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).[3] 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.[4] 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.

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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,[5] 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 ≥50% 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.[7,8] 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.[9]

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

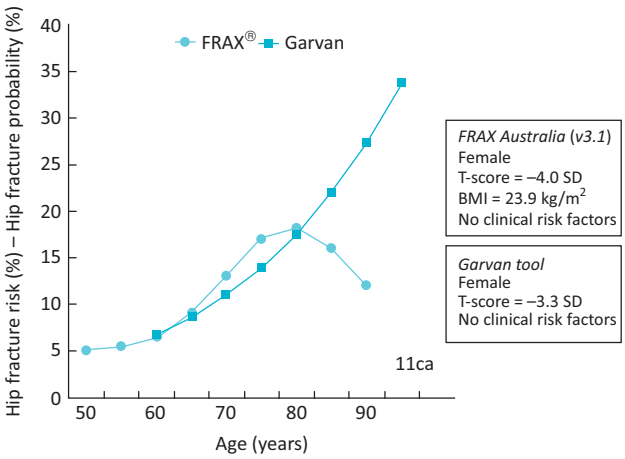

Fig 1. Fracture risk vs fracture probability. BMI = body mass index; SD = standard deviation. Adapted with permission from Kanis *et al* (2012).[15]

limitations, they share the advantages of identifying those at high risk of fracture without the need for DXA and identifying greater numbers at high risk than DXA alone. Two such tools, QFracture and FRAX®, were endorsed for use in the UK by the recent guideline on fracture risk assessment from the National Institute for Health and Care Excellence (NICE).[10]

The QFracture score incorporates more than 20 risk factors, including falls, and so may be time consuming in a busy clinical setting.[11] It provides an estimate of absolute fracture risk from 1 year to 10 years, although it is validated based on 10-year risk.

The FRAX® 10-year fracture probability model is the tool most widely used globally.[3,12] A BMD reading is optional but improves accuracy. This tool does not include a falls history. The FRAX® tool uniquely accounts for mortality, unlike other calculators, although its lack of independent evaluation has been criticised. FRAX® may lead to underestimation of the short-term risk of fracture in older age, as the competing high risk of death within 10 years (without fracture) mean fracture *probability* will be lower than fracture *risk* in an older patient, as risk assume they will all survive to 10 years (Fig 1).[15] This approach may be wise at a population level, but it is important to consider this limitation when assessing individual older patients.

The Garvan risk calculator includes a falls history and estimates the fracture risk at 5 and 10 years.[16] As it was derived from data from an older cohort, it may be more appropriate for older people; however, to date, no one tool has shown superiority over another.

Who should be screened for fracture risk?

A prior fragility fracture is a leading risk factor for further fracture, and treatment is advised in such cases. Evidence of silent vertebral fractures should be actively sought therefore. Outside of this, a routine assessment of fracture risk should be carried out in women aged over 65 years and men aged over 75 years, except in those where risk assessment would not influence management – for example, when life expectancy may be too short to derive a benefit from bone-sparing therapy or where 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.[3,17,18] The FRAX® tool and the UK National Osteoporosis Guideline Group (NOGG) guideline also advise treating women with a prior fragility fracture.[19] 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.[20] 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.[18] 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.[3,19]

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.[20] 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.[14,19,21] 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

