

Update on postmenopausal osteoporosis management

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Osteoporosis is characterised by bone fragility and fracture. Components of bone fragility include low mass, increased bone turnover and suboptimal microarchitecture.

Epidemiology and burden of osteoporosis

One in two women has a fracture after the age of 50;¹ most will be osteoporotic. Fracture incidence will probably increase as people live longer. After hip fracture there is 20% mortality within three months² and increased disability, with >50% of people who previously walked unaided needing aids and >50% requiring help at home.³ Morbidity, disability and dependence increase progressively with increasing numbers of fractures.⁴ Managing osteoporotic fractures is costly: in the UK the annual direct and indirect costs amount to more than £1.73 billion.⁵

Aetiology

Many factors either increase bone turnover and/or reduce bone mass and are contributory to osteoporosis risk (Table 1). Genetic predisposition is likely. Discovery of allelic variation in aromatase activity (CYP19A1), low-density lipoprotein receptor-related protein 5 genes⁶ and the focus on the vitamin D receptor⁷ illustrate, for example, advances in understanding of some genetic influences of osteoporosis referred to as 'idiopathic'.

Table 1. Risk factors for osteoporosis.

Bone health assessment is prudent in all situations listed below (this may include a DXA scan):		
Drugs	Conditions	General risk factors
Phenobarbitone/phenytoin	Ankylosing spondylitis/SLE/RA	Previous fragility fracture
Cytotoxic drugs	AIDS/HIV	Low BMI (<19)
Glucocorticoids	Anorexia nervosa	Early menopause (<45 years)
GnRH agonists	Female athlete triad syndrome	Recurrent falls
Long-term heparin	COPD	Current smoking
Excess thyroxine	Hyperparathyroidism	Excess alcohol
Total parenteral nutrition	Type 1 diabetes	Long-term poor calcium intake
	Thyrotoxicosis	Family history of fragility fractures
	IBD	
	Chronic liver disease (esp PBC)	
	Coeliac disease	
	Malabsorption	
	Previous gastrectomy	
	Haemochromatosis	
	Spinal cord injury/immobility	
	Multiple sclerosis	

BMI = body mass index; COPD = chronic obstructive pulmonary disease; DXA = dual X-ray absorptiometry; GnRH = gonadotrophin releasing hormone; IBD = irritable bowel disease; PBC = primary biliary cirrhosis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

Diagnosis

Fractures

Osteoporosis commonly presents with fragility fracture (low-impact trauma such as a fall from standing height), commonly distal forearm, vertebra, hip, proximal humerus and pelvis. Vertebral fractures are often initially asymptomatic ('silent') and are underreported on spinal radiographs and underrecorded.⁸

Bone mineral density

Bone loss can precede osteoporotic fracture and the lower the bone mineral density (BMD), the higher the risk of osteoporosis and fracture. In 1994 the

World Health Organization defined osteoporosis in Caucasian women as a relative deficit in BMD ≤ 2.5 standard deviations (SDs) below mean peak BMD which occurs in the 3rd decade (Fig 1).⁹ This T-score definition has been widely accepted, it has defined osteoporosis patients for therapeutic trials and been adopted into therapy guidelines.^{10,11} However, using T-scores for diagnosis is compromised by problems:

- T-scores are not equivalent across either multiple skeletal sites of assessment or different scanning systems
- T-score correlations from different skeletal sites are too low for non-site specific prediction of fracture risk

Key Points

The main determinants of fracture risk are: increasing age, previous fragility fracture, low bone density and falls frequency/risk

Controversy exists as to whether treating osteoporosis with bisphosphonates or Strontium ranelate is cost-effective in 'early' post-menopausal women (age <60)

Strontium ranelate is a reasonable first-line alternative treatment to bisphosphonates particularly in the elderly

KEY WORDS: bisphosphonates, fracture risk assessment, postmenopausal osteoporosis, osteoporosis treatment

- population T-score variances differ
- there is controversy how T-scores should be interpreted in men.

Treatment: who should be treated?

