risk of fracture after the initial treatment period, based on fracture history and BMD. If a drug holiday is advised, BMD should be assessed after 2–3 years and the need for continued treatment re-evaluated.[11]

Potential adverse effects of long-term therapy

Osteonecrosis of the jaw is defined as exposed bone in the maxillofacial region that is present for at least eight weeks in individuals who have not received radiation to that area. It has been described in association with both bisphosphonate and denosumab therapy, with an incidence of around 1.5–2% in patients treated with high doses for skeletal malignancy. It is much less common in patients treated with the lower doses used for osteoporosis, with an estimated incidence of one in 10,000 to one in 100,000 person-years of bisphosphonate exposure and only two cases so far reported in women treated with denosumab. Dental disease and trauma are well-established risk factors for osteonecrosis of the jaw, and severe dental disease should be treated before initiation of bisphosphonate or denosumab therapy.

Atypical femoral fractures occur mainly in the subtrochanteric or diaphyseal region of the femur and comprise about 1% of all femoral fractures. They occur on minimal or no trauma, are often preceded by prodromal pain for weeks or several months and are bilateral in nearly 50% of cases. They heal poorly and are associated with substantial morbidity. Radiologically, they present as simple transverse or oblique fractures, with diffuse cortical thickening and medial beaking. They seem to originate in the lateral cortex, where they show features characteristic of stress fractures. Several studies have indicated an association between the risk of these fractures and duration of bisphosphonate therapy, although they may also occur in bisphosphonate-naïve patients. To date, atypical fractures have not been described in patients receiving other antiresorptive treatments.

The pathophysiology of both conditions is incompletely understood; in particular, the role of decreased bone turnover is uncertain.[12] In individuals at increased risk of fracture, the very low risk of these adverse events is far outweighed by the benefits of treatment. Nevertheless, they emphasise the importance of targeting treatment to high-risk individuals and the avoidance of long-term therapy in those at low risk.

New treatments in development

Several new approaches to the treatment of osteoporosis are being explored. These include transdermal and oral parathyroid hormone formulations, calcium-sensing receptor antagonists, cathepsin K inhibitors and anti-sclerostin antibodies. Odanacatib, a cathepsin K inhibitor, has been shown to increase BMD in the spine and hip and is now in phase 3 development. Preclinical studies with an anti-sclerostin antibody have shown marked improvements in bone mass and strength and indicate a dual mechanism of action, with both antiresorptive and anabolic effects. Phase 1 studies in humans have shown rapid increases in spine and hip BMD after a single injection of the antibody.

Conclusions

Osteoporosis is a major health problem in the elderly population. Recent advances in prediction of the risk of fracture provide a means by which individuals can be accurately targeted for treatment, and a range of effective pharmacological interventions to reduce fracture risk is now available. However, despite the availability of cost-effective interventions to reduce fracture, many high-risk individuals do not undergo appropriate investigation and treatment, and the development of effective strategies to close this treatment gap is urgently required. Other important issues for future research include the optimal timing and duration of therapy, measures to improve adherence and the use of combination and sequential therapies.

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