

# Osteoporosis

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Osteoporosis is a progressive systemic skeletal disease characterised by reduced bone mass/density and micro-architectural deterioration of bone tissue. Bone formation initially exceeds bone resorption, but by the third decade this has reversed resulting in a net loss of bone mass. This leads to an increased bone fragility and susceptibility to fracture.<sup>[1]</sup>

Osteoporotic (fragility) fractures are fractures that result from mechanical forces that would not ordinarily result in fracture. Osteoporotic fractures are defined as fractures associated with low bone mineral density (BMD) and include clinical spine, forearm, hip and shoulder fractures.<sup>[2]</sup>

## Bone density

Bone density values in individuals can be expressed in relation to a reference population in standard deviation (SD); when SDs are used in relation to the young healthy population, this measurement is referred to as the T-score.<sup>[3]</sup>

BMD categories proposed by the World Health Organization (WHO) and the International Osteoporosis Foundation (IOF)<sup>[3]</sup>

- **Osteoporosis:** hip BMD 2.5 SD or more below the young adult reference mean (T-score  $\leq -2.5$ ).
- **Severe osteoporosis:** hip BMD 2.5 SD or more below the young adult reference mean in the presence of one or more fragility fractures (T-score  $\leq -2.5$  PLUS fracture).

Other possible BMD results:

- **Low bone mass (osteopenia):** hip BMD between 1 and 2.5 SD below the young adult reference mean (T-score less than -1 but above -2.5).
- **Normal:** hip BMD greater than the lower limit of normal which is taken as 1 SD below the young adult reference mean (T-score  $\geq -1$ ).

## Epidemiology

Reduced bone density is a major risk factor for fragility fracture. Other factors that may affect the risk of fragility fracture include the use of oral or systemic glucocorticoids, age, sex, previous fractures, and family history of osteoporosis.<sup>[2]</sup>

Because of increased bone loss after the menopause in women, and age-related bone loss in both women and men, the prevalence of osteoporosis increases markedly with age, from 2% at 50 years to more than 25% at 80 years in women.<sup>[2]</sup>

The National Institute for Health and Clinical Excellence (NICE) estimates there are 2 million women who have osteoporosis in England and Wales.<sup>[1]</sup>

## Risk factors

As well as increasing age and reduced BMD, other independent clinical risk factors for fracture are:<sup>[1]</sup>

- Parental history of **hip fracture**.
- Alcohol intake of four or more units per day.
- **Rheumatoid arthritis**.

Risk factors for reduced BMD are:

- Female gender.
- Corticosteroid therapy or **Cushing's syndrome**.

- Ankylosing spondylitis.
- Crohn's disease.
- Untreated premature menopause (<45 years) or prolonged secondary amenorrhoea.
- Low body mass (<19 kg/m<sup>2</sup>) and anorexia nervosa.
- Poor diet (particularly if calcium-deficient) or malabsorption syndromes, eg coeliac disease.
- Prolonged immobilisation or a very sedentary lifestyle.
- Smoking.
- Primary hypogonadism (men and women).
- Primary hyperparathyroidism.
- Hyperthyroidism.
- Osteogenesis imperfecta.
- Caucasian or Asian origin.
- Post transplantation.
- Chronic renal failure.

**NB:** although females are at higher risk, men (especially older men) are also susceptible and are often inadequately screened for the disease despite having relevant risk factors.

## Presentation

Unfortunately, the process that leads to established osteoporosis is asymptomatic and the condition usually presents only after bone fracture. It is important that clinicians be alert to recognise low trauma 'fragility fractures' (fracture caused by a force equivalent to the force of a fall from the height of an ordinary chair or less).<sup>[1]</sup>

Fragility fractures occur most commonly in the spine (vertebrae), hip (proximal femur), and wrist (distal radius). They may also occur in the arm (humerus), pelvis, ribs, and other bones.<sup>[2]</sup> Signs differ according to the fracture site.

## Investigations

See also separate article [Osteoporosis Risk Assessment and Primary Prevention](#).

