Osteoporosis

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Osteoporosis is a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration, with a consequent increase in bone fragility and susceptibility to fracture. A diagnosis of osteoporosis is made if the patient sustains a low trauma fracture or if bone mineral density (BMD) is more than 2.5 standard deviations (SD) below the mean for young people (Fig 1).

Pathophysiology
Bone undergoes a continual process of resorption and formation in discrete bone remodelling units, with about 10% of the adult skeleton remodelled each year. This turnover prevents fatigue damage, and is important in maintaining calcium homeostasis. Bone loss results from an imbalance between the rates of resorption and formation.

The human skeleton comprises about 80% cortical bone and 20% trabecular bone, which is more metabolically active. Osteoporotic fractures tend to occur at sites with more than 50% trabecular bone. Bone loss leads to thinning, and sometimes perforation, of the trabecular plates. The resulting change in architecture leads to a loss of strength disproportionate to the amount of bone lost.

Figure 1. Bone mass across life. The reference range is represented as mean ± 2 standard deviations (SD). The broken line indicates the diagnostic threshold for osteoporosis according to the World Health Organisation criteria (2.5 SD below the young adult mean). Peak bone mass is achieved by the age of 30 years. After skeletal maturity, bone is lost in both sexes at a rate of about 1% per year, and women experience a phase of accelerated bone loss for three years after the menopause. Various factors may affect the rate of bone loss (eg calcium intake, exercise) (BMD = bone mineral density).
Clinical consequences of osteoporosis

Osteoporosis does not cause pain or deformity in the absence of fractures. Its importance lies in the fact that it greatly increases the risk of fracture, notably forearm (Colles'), hip and vertebral fracture. After the age of 50 years, the risk of sustaining an osteoporotic fracture is 40% for a woman and 15% for a man. This risk is referred to as the 'lifetime fracture risk', and is useful when discussing the results of bone density measurements.

**Increased mortality.** Mortality is increased by 20% in the first year after a hip fracture. It is also increased after vertebral fracture, possibly as a result of diseases that increase the risk of fractures and death.

**Pain.** Following a vertebral fracture, pain usually subsides after three months, although prolonged pain may result from secondary osteoarthritis. Pain can also occur when the costal margin impinges on the pelvic brim.

**Deformities** include kyphosis, loss of height and abdominal protrusion.

**Loss of independence** has a considerable financial impact because it may necessitate long-term community support or care in a nursing home after a hip fracture.

**Key Points**

- Osteoporosis is very common, affecting one in three women and one in 10 men by the age of 70
- Osteoporosis is associated with significant morbidity and increased mortality
- Measurement of bone mineral density is the best way to identify individuals at increased risk of osteoporotic fracture
- A secondary cause for osteoporosis may be identified in approximately 40% of women and 60% of men
- Osteoporosis is preventable
- Pharmacological treatment of osteoporosis reduces the risk of fracture by as much as 50%

**Investigations** (Table 1)

Patients with an osteoporosis-related fracture resulting from minor trauma should undergo systematic investigation.

**Radiology**

The identification of low-trauma fracture (resulting from a fall from standing height or less) of the hip or distal forearm is straightforward. However, identification of vertebral fracture can be difficult. Not all vertebral fractures are painful, and vertebrae may be deformed for reasons other than fracture (eg juvenile epiphysitis).

Subtle changes of osteoporosis may be identified on plain radiographs (eg low density compared with soft tissue, prominence of vertical trabeculae), but these changes are unreliable and the suspicion of osteoporosis must be confirmed by measurement of bone density.

The most reliable finding on a spine radiograph to support the diagnosis of osteoporosis is the presence of a deformed vertebra. Vertebral deformities include:

- wedge deformity (loss of anterior height),
- end-plate deformity (loss of middle height), and
- compression deformity (loss of anterior, posterior and middle height).

**Bone density measurement**

Measurement of bone density has recently become more reliable and more widely available.

**Absorptiometry**

Dual energy X-ray absorptiometry (DXA) is precise, accurate, involves exposure to only low doses of X-rays, and allows measurement of sites of clinical interest (ie lumbar spine, proximal femur). Two energy peaks of X-rays are absorbed to different extents by bone and soft tissue, and the density of bone is calcu-
Table 2. Uses of bone density measurements.

| To establish current fracture risk by comparison with young adult reference range |
| --- |
| • Decrease in spine density of 1 SD (or 12%) is associated with doubling of fracture risk |

| To establish future fracture risk by comparison with age-matched adults |
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| • Particularly useful in perimenopausal women |
| • Assuming that bone loss proceeds at the average rate, those at high risk of fracture by 70 years of age can be detected |

| To monitor the effect of treatment |
| --- |
| • Annual measurements |
| • A difference greater than 3% can be detected by dual energy X-ray absorptiometry of the lumbar spine (average rate of bone loss in untreated osteoporosis: ca 2% per year; average rate of bone gain in osteoporosis treated with antiresorptive agents: 3% per year) |

Lated, in g/cm² using simultaneous equations. The measurement is compared with two reference ranges (young adults, age 30 years, and age-matched adults). These bone density measurements have several uses (Table 2) (Figs 2 and 3).

Single energy X-ray (or photon) absorptiometry has similar advantages to DXA and the equipment is less expensive. However, the sites in which bone density can be measured (distal forearm, calcaneum) may not be of clinical interest.

Computed tomography

Three-dimensional measurements of the bone density of the lumbar spine can be made using quantitative computed tomography, a technique which also allows measurement of trabecular bone alone (ie the type of bone usually lost first in the development of osteoporosis). It is, however, more expensive, less precise and involves a higher radiation dose than DXA.

