Osteoporosis and fracture risk in older people

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Introduction

Until the 1940s, when Albright associated osteoporosis with a defect of bone anabolism, it was not considered a disease entity but an inevitable consequence of the ageing process for which there was little remedy.1 Bisphosphonates, first synthesised in the 1800s but in clinical use only since the 1960s, demonstrated that this process of age-related decline in bone was, in fact, modifiable.2 More recently, a wealth of basic and clinical research has greatly enhanced our understanding of the complexity of bone metabolism, enabling the development of novel therapeutic strategies. The resultant reduction in fracture risk is greatest in those with more severe osteoporosis, suggesting that older people can have considerable gains from bone-sparing treatments.

Osteoporosis, now acknowledged as the most prevalent bone disorder in the world, is characterised by low bone mass, microarchitectural deterioration of bone tissue and decreased bone strength. Adult bone mass results from peak bone mass achieved during adolescence and subsequently maintained until perturbations in the bone remodelling cycle – usually a very tightly coupled process – occur and alter the balance between bone-forming osteoblasts and bone-resorbing osteoclasts. In a normal remodelling cycle, the amount of bone lost is the same as the amount of new bone formed. When this process becomes ‘uncoupled’ – as is the case in people with oestrogen deficiency, high levels of glucocorticoids, changes in serum calcium levels, fluctuations in levels of parathyroid hormone (PTH) and changes in levels of growth hormone – there is a net loss of bone. Estimates indicate that 50% of women and 20% of men aged over 50 years will experience an osteoporosis-related fracture; hip fracture is the most devastating of these due to the consequent disability, mortality and costs – both personal and societal. Due to changing population demographics, estimates suggest a doubling of the number of people with osteoporosis in the next 20 years. Consequently, an exponential increase in the numbers of fractures is anticipated, with an inevitable increased financial burden for healthcare systems – the total economic burden of osteoporosis in the European Union in 2010 was estimated at €39 billion (about £32 billion).2 Without taking into account the personal cost to the individual, one can see why prevention and treatment of osteoporosis should be a priority for all those who care for older people. Osteoporosis is underdiagnosed and undertreated, particularly in those aged over 75 years, in whom treatment is probably most beneficial and cost effective.3 This fact suggests that treatment of the older cohort remains a challenge, not helped by the limited representation of older adults in major trials of osteoporosis treatments.

Identifying osteoporosis and people with a high risk of fracture

Dual energy X-ray absorptiometry scanning

Osteoporosis is defined by the World Health Organisation (WHO) as a T-score of –2.5 standard deviations (SD) below the bone mineral density (BMD) of a healthy younger person of the same sex,4 which is most widely measured using dual energy X-ray absorptiometry (DXA). The T-score has traditionally been used as an entry criterion for the major clinical trials, in which a reduction in the risk of fracture of 25% within 3 years has been demonstrated for most therapies, with benefits seen as early as 1 year for some treatments.3,4 However, in recent years there has been greater focus on clinical risk factors for fracture besides bone density; while risk of fracture in the individual does have an inverse relationship with BMD, the fact that there are a greater number of individuals with low bone mass or osteopenia (T-score of –1 to –2.5 SD below normal) than with osteoporosis in the population means that the absolute number of fragility fractures is higher in the group with osteopenia.5,6 This has led to the development of a number of tools to predict future fracture risk more accurately. Studies on the efficacy of bone-sparing medications have largely involved populations with known osteoporosis; however, increasing evidence shows that selection of patients based on clinical risk factors alone still equates with benefit from pharmacological therapy.5,7 Further trials using this approach are ongoing and will no doubt inform future approaches to fracture prevention in order to more accurately predict future fracture risk and effectively target high-risk groups.7

Fracture risk assessment tools

Fracture risk predictor tools are derived using data from large cohort and population studies. These tools, which are akin to the Framingham cardiovascular risk predictor tools, variably include from just two clinical fracture risk factors to more than 20 such factors in order to derive a 10-year predicted fracture probability. Although all of the tools have individual...
The presence of comorbidities would preclude pharmacological therapy. Opportunistic rather than population screening is advised, although older patients who present to healthcare professionals are likely to be at higher risk of fractures and would benefit from this screening. Younger people should be assessed routinely only if significant risk factors are present.