- Case finding:
  - If a fragility fracture occurs this should trigger bone density measurement (although in women aged ≥75 years osteoporosis can be assumed and first-line treatment initiated (alendronate) without dual-energy X-ray absorptiometry (DEXA) scan if the clinician feels this is appropriate).
  - Patients with any risk factors above should be considered for DEXA scanning, particularly if there are one or more risk factors for fractures (family history, increased alcohol intake or rheumatoid arthritis).
- Diagnosis of osteoporosis centres on the assessment of BMD:<sup>[4]</sup>
  - Single-energy X-ray absorptiometry (SXA) and DEXA/digital X-ray radiogrammetry (DXR) assessment of mineral content of the entire skeleton and particularly at specific, vulnerable sites.
  - DEXA is regarded as the gold standard technique for diagnosis; the accuracy at the hip exceeds 90%. Residual errors arise for various reasons. Incorrect diagnosis of osteoporosis can be caused by osteomalacia, osteoarthritis or soft-tissue calcification.<sup>[4]</sup>
  - DXR is much simpler and less time-consuming than DEXA. It can be carried out anywhere where there is the facility to perform a standard radiograph of the hand. It appears to have similar precision and accuracy to DEXA in terms of diagnosing osteoporosis.<sup>[5]</sup> It is a useful screening tool for osteoporosis following Colles'/other forearm fractures, without the need for additional radiographs. DXR seems to be slightly less sensitive than DEXA in detecting osteoporosis.
  - Other modalities used include ultrasonic measurement of bone. This can be used for the assessment of fracture risk, or selection of those in need of DEXA/DXR. It is unreliable for diagnosis of osteoporosis and is associated with underdiagnosis. Radiography is useful for selection of patients in need of screening/formal diagnosis.

- Consider the following screening blood tests, in patients suffering from osteoporosis, to identify treatable underlying causes:
  - FBC and ESR.
  - U&E, LFTs, TFTs, serum calcium, alkaline phosphatase.
  - Testosterone/gonadotrophins in men.
  - Serum immunoglobulins and paraproteins, urinary Bence-Jones' proteins.

### Assessment of fracture risk<sup>[6]</sup>

Although osteoporosis indicates a high likelihood of fracture, many fragility fractures occur in people with bone density values above the defined level. Fractures can be better predicted by adding clinical risk factors that contribute to fracture risk independently of BMD.<sup>[4]</sup>

There is now a WHO risk calculator available (FRAX®) which calculates the ten-year probability of a major osteoporotic fracture, (with or without BMD result).<sup>[7] [8]</sup>

For UK populations, the recent QFracture® score may be more appropriate for fracture risk assessment.<sup>[9] [10]</sup>

## Management<sup>[1]</sup>

Treatment for osteoporosis should include not only drug treatment but also advice on lifestyle, nutrition, exercise and measures to reduce falls. Ensure adequate calcium intake and vitamin D status, prescribing supplements if required.<sup>[11]</sup>

Patients with osteoporosis (T-score -2.5 or worse) at any age:

- Consider hip protectors and assessment of ongoing risk of falls.
- Reduce polypharmacy, especially sedatives.
- Ensure adequate calcium (0.5-1 g) and vitamin D (800 IU) - supplementation may be necessary.

Postmenopausal osteoporosis may be treated with a bisphosphonate. If bisphosphonates are unsuitable then calcitriol may be considered. The bisphosphonates (alendronic acid, disodium etidronate, and risedronate) are effective for preventing postmenopausal osteoporosis.<sup>[12]</sup>

Hormone replacement therapy (HRT) should not be considered first-line therapy for long-term prevention of postmenopausal osteoporosis but is an option where other therapies are contra-indicated, cannot be tolerated, or if there is a lack of response.<sup>[12]</sup>

### Further management in women who have never had an osteoporotic fragility fracture (primary prevention)

- First-line bisphosphonate (usually alendronate on the basis of cost) is only recommended in postmenopausal women aged under 65 with confirmed osteoporosis but without fragility fractures, if they have an independent clinical risk factor for fracture **and** at least one additional indicator of low BMD.
- Start **bisphosphonates** in osteoporotic women without fragility fracture once they reach age 65 if they have any independent clinical risk factor for fracture, or over the age of 70 if they just have an indicator of low BMD.
- The responsible physician may decide a DXA scan is not required in women aged 75 years or older who have two or more independent clinical risk factors for fracture or indicators of low BMD.

Second-line treatments (risedronate and etidronate) may be considered if the patient is aged over 65 and unable to take alendronate:

Primary prevention - T-score treatment threshold for second-line treatment in patients without previous fragility fracture <sup>[3]</sup>				
Age	If T-score not available	When alendronate not an option, treat with <b>risedronate</b> or <b>etidronate</b> at these values or worse <sup>[3]</sup> Risk factors = family history, alcohol >3 units/day or rheumatoid arthritis		
		No fracture risk factors	1 fracture risk factor	2 fracture risk factors
65-69	Refer for DEXA	Not recommended	-3.5	-3.0
70-74	Refer for DEXA	-3.5	-3.0	-2.5
75 or older	Refer for DEXA unless over 75 and 2 risk factors	-3.0	-3.0	-2.5

**Denosumab** is a monoclonal antibody that reduces osteoclast activity (and hence bone breakdown) which is given by 6-monthly subcutaneous injections. It may be a suitable option in women who are unable to comply with instructions for alendronate and either risedronate or etidronate.<sup>[13]</sup>

**Strontium ranelate** is also licensed for the prevention of osteoporotic fractures in postmenopausal women with osteoporosis. The European Medicines Agency (EMA) has recently advised that it is only used where other medications are not tolerated and there are few cardiovascular risk factors. In other situations the risks of treatment may outweigh the benefits.

Primary prevention - T-score treatment threshold for denosumab treatment in patients without previous fragility fracture <sup>[13]</sup>			
Age	Number of independent clinical risk factors for fracture Parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis		
	No fracture risk factors	1 fracture risk factor	2 fracture risk factors
65-69	not recommended	-4.5	-4.0
70-74	-4.5	-4.0	-3.5
75 or older	-4.0	-4.0	-3.0

**Raloxifene** is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures.<sup>[3]</sup>

### Further management in women who have had an osteoporotic fragility fracture (secondary prevention)

Start first-line bisphosphonate (usually alendronate on the basis of cost), and calcium and vitamin D supplementation is usually co-prescribed. If the initial alendronate is not tolerated or is inappropriate, or there is an inadequate response, the next step depends on BMD, age, whether there has been a fragility fracture and risk factors:<sup>[1]</sup>

**Secondary prevention - T-score treatment threshold for second-line treatment in patients with previous fragility fracture<sup>[1]</sup>**

Age	If T-score not available	When alendronate not an option, treat with risedronate or etidronate at these values or worse <sup>[3]</sup> Risk factors = family history, alcohol >3 units/day or rheumatoid arthritis		
		No fracture risk factors	1 fracture risk factor	2 fracture risk factors
50-54	Refer for DEXA	Not recommended	-3.0	-2.5
55-59	Refer for DEXA	-3.0	-3.0	-2.5
60-64	Refer for DEXA	-3.0	-3.0	-2.5
65-69	Refer for DEXA	-3.0	-2.5	-2.5
70-74	Refer for DEXA	-2.5	-2.5	-2.5
75 and over	DEXA may not be required (see any local guidelines)	-2.5	-2.5	-2.5

If second bisphosphonate is not an option, treat with raloxifene at these thresholds:

**Secondary prevention - T-score treatment threshold for third-line treatment in patients with previous fragility fracture****Threshold for treatment with raloxifene<sup>[1]</sup>**

Risk factors = family history, alcohol >3 units/day or rheumatoid arthritis

Age	0 risk factors	1 risk factor	2 risk factors
50-54	Not recommended	-3.5	-3.5
55-59	-4.0	-3.5	-3.5
60-64	-4.0	-3.5	-3.5
65-69	-4.0	-3.5	-3.0
70-74	-3.0	-3.0	-2.5
75 and over	-3.0	-2.5	-2.5

If raloxifene is not an option, consider referral to secondary care for assessment for teriparatide or denosumab:

