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Review Article

Osteoporosis

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Abstract

The clinical significance of osteoporosis lies in the fractures that arise, but the diagnosis of osteoporosis relies on the quantitative assessment of bone mineral density. There are a number of other indications for bone densitometry including monitoring of treatment, determining the extent of bone loss and assessment of suitability for certain treatments. Most commonly, bone density is used to determine eligibility for treatment. However, diagnostic thresholds differ from intervention thresholds for several reasons. Firstly, the fracture risk varies at different ages, even with the same T-score. Other factors that determine intervention thresholds include the presence of clinical risk factors such as a prior fracture, a family history of hip fracture, smoking and high alcohol consumption and secondary causes of osteoporosis. Algorithms that integrate the weight of clinical risk factors for fracture risk have been developed by the World Health Organization. This FRAX® tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture (clinical spine, hip, forearm or humerus). Probability-based intervention thresholds are now being incorporated into new management guidelines that integrate FRAX® with clinical management algorithms.

Keywords: Definition, epidemiology, FRAX, fracture risk assessment, treatment.

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Epidemiology and Aetiology

Epidemiology

Osteoporosis is described by the World Health Organization as a 'progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture'.[1] The clinical significance of osteoporosis lies in the fractures that arise. In the UK, osteoporosis results in over 200,000 fractures each year, causing severe pain and disability to individual sufferers at an annual cost to the National Health Service of over £1.73 billion.

More than one-third of adult women and one in five men will sustain one or more osteoporotic fractures in their lifetime.[2] Common sites of fracture include the vertebral bodies, distal radius, proximal femur and the proximal humerus (*Fig. 1*). Hip fractures alone account for more than 20% of orthopaedic bed occupancy in the UK, and the majority of the direct health service cost of osteoporosis. Approximately 50% of patients suffering a hip fracture can no longer live independently and 20% die within 12 months of the fracture.

Fractures in patients over 60 years account for more than 2 million hospital bed days in England each year. This exceeds the bed occupancy attributable to diabetes, ischaemic heart disease, heart failure or chronic obstructive pulmonary disease. The ageing of the UK population will double the number of osteoporotic fractures over the next 50 years if changes are not made in present practice.

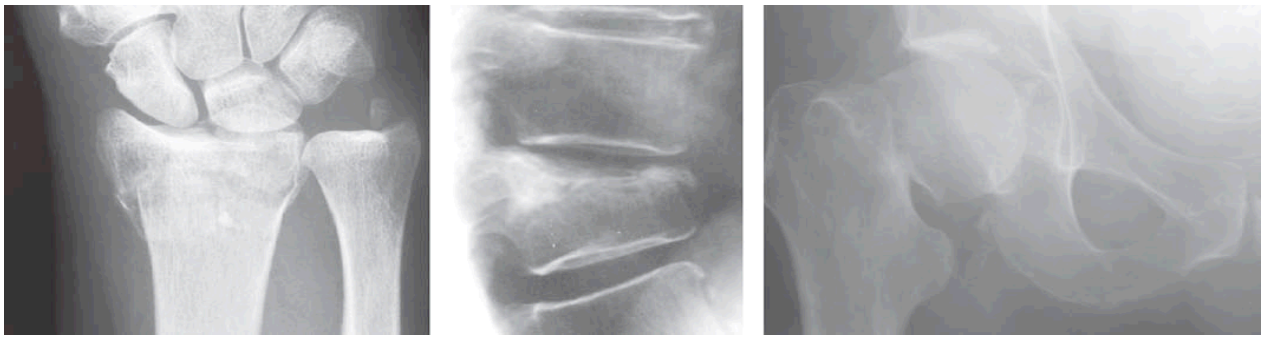


Fig. (1). Typical sites of osteoporotic fracture: wrist (left), spine (centre) and hip (right).

Already, the admission rate for hip fractures has increased in England by 2.1% per year since 1999, whilst hospital bed days have increased by 5.9% per year.

Aetiology

The most common cause of osteoporosis arises from oestrogen deficiency that begins some years before the time of menopause. The skeleton comprises approximately 20% trabecular bone and 80% cortical bone and undergoes a continual process of resorption and formation, governed by the activity of bone cells in bone remodelling units.[3] Approximately 10% of the adult skeleton is remodelled every year. Oestrogen deficiency accelerates the normal turnover of bone tissue, but the net activity of bone resorbing cells (osteoclasts) is greater than that of bone forming cells (osteoblasts). This gives rise to thinning of the cortices of bones, thinning of trabecular bone and loss of trabecular elements (*Fig. 2*). The architectural changes weaken bone disproportionately compared to the loss of skeletal mass. The rate of loss of bone tissue is particularly rapid around the time of menopause to give rise to postmenopausal osteoporosis, but bone loss continues throughout later life (age-related or involutional bone loss) in men as well as women.

Many other disorders can give rise to osteoporosis (*Table 1*) by accelerating bone loss (termed secondary osteoporosis).

Diagnosis

Clinical Features

The clinical features of osteoporosis are a consequence of the fractures that arise. Non-vertebral fractures are easily detected by the associated acute pain and deformity, both of which resolve well with appropriate management. In contrast, vertebral fractures are often un-diagnosed due to a lack of symptoms (detected on x-rays only) or the attribution of back pain to other causes. Multiple vertebral fractures commonly cause symptoms and may give rise to a thoracic kyphosis (unkindly termed dowager's hump) and long-term morbidity.[2]

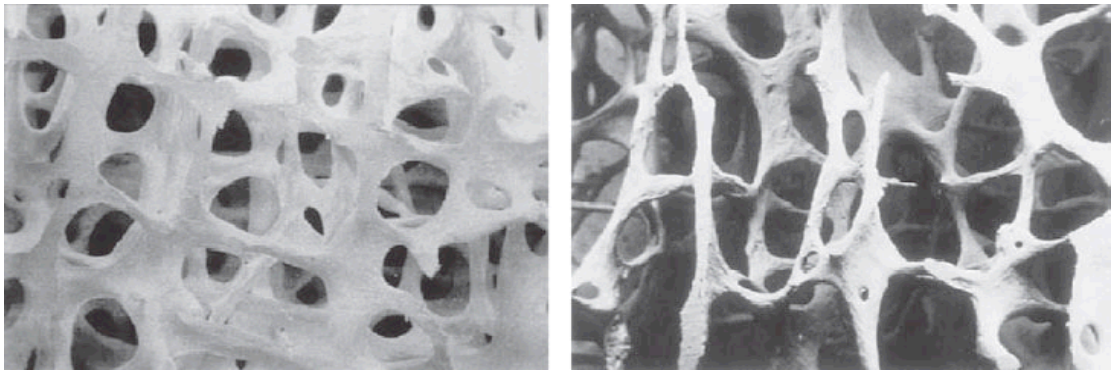


Fig. (2). Comparison of structure of trabecular bone in health (left panel) and osteoporosis (right), illustrating the architectural damage including trabecular thinning and perforation.

Table 1. Relatively common causes of secondary osteoporosis[4]

Endocrine Malignancy Drugs
Thyrotoxicosis
Primary hyperparathyroidism
Cushing's syndrome
Hypogonadism, including anorexia nervosa
Diabetes type I
Gastrointestinal
Malabsorption syndrome, e.g. coeliac disease, partial gastrectomy
Inflammatory bowel disease
Liver disease, e.g. primary biliary cirrhosis
Rheumatological
Rheumatoid arthritis
Ankylosing spondylitis
Malignancy
Multiple myeloma
Cancer-treatment-induced bone loss (see drugs)
Drugs
Glucocorticoids
Anticonvulsants
Heparin
Aromatase inhibitors
Androgen-deprivation therapy

Diagnosis of Osteoporosis

The diagnosis of osteoporosis relies on the quantitative assessment of bone mineral density (BMD), usually by central dual energy X-ray absorptiometry (DXA). BMD at the femoral neck provides the reference site. [2-5] It is defined as a value for BMD 2.5 standard deviations (SD) or more below the young female adult mean (T-score less than or equal to –2.5 SD). Severe osteoporosis (established osteoporosis) describes osteoporosis in the presence of 1 or more fragility fractures.

There are a number of other indications for bone densitometry including monitoring of treatment, determining the extent of bone loss and assessment of suitability for certain treatments.

Diagnostic thresholds differ from intervention thresholds for several reasons.

Firstly, the fracture risk varies at different ages, even with the same T-score. Other factors that determine intervention thresholds include the presence of clinical risk factors and the cost and benefits of treatment.

Investigation of Osteoporosis

The range of tests will depend on the severity of the disease, age at presentation and the presence or absence of fractures. The aims of the clinical history, physical examination and clinical tests are to:

- Exclude diseases that mimic osteoporosis (e.g. osteomalacia, myeloma);
- Identify secondary causes of osteoporosis and contributory factors;
- Assess the risk of subsequent fractures;
- Select the most appropriate form of treatment.

Tests that may be relevant to the investigation of osteoporosis are shown in *Table 2*.[6]

Table 2 Common tests used in the investigation of osteoporosis

Routine
History and physical examination
Blood cell count, sedimentation rate or C-reactive protein, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
Thyroid function tests
Bone densitometry (DXA)
Other investigations, if indicated
Lateral radiographs of lumbar and thoracic spine/DXA-based vertebral imaging
Protein immunoelectrophoresis and urinary Bence-Jones proteins
Serum testosterone, SHBG, FSH, LH (in men),
Serum prolactin
24 hour urinary cortisol/dexamethasone suppression test
Endomysial and/or tissue transglutaminase antibodies (coeliac disease)
Isotope bone scan
Markers of bone turnover, when available
Urinary calcium excretion

SHBG – sex-hormone binding globulin
FSH – follicle stimulating hormone,
LH – luteinising hormone

Management

Acute Fracture

The management of acute fracture is not different from that of a non-osteoporotic fracture. It is important to restore mobility as soon as possible since immobilisation is an important cause of bone loss.

Lifestyle Advice

This includes adequate intakes of protein, calcium and vitamin D. Intakes of 1000 mg/day of calcium, 800 IU of vitamin D and of 1 g/kg body weight of protein are recommended. Smoking and high intakes of alcohol are recognised risk factors for fractures and are to be avoided. Many fractures occur after a fall and strategies for the avoidance of falls should be considered.

Assessment of Fracture Risk

The longer term management of osteoporosis requires the assessment of future fracture risk which, in turn, determines the need for intervention. At present there is no accepted policy for population screening in the UK to identify individuals with osteoporosis or those at high risk of fracture. Rather, patients are identified opportunistically using a case-finding strategy on the finding of a previous fragility fracture or the presence of significant clinical risk factors (CRFs). Some of these risk factors act independently of BMD to increase fracture risk (*Table 3*) whereas others increase fracture risk through their association with low BMD (e.g. some of the secondary causes of osteoporosis in *Table 2*).[2]

Algorithms that integrate the weight of CRFs for fracture risk have been developed by the World Health Organization. [2,7] This FRAX® tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture (clinical spine, hip, forearm or humerus) (*Fig. 3*). The algorithm incorporates BMD as an additional, measurable risk factor to information gleaned from clinical risk factors and adds value to the prediction of risk. BMD is probably of most value in those deemed to be at intermediate or high risk.

Table 3 Clinical risk factors used for the assessment of fracture probability

Age
Sex
Low body mass index (≤19kg/m^2)
Previous fragility fracture, particularly of the hip, wrist and spine including
morphometric vertebral fracture
Parental history of hip fracture
Current glucocorticoid treatment (any dose, by mouth for 3 months or more)
Current smoking
Alcohol intake of 3 or more units daily
Secondary causes of osteoporosis including:
• Rheumatoid arthritis
• Untreated hypogonadism in men and women
• Prolonged immobility
• Organ transplantation
• Type I diabetes
• Hyperthyroidism
• Gastrointestinal disease
• Chronic liver disease
• Chronic obstructive pulmonary disease
Falls*

* Not presently accommodated in the FRAX® algorithm

The National Osteoporosis Guideline Group (NOGG) has recently published a new management guideline (*Fig. 4*) that integrates FRAX® with clinical management algorithms.[8,9] The approach adopts the previous guidance of the Royal College of Physicians in that treatment should be considered when an individual's probability of fracture is comparable to or exceeds that of a woman of the same age who has already sustained a low trauma fracture.[10-12] Thus the intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture and, therefore rises with age.