Addressing and treating fracture risk in older people

In those with a prior fracture (secondary prevention), NICE technology appraisal guidance advises treatment of women aged over 75 years with a prior fragility fracture without the need for DXA, although many national and international guidelines extend this to all postmenopausal women. The FRAX® tool and the UK National Osteoporosis Guideline Group (NOGG) guideline also advise treating women with a prior fragility fracture. It is not necessary to use a fracture risk tool or DXA in the secondary prevention setting, but it may still be appropriate before starting what may be long-term treatment (Fig 2).

In the primary prevention setting where there is no history of fragility fracture, NICE supports treatment in women aged over 75 years without DXA if they have risk factors for fracture and/or low bone mineral density. Otherwise, it bases treatment recommendations on T score and is stringent in this for younger women even with confirmed osteoporosis, but does not provide any guidance in men. This considerable shortfall is largely due to the lack of clinical trials addressing fracture risk reduction in men.

Fracture risk assessment tools are increasingly used to bridge the gaps in NICE guidance. Where an absolute fracture risk is generated, there is variability in how to interpret the absolute risk figure, which also depends on local availability and cost effectiveness of treatments. For example, physicians in the USA use a FRAX® treatment threshold of >20% for 10-year probability of major osteoporotic fracture and >3% for hip fracture when low bone mass (osteopenia) is present, advocating the treatment of all patients with T-scores <−2.5 SD and women with prior fracture. This approach, which might lead to overtreatment of many older people, has not been evaluated in the UK, although some European countries use a similar fixed-treatment threshold regardless of age. In the UK, the National Osteoporosis Guideline Group (NOGG) devised age-related intervention thresholds based on cost effectiveness, but they also advocate treatment of all older women with prior fracture. The NOGG treatment intervention thresholds, being based on FRAX® fracture probability, increase substantially with age (other than in older women with prior fracture), which means that rigid adherence to such thresholds would result in far fewer older individuals being recommended for DXA or treatment than younger patients. However, NOGG recommends that clinical judgement must prevail over use of its guideline, as is the case with the use of any fracture risk assessment tool or treatment guideline. This is particularly important when managing older patients.

In the absence of a prior fracture, those deemed at low risk of fracture generally require no further action other than addressing the risk of falls. Those deemed to be at high risk by a risk-assessment tool are very likely to have osteoporosis and to benefit from pharmacological therapy; however, a DXA scan may still be appropriate, particularly to give a baseline
reading before pharmacological treatment in ‘younger’ old patients. For those deemed to be at intermediate risk, a DXA scan may determine the next step. For frail older people, treatment based solely on clinical risk factors may be advisable, particularly if there is an added risk of frequent falls, which is not accounted for with the FRAX® tool. After a DXA scan, treatment decisions can be based on the DXA result as per NICE technology appraisals 160 and 161, the FRAX® 10-year absolute fracture probability incorporating total hip T-score or the NOGG treatment thresholds.17,18,20,22 For older patients, NICE technology appraisal guidance may be too restrictive in the primary prevention setting for those younger than 75 years; the fixed thresholds of the FRAX® 10-year probability tool, as used in the USA, may lead to overtreatment; and the NOGG thresholds are likely to advocate undertreatment. Ultimately, the clinician’s own judgement must prevail when managing older individuals for whom these approaches do not take into account the added risk of falls and short-term benefits vs side effects of treatment.

Fig 2. Assessing fracture risk in older people. *Dual-energy X-ray absorptiometry (DXA) may still be appropriate, especially for younger people and as a baseline before pharmacological treatment. †Option 1 may undertreat if the patient has osteopenia; option 2 may overtreat depending on the fixed threshold; and option 3 may undertreat older people. Clinical judgement should be used in deciding the best option for individual patients. The falls risk is not accounted for in the FRAX® tool, so this risk factor should be borne in mind when evaluating the benefits of treatment. BMD = bone mineral density; NICE = National Institute for Health and Care Excellence; NOGG = National Osteoporosis Guideline Group, TAG = technology appraisal guidance.