Conventionally patients with risk factors (Table 1) should have a dual X-ray absorptiometry (DXA) scan and if the BMD of total hip/femoral neck areas or spine is 'low', treatment is recommended. T-score intervention thresholds vary in guidelines, partly due to differences in analysing treatment cost-effectiveness in different health systems.^{10–12} Also, because age is a strong independent risk for fracture, any given T-score suggests different fracture risks at different ages (Fig 2). This weakness of T-scores might be overcome by estimating *absolute* fracture risk, based on a combination of T-score, age and clinical risk factors, to target treatment more effectively.^{13–15} Reporting of BMD incorporating absolute fracture risk algorithms is now being encouraged¹⁶ but this strategy has not yet been widely adopted.

Secondary fracture prevention

A fragility fracture is a strong risk for further fracture. In some hospitals, fracture liaison services (FLSs) screen patients with fragility fractures.^{17,18} Ideally, FLSs evaluate clinical risk factors, the risk of falls, BMD results and laboratory tests (to address relevant comorbidity). Patients can be triaged for onward referral to falls or endocrine clinics or treatment recommended. Notably, 15–20% of patients over 50 years seen in an FLS may have previously undiagnosed conditions, often endocrinopathies.¹⁸ FLSs are usually nurse-led and can be conducted according to national^{11,19,20} and locally-agreed guidelines.

Fracture and low BMD (T-score ≤ -2.5) together suggests high subsequent fracture risk and treatment is likely to be cost-effective in patients over 60–65 years.^{19,21} Cost-effectiveness of introducing treatment in younger postmenopausal women with fracture, even with low BMD, is controversial. However, current analyses¹⁹ may need to change, given the likelihood of the cost of some treatments decreasing

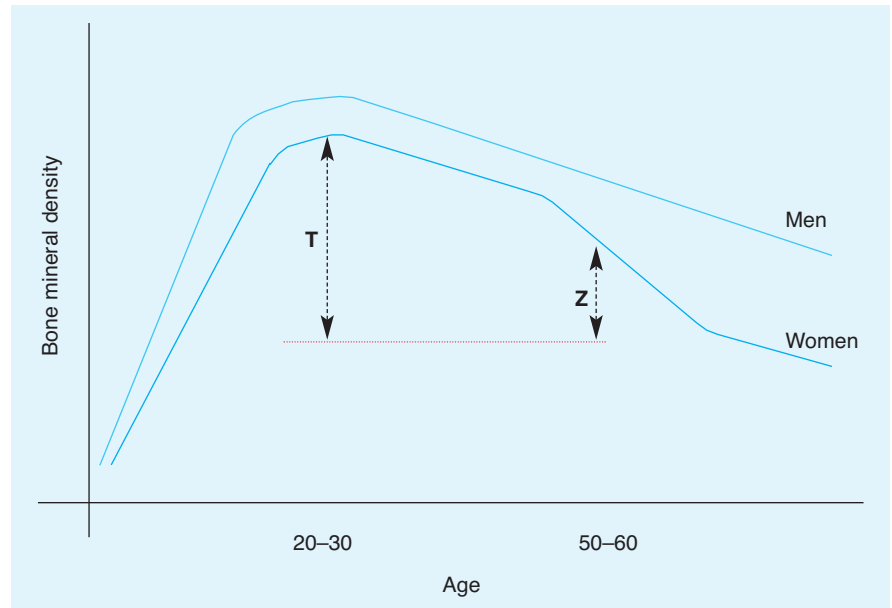


Fig 1. Changes in bone mineral density (BMD) with age. The lower the BMD, the higher the fracture risk. The T-score is the difference in standard deviations (SDs) between measured and average peak BMD. Negative T-score thresholds can be used, though somewhat arbitrarily, for either diagnosis of osteoporosis (eg World Health Organization T-score ≤ -2.5) or as a treatment intervention threshold (eg red dotted line). The Z-score is the number of SDs from average BMD for age.

and adherence to therapy improving with less frequent therapy, both oral and intravenous (iv).

Primary osteoporosis fracture prevention

A T-score ≤ -2.5 in patients without fracture, thus suggesting 'osteoporosis', has been viewed as an indication to recommend therapy to reduce fracture risk (Table 2). The National Institute for Health and Clinical Excellence is working on advice for primary prevention of osteoporosis.²² A key evaluation will be whether, even at low T-scores, treatment is deemed cost-effective in 'younger' postmenopausal women in whom age-dependent fracture risk is low (Fig 2) and 'numbers-needed-to-treat' to prevent a single fracture are high.²²

Gastroenterologists are reminded of the availability of guidelines to aid managing osteoporosis risk in inflammatory bowel and chronic liver diseases.^{23,24}

The elderly

A DXA scan is not required in elderly fracture patients (>75 years) to confirm a

diagnosis of osteoporosis,¹⁹ given high likelihood of a T-score of -2.5 or less. It is important to rule out relevant comorbidity (Table 1) and assess falls risk.²⁰ Absolute fracture risk in the elderly is high regardless of BMD (Fig 2) and hypovitaminosis D is common.

The impact of treatment on overall fracture risk reduction may be minor compared with the impact of reducing falls, but treatment should not automatically be withheld on account of age given some evidence for fracture reduction in relevant studies.^{25,26} However, recommending treatment requires careful consideration of the risk of adverse events, likely adherence to regular medication and likely longevity.

Patients taking systemic glucocorticoids

Glucocorticoids (GCs), even at low doses, cause immediate changes in bone cell function, increase renal excretion and gut absorption of calcium and impair the osteo-anabolic effects of sex steroids;²⁷ they are the most important cause of drug-induced osteoporosis. All patients on GCs should be assessed for

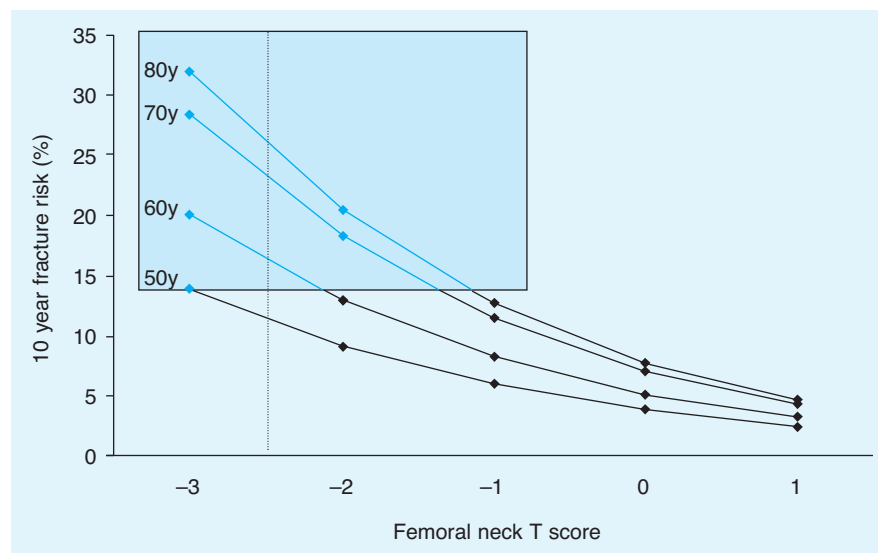


Fig 2. Bone density age-dependent osteoporotic fracture risk. Currently, treatment might be recommended at a T-score of -2.5 (vertical dotted line). However, for the same -2.5 T-score, fracture risk at 50 or 60 years will be lower than it will be at 70 or 80 years. T-score treatment intervention thresholds may need to account additionally for age (shaded box), although clinical risk factors might also reasonably be incorporated into this model (data sourced from Kanis¹³).

osteoporosis at the outset of their treatment course if planned for longer than three months and be advised to take calcium and vitamin D supplements.²⁸ Patients over the age of 65 starting GCs should be advised to take a bisphosphonate as well, without the need for DXA. A predicted delay in obtaining DXA in younger postmenopausal women requires bisphosphonate protection to be given initially, with withdrawal if all BMD T-scores are above -1.5 .

Treatment

General points

Choice of therapy is expanding (Table 2) and should be made in the light of specific fracture prevention evidence and drug licence. All drug efficacy studies have been designed to avoid, or reduce the effect of, calcium and vitamin D deficiency by either excluding patients at baseline or providing supplements throughout the study. An evidence-based management approach requires co-

prescription of calcium and vitamin D with all osteoporosis therapies.

Calcium/Vitamin D

No study has shown antifracture efficacy of calcium supplementation alone and antifracture data for therapeutic vitamin D2/D3 is conflicting.²⁹ Notably, calcium and vitamin D combined reduced hip fractures in the frail elderly.³⁰

Hypovitaminosis D is common in elderly fracture patients;³¹ correcting it can reduce falls frequency, improve muscle strength, postural sway and secondary hyperparathyroidism.²⁹ It is sensible to recommend long-term calcium (1 g/day) and vitamin D (800 iu/day) supplements in the elderly (>75 years) provided that coincidental hypercalcaemia has been ruled out.

Bisphosphonates

Alendronate (Fosamax/Fosavance/Alendronic acid) and risedronate (Actonel) reduce the risk of vertebral and non-vertebral fractures in women with fragility fractures or low BMD.^{32,33} Studies using etidronate suffered from methodological problems but antivertebral fracture efficacy in women is generally accepted. Ibandronate (Bonviva) is licensed as daily (2.5 mg) or monthly (150 mg) oral or three-monthly iv for postmenopausal women at risk of vertebral fractures. Fracture prevention over three years was shown for the daily dose³⁴ and 'non-inferiority' for the monthly dose (implied by comparing BMD changes and reduction in bone turnover with daily and monthly doses over one year).³⁵ Historically, iv pamidronate 30–60 mg every 3–4 months has been used for patients intolerant to oral bisphosphonates but antifracture efficacy has not been proved. Studies are currently evaluating yearly iv zoledronate. Adherence to treatment, a known difficulty with bisphosphonates,³⁶ may improve with monthly oral – and obviously iv – bisphosphonates. Only alendronate (Fosamax) is licensed to treat male osteoporosis.

Intolerance of oral bisphosphonates is common (dyspepsia, diarrhoea, joint pains). Osteonecrosis of the jaw following

Table 2. The major osteoporosis therapies and their licensed uses in the UK (only Fosamax or alendronate are licensed to treat all categories of osteoporosis).

Therapy	Treatment of postmenopausal osteoporosis to reduce the risk of fractures:		Glucocorticoid-induced osteoporosis	Men
	Vertebral	Hip		
Fosamax/Alendronic acid (alendronate)	✓	✓	✓	✓
Actonel (risedronate)	✓	✓	✓	×
Protelos (strontium ranelate)	✓	✓	×	×
Bonviva (ibandronate)	✓	×	×	×
Evista (raloxifene)	✓	×	×	×
Forsteo (teriparatide)	✓	×	×	×

iv bisphosphonates has recently been reported, chiefly in cancer patients who have dental pathology.³⁷ It is prudent to identify and address poor dentition before giving iv bisphosphonates.

Strontium ranelate (Protelos)

Strontium binds avidly to bone, it reduces osteoclast activity and promotes osteoblast differentiation and activity,³⁸ reducing both vertebral and non-vertebral fractures in women with osteoporosis.^{26,39} Strontium is a reasonable alternative choice to bisphosphonates, especially in the elderly. Given daily as granules to be dissolved in water, the main adverse effect is diarrhoea. It should be avoided if the glomerular filtration rate is below 30 ml/min and in patients with a history of thrombosis.

Recombinant human parathyroid hormone

Recombinant human parathyroid hormone (rhPTH) (1–34) (Forsteo) has an anabolic action on bone which differs from the profound (endosteal osteolytic) effect of continuous high endogenous PTH. This is achieved through a greater effect on osteoblast differentiation and activation, without excessive stimulation of osteoclast-driven resorption. Given over 18 months rhPTH (daily subcutaneous (sc) injection 20 µg) (Forsteo) reduced vertebral fractures by 65% in women with osteoporosis.⁴⁰ Funding may be restricted for NHS patients to women over the age of 65 in whom bisphosphonates have failed and who have very low BMD (T-score <–3.0) and multiple fractures.¹⁹

Treatment duration and monitoring

Optimal duration for all treatments is unknown. It appears that alendronate treatment given for 10 years is effective and safe.⁴¹ BMD then declines, but fracture prevention effects may remain for a few years longer.

Use of DXA for monitoring is controversial. Analyses from therapy studies suggest change in BMD accounts for only

a small amount of change in fracture risk. However, repeat BMD measures might aid adherence to therapy. Change in BMD is slow and measurement precision constraints suggest that rescanning in under two years is not usually appropriate.

Conclusions

Although the BMD T-score definition for diagnosis of osteoporosis continues to be used, in future the treatment intervention threshold is likely to differ and depend on an absolute fracture risk assessment, based on age, BMD and clinical factors rather than on relative risk alone (T-score). The choice of therapy for treating osteoporosis is expanding. There are numerous guidelines to aid physicians in managing this condition.

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