The guideline suggests that fracture probability should be assessed with FRAX® in postmenopausal women and in men aged 50 years or more with the risk factors given in *Table 3* where assessment would influence manage-

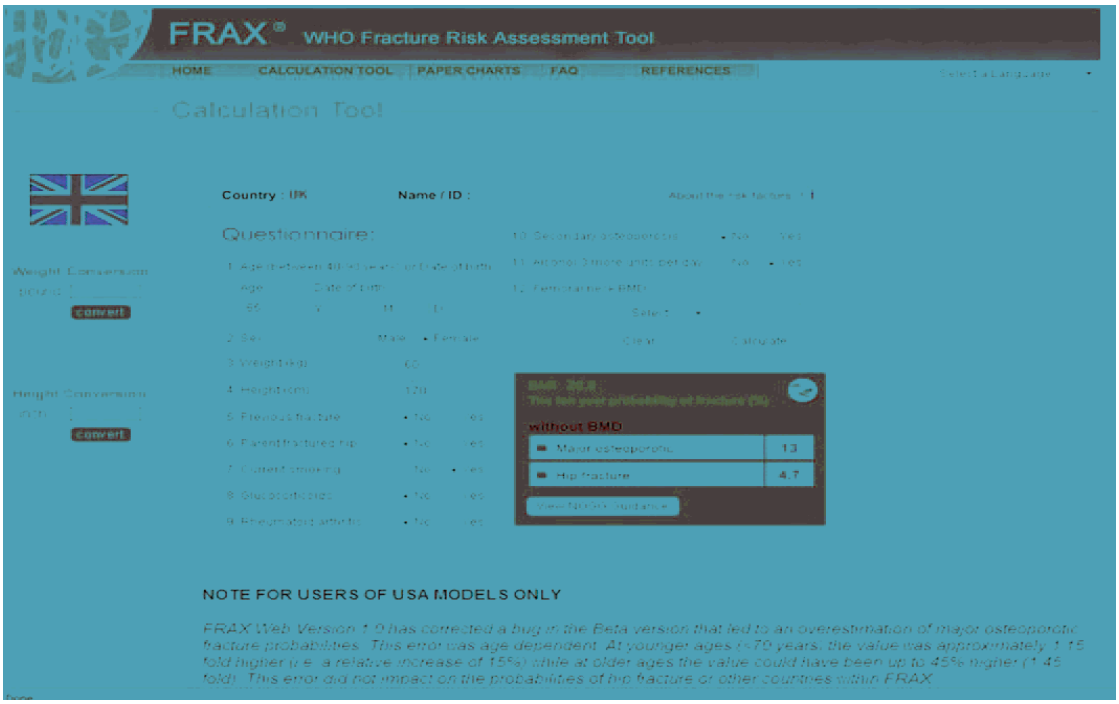
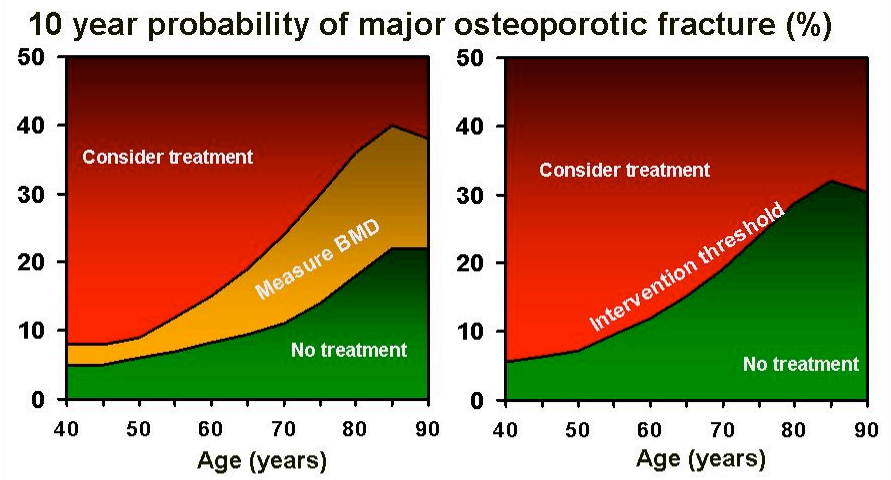