Other general measures
Where osteoporosis or high fracture risk is identified, multiple myeloma should be excluded in younger ages and in those with anaemia. Androgen deficiency should be considered in men only where androgen-replacement would be appropriate. Lifestyle factors of alcohol intake and smoking cessation should be reinforced in all cases. Weight-bearing exercises for both falls and fracture prevention are advised, and may modestly improve bone density.18

Treatment
Calcium and vitamin D
Most studies show that vitamin D and calcium supplementation reduce the risk of fracture, and all studies of bone-sparing treatments ensured that subjects were calcium and vitamin D replete, generally through supplementation, so this has become standard practice.
Recently, concerns about increased cardiovascular risk from supplemented calcium in patients with adequate dietary intake have arisen, although this remains controversial. Expert societies now advocate estimating dietary intake of calcium before the addition of calcium supplements to vitamin D supplementation. Online dietary calcium calculators are available for this, but an enquiry about intake of dairy products and oily fish can suffice. Vitamin D intake from diet and/or sun exposure in Western Europe is rarely adequate, particularly in older people, so supplementation is necessary in almost all cases unless serum levels of colecalciferol (with seasonality considered) show otherwise. Single high-dose boluses of vitamin D have been linked to possible increased risks of falls and fractures and so should be avoided.

**Pharmacological treatment**

Older people are at highest risk of fracture and so will derive substantial benefits from treatment. The choice of therapy should take into account the frequency and route of administration, cost, efficacy and potential adverse effects given that polypharmacy is already common among older people. Bisphosphonates remain the mainstay of treatment for osteoporosis. Other agents include denosumab, strontium ranelate, selective oestrogen receptor modulators (SERMs) and parathyroid hormone peptides (Table 1). All reduce fracture risk at vertebral sites, and some reduce the risk of non-vertebral and hip fractures to varying degrees. Generic alendronic acid remains first line in most centres, despite the lack of trial evidence in those aged over 80 years. Strontium, a drug for which such evidence is available, was recently linked with increased cardiovascular risk from its mode of administration, cost, efficacy and potential adverse effects given that polypharmacy is already common among older people.

**Table 1. Efficacy of osteoporosis therapies. Adapted with permission from Inderjeeth et al (2010).**

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<th>Drug</th>
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+ = evidence for specific fracture prevention; – = no subgroup analysis has been carried out in this population or this age-group has not been involved in trials; HF = hip fracture; NA = no evidence available; NVF = non-vertebral fracture; VF = vertebral fracture.

Duration and follow up of treatment

The optimal duration of bone-sparing treatment is unclear, but bisphosphonates can maintain bone density for at least 2 years after treatment withdrawal, as measured by bone turnover markers, BMD and subsequent fracture rates. Bone-maintaining effects of other agents, such as denosumab, strontium ranelate and raloxifene, wear off soon after stopping. A treatment ‘holiday’ after 5 years of oral bisphosphonate or 3 years of parenteral zoledronate is now a recognised treatment strategy and this also helps avoid the notable, although very rare, complications of osteonecrosis of the jaw and atypical femoral fractures. The BMD should be evaluated at these timepoints, where possible. Ongoing treatment with the same or an alternative agent is advised if there is a history of vertebral fractures, the person has any new fracture, BMD remains osteoporotic or the risk of fracture remains high, which would

**Box 1. Treatment duration in older people.**

- **Bisphosphonates**
  - Review after:
    - 5 years of oral therapy
    - 3 years of intravenous therapy
  - Continue for up to a further 5 years if:
    - vertebral fracture history
    - new fragility fracture
    - T-score < −2.5
    - ongoing steroid use
    - persistent high risk of fracture
  - Consider ‘drug holiday’ for 2–3 years if:
    - T-score > −2.5 and none of the above

- **Denosumab, teriparatide, raloxifene, strontium**
  - Effects wear off soon after discontinuation, so alternative agent should be considered if stopping, rather than treatment holiday

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include many older people (Box 1). In these groups, the benefits of ongoing active therapy will greatly outweigh the small risk of these rare complications. Reassessment should take place earlier than 3–5 years if a new fragility fracture has occurred despite adequate adherence with medication and if adequate vitamin D and calcium intake is assured. The risk of falls should be evaluated in this context and alternative therapy should be considered if BMD has failed to improve and has contributed to a subsequent fracture. Monitoring of bone turnover markers may also be useful in this setting, as well as during a treatment holiday, to ensure suppressed bone turnover, although the role of these markers for fracture prediction in wider clinical use is yet to be established. ■

References
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