**T score threshold for secondary care referral for teriparatide<sup>[1]</sup>**

Risk factors = family history, alcohol >3 units/day or rheumatoid arthritis

Age	2 fragility fractures or less	More than 2 fragility fractures
50-54	Not recommended	Not recommended
55-60	Not recommended	-4.0
61-64	Not recommended	-4.0
65-69	-4.0	-3.5
70-74	-4.0	-3.5
75 and over	-4.0	-3.5

Denosumab may also be a treatment option for the secondary prevention with increased risk of fractures in patients who cannot comply with the special instructions for administering alendronate, risedronate or etidronate, or have an intolerance or a contra-indication to those treatments.<sup>[13]</sup>

**Osteoporosis in men**

Alendronate 70 mg is used in men (unlicensed indication). Seek specialist advice re alternatives if this is not tolerated or if other first-line bisphosphonates are not tolerated.

## Notes on treatments

- **Bisphosphonates** are the mainstay of treatment for osteoporosis. They are, however, poorly absorbed and need to be taken separately from food. They may cause oesophageal irritation and should be taken by the patient sitting up with plenty of water.<sup>[11]</sup> Etidronate was the first but has been superseded by the more powerful alendronate and risedronate, both of which can be taken daily or weekly, and the newer ibandronate that can be taken monthly. Less frequent dosing may improve adherence to therapy. All bisphosphonate trials have been controlled for calcium/vitamin D and so bisphosphonates should usually have calcium/vitamin D co-prescribed. Bisphosphonates act by inhibiting the action of osteoclasts. They have been shown to be cost-effective in European studies.<sup>[14]</sup>
  - **Zoledronic acid** (Aclasta®)<sup>[15]</sup> is a bisphosphonate given by a single intravenous infusion once a year, licenced for the treatment of postmenopausal osteoporosis and osteoporosis in men. It is very expensive compared with oral formulations.
- **Raloxifene**, a selective oestrogen receptor modulator (SERM), reduces postmenopausal bone loss and reduces vertebral fractures but, like HRT, may increase the risk of **venous thromboembolism**. Unlike HRT, however, it decreases the risk of **breast cancer** (oestrogen-positive tumours) but may exacerbate hot flushes. The Commission on Human Medicines (CSM) has advised that HRT should not be considered as first-line therapy for long-term prevention of osteoporosis, due to the increased risk of breast cancer and **cardiovascular disease**.
- **Parathyroid hormone peptides:**
  - Teriparatide (recombinant 1-34 parathyroid hormone) may be considered as an alternative for women in whom alendronate and either risedronate or etidronate are contra-indicated or not tolerated, or where treatment with alendronate, risedronate or etidronate has been unsatisfactory (another fragility fracture and a decline in BMD despite treatment for one year).<sup>[12]</sup>
  - Preatact® (the full 1-84 parathyroid hormone peptide) has also been approved. Neither has been shown to reduce hip fractures.
  - They are more expensive than other options, so are reserved for patients with severe osteoporosis who are unable to tolerate, or are unresponsive to, bisphosphonates.

## Screening

See separate article [Osteoporosis Risk Assessment and Primary Prevention](#).

## Prognosis

Osteoporotic fragility fractures can cause substantial pain and severe disability, often leading to a reduced quality of life, and hip and vertebral fractures are associated with decreased life expectancy. Hip fracture nearly always requires hospitalisation, is fatal in 20% of cases and permanently disables 50% of those affected; only 30% of patients fully recover.<sup>[2]</sup>

- Approximately 14,000 people die per year from osteoporosis (greater than **carcinoma of ovary**, uterus and cervix put together).
- The mortality of hip fracture in older patients is 20% at three months.
- Only 50% of survivors regain full independence after fracture.
- Survivors consult their GP approximately nine extra times in the year following their fracture.
- Only one in three vertebral fractures is diagnosed.
- One vertebral fracture increases a patient's risk of sustaining another vertebral fracture fivefold, 20% of these within a year.
- Patients who sustain a vertebral fracture consult their GP, on average, 14 extra times in the year following it.

## Further reading & references

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Last Checked: 02/10/2012	Document ID: 1613 (v30)	© EMIS

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