Fig. (3). The FRAX tool for the assessment of an individual's 10-year probability of fracture (http://www.shef.ac.uk/FRAX). Once the calculation is completed, clicking on the "View NOGG guidance" button will automatically display the individual's probability within the suggested care pathways published by the National Osteoporosis Guideline Group (http://www.shef.ac.uk/NOGG).



4a 4b

Fig. (4). Assessment and treatment thresholds in the absence of a BMD test (4a) and with a BMD test (4b) to compute fracture probability for men and women (Kanis et al., 2008b).

ment.[9] Women with a prior fragility fracture can be considered for treatment without the need for further risk assessment although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women.

In the presence of other CRFs, the ten year probability of a major osteoporotic fracture (clinical spine, hip, forearm or humerus) should be determined using FRAX®. Men and women with probabilities below the lower assessment threshold (*Fig. 4a*) can be reassured. Those

with probabilities above the lower assessment threshold but below the upper assessment threshold can be considered for testing with BMD using DXA and their fracture probability reassessed. Men and women with probabilities above the upper assessment threshold (*Fig. 4a*) should be considered for treatment.

In men and women who require a BMD test, fracture probabilities should be recomputed with FRAX®. Treatment can be considered in those in whom fracture probabilities lie above the intervention threshold (*Fig. 4b*).

Probabilities of a major osteoporotic fracture (as well as hip fracture probabilities) can be plotted at the NOGG web site (www.shef.ac.uk/NOGG) available through FRAX®.

Pharmacological Interventions

Major pharmacological interventions are the bisphosphonates, strontium ranelate, raloxifene and parathyroid hormone peptides.[6] All these interventions have been shown to reduce the risk of vertebral fracture when given with calcium and vitamin D supplements. Some have been shown to also reduce the risk of non-vertebral fractures, in some cases specifically at the hip (see *Table 4*).

The low cost of generic alendronate, which has a broad spectrum of anti-fracture efficacy, makes this the first line treatment in the majority of cases. In individuals who are intolerant of alendronate or in whom it is contraindicated, other bisphosphonates, strontium ranelate or raloxifene may provide appropriate treatment options. The high cost of parathyroid hormone peptides restricts their use to those at very high risk, particularly for vertebral fractures.

Alendronate, risedronate, zoledronate and teriparatide are also approved in the UK for treatment of men at high risk of fracture. Alendronate is approved for the prevention and treatment of glucocorticoid induced osteoporosis. Risedronate and etidronate are approved for the prevention and treatment of glucocorticoid-induced osteoporosis in post-menopausal women whilst zoledronate is approved for the treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in men at increased risk of fracture. Teriparatide is approved for treatment of glucocorticoid-induced osteoporosis in men and women at increased risk of fracture.

Other approved pharmacological interventions for postmenopausal women include calcitonin, calcitriol, etidronate and hormone replacement therapy. In the near future, additional therapies will include other SERMs (same class as raloxifene) and a novel monoclonal antibody therapy, denosumab that inhibits osteoclast activity by inhibiting the RANKL/RANK pathway.

Table 4. Effect of major pharmacological interventions on fracture risk when given with calcium and vitamin D in postmenopausal women with osteoporosis[6]

	Vertebral fracture	**Non-vertebral fracture**	**Hip fracture**
Alendronate	A	A	A
Ibandronate	A	A[1]	nae
Risedronate	A	A	A
Zoledronate	A	A	A
Raloxifene	A	nae	nae
Strontium ranelate	A	A	A[1]
Teriparatide	A	A	nae
PTH (1-84)	A	nae	nae

nae: not adequately evaluated
[1]in subsets of patients (post-hoc analysis)
PTH: recombinant human parathyroid hormone

Monitoring of Treatment

Monitoring of treatment commonly uses repeated estimations of BMD and markers of bone formation and/or bone resorption.

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