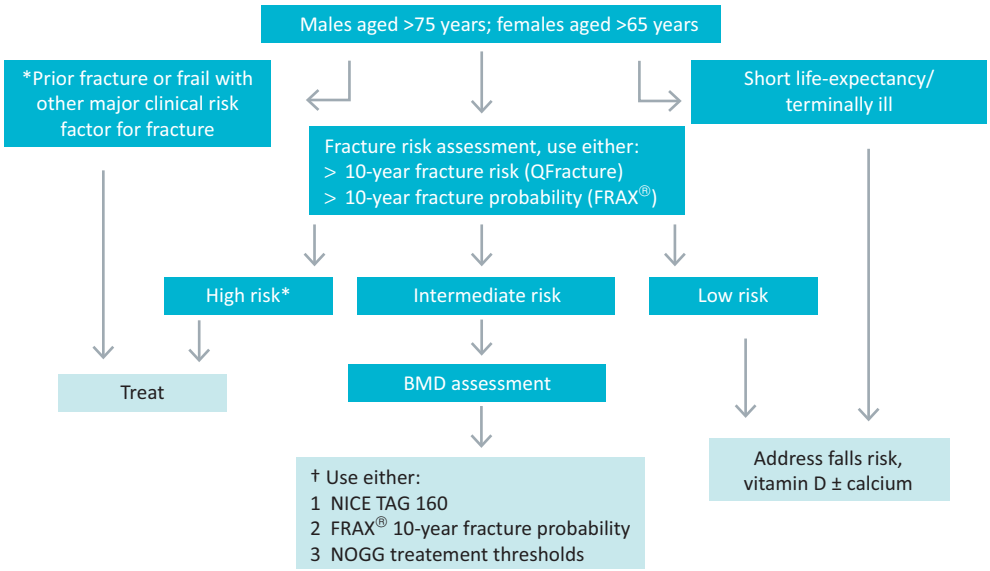

Fig 2. Assessing fracture risk in older people. *Dual-energy X-ray absorptiometry (DXA) may still be appropriate, especially for younger people and as a baseline before pharmacological treatment. †Option 1 may undertreat if the patient has osteopenia; option 2 may overtreat depending on the fixed threshold; 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.

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.

Falls

Other than vertebral fractures, the vast majority of fragility fractures result from a fall. An enquiry about the risk of falls is essential given that several interventions are proved to reduce such risk. Falls intervention studies have been of insufficient size or duration to demonstrate reductions in the risk of fractures, but leading osteoporosis societies have adopted common sense by promoting the importance of addressing this risk factor.[3,18]

Medication review

A medication review should dually assess bone health and the risk of falls and is a further opportunity to identify those at higher risk of fracture. Proton pump inhibitors decrease the acid-dependent absorption of calcium carbonate (the most common form of calcium supplementation),[23] while calcium citrate's absorption is acid-independent. Anticonvulsants impair vitamin D absorption, which should be addressed through supplementation.

Anti-serotonergic antidepressants may impact on bone density, although this link is not entirely proved.[23] Anti-oestrogens in women and anti-androgens in men have a significant adverse impact on bone density and the risk of fractures, so these patients should be treated as being at high risk of fracture. Many chemotherapy regimens also have this effect, with or without co-administered high-dose steroids.[23]

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.

Table 1. Efficacy of osteoporosis therapies. Adapted with permission from Inderjeeth *et al* (2010).[27]

Drug	Primary analysis			Secondary older subgroup analysis		
	VF	NVF	HF	VF	NVF	HF
Alendronate	+	+	+	+	NA	NA
Denosumab	+	+	+	+	NA	+
Ibandronate	+	–	–			
Raloxifene	+	–	–			
Risedronate	+	+	+	+	–	–
Strontium	+	+	–	+	+	+
Teriparatide	+	+	–			
Zoledronate	+	+	+	+	+	–

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

Recently, concerns about increased cardiovascular risk from supplemented calcium in patients with adequate dietary intake have arisen, although this remains controversial.[24,25] Expert societies now advocate estimating dietary intake of calcium before the addition of calcium supplements to vitamin D supplementation.[26] 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.[26]

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.[3,23,27] 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 and a caution by the European Medicines Agency is likely to reduce its use in the future.[28] Denosumab, a human monoclonal antibody that inhibits osteoclast formation and survival, is the only agent suitable for use in renal impairment, which is highly prevalent in older people;[29] however, there is a small increased risk of infections due to its mode of action. Several other novel drugs with a biological approach are in development and will no doubt increase future treatment options.

Key points

Osteoporosis is under diagnosed and under treated

Bone-sparing treatment may benefit older people even after 1–2 years, and is cost-effective

Falls risk assessment is an essential component of treatment

Fracture risk assessment tools based on a 10-year risk may not be appropriate for older individuals

Treatment must be individualised, based on shorter term risk and benefits vs. expected survival

KEY WORDS: Alendronate, bisphosphonates, bone mineral density, calcium, falls, fractures, older people, osteoporosis ■

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.[30–32] Bone-maintaining effects of other agents, such as denosumab, strontium ranelate and raloxifene, wear off soon after stopping.[31] A treatment 'holiday' after 5 years of oral bisphosphonate or 3 years of parenteral zoledronate is now a recognised treatment strategy[32,33] 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, teraparatide, raloxifene, strontium

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

*Treatment re-evaluation and repeat falls risk assessment advised when this occurs.

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. ■

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