Ultrasound

Quantitative ultrasound measurements are usually made on the calcaneum. The ultrasound signal has a lower frequency (200–600 kHz) than that used in obstetrics (>1 MHz). The attenuation of the signal (broad-band ultrasound attenuation) may reflect both the density and the architecture of bone, and the velocity of the signal reflects the density and biomechanical properties (elasticity). Quantitative ultrasonography is currently used only in research but, if recent studies of its predictive ability in osteoporosis are confirmed, it could become an established technique.

Secondary osteoporosis

Secondary osteoporosis must be excluded. An underlying cause is present in approximately 40% of women and 60% of men with osteoporosis. Investigations to identify a cause are recommended if the BMD is more than 2 SDs below the age-matched mean, or if the patient has low trauma vertebral fractures.

Bone biopsy

Bone biopsy may be useful in unusual forms of osteoporosis (eg idiopathic osteoporosis in young adults). It provides information about the rate of bone turnover and the presence of secondary forms of osteoporosis (eg systemic mastocytosis). Patients with high bone turnover usually respond better to antiresorptive drugs.

Biochemical markers of bone turnover

The processes of bone resorption and formation are reflected in biochemical markers of bone turnover. Markers specific to bone (eg osteocalcin, deoxypyridinoline) are being investigated, and may be useful for monitoring the effect of drugs used in the treatment of osteoporosis. Biochemical markers of bone resorption are maximally suppressed by three months' treatment with oestrogens or bisphosphonates. They could therefore be particularly useful for monitoring treatment because changes in bone density may not be detected for two years and not all patients have access to bone densitometry.

Figure 2. Bone mineral density measurement of the lumbar spine (L2–L4), expressed as an areal density (g/cm²) and shown graphically in comparison to an age- and sex-matched reference range.
Treatment and prevention

Treating established osteoporosis

The aims of the treatment of established osteoporosis are alleviation of patients' symptoms and reduction of the risk of further fractures. Currently available drugs are used to prevent more bone loss and can reduce the risk of further fractures by up to 50%. Drug treatments should be monitored by measuring bone density, because some patients fail to respond to certain drugs.

Pain relief is provided mainly by analgesic drugs. Physical measures are also useful (eg lumbar support for a limited period of time, a transcutaneous nerve stimulator). The pain from a fracture usually resolves within three months, but patients with vertebral fractures may require long-term analgesia because of secondary degenerative disease.

Drugs to improve bone mass either inhibit bone resorption or stimulate bone formation. Most drugs approved for use in osteoporosis inhibit bone resorption, but some of them (eg hormone replacement therapy (HRT), bisphosphonates) increase BMD by 5–10% over the first two years of treatment by enabling infilling of the remodelling space.

Antiresorptive drugs

HRT is considered the treatment of choice. The most effective alternative treatment is the bisphosphonates. In the UK, two agents, etidronate and alendronate, are currently approved for use in osteoporosis.

HRT is an effective treatment for osteoporosis, even in elderly women. Oestrogen is given alone in hysterectomised women, and with cyclical or continuous administration of progestogen in women with an intact uterus. Compliance is poor (50% at one year), but this can be improved by using continuous combined HRT (or tibolone) which does not usually result in regular menstrual bleeding. Risks with HRT include breast cancer (50% increase in risk after 10 years' treatment) and deep vein thrombosis (DVT) (threefold increase in risk, particularly in patients with previous DVT). The benefits of HRT include decreased risk of ischaemic heart disease (IHD) (by 50%) and possibly Alzheimer's disease, and an improvement in menopausal symptoms.

Some of the disadvantages of HRT may be overcome by the development of a new class of drugs: the selective (o)estrogen receptor modulators (SERMs). Data recently reported show that, like oestrogen, raloxifene increases BMD and lowers serum total and low-density lipoprotein cholesterol but, unlike oestrogen, does not appear to stimulate the endometrium. As yet, no SERM is licensed for the prevention or treatment of osteoporosis.

Testosterone therapy is effective in men with hypogonadism. It is not currently used in eugonadal men because of concerns about the increased risk of prostate cancer and IHD (via lowering of high-density lipoprotein cholesterol).

Etidronate is given in a cyclical regimen in a dose of 400 mg/day for two weeks, followed by elemental calcium, 500 mg/day for 11 weeks. The effects on spine bone density are similar to those of HRT. Side-effects are uncommon. Etidronate must be taken on an empty stomach (2 hours after the last meal and 2 hours before the next meal).

Alendronate is given in a dose of 10 mg/day continuously. If the patient's diet does not contain sufficient calcium, a calcium supplement, 500 mg/day, should be given in the evening. Alendronate must be taken at least 30 min before breakfast (to help absorption) with a full glass of water, and the patient must not lie down after taking the tablet (to avoid oesophagitis). Alendronate is equally effective on the hip, forearm and spine, and has been shown to prevent fracture at all these sites.

The strict dosing instructions for the bisphosphonates may reduce compliance in the elderly. Three other agents can be useful in special circumstances:

- Calcium, 1,200 mg/day, plus vitamin D, 800 IU/day, have been shown to prevent hip fracture in house-bound elderly patients. This treatment is safe, and does not require monitoring.

- Calcitonin (salmon calcitonin), 50 IU subcutaneous on alternate days, is not as effective as either HRT or bisphosphonates, and it has a number of side effects (eg nausea, diarrhoea, flushing). However, it has an analgesic effect and can be useful in patients with acute vertebral fracture. A nasal preparation is available in some countries.

- Calcitriol stimulates calcium absorption and may stimulate osteoblasts directly. It appears to be effective in corticosteroid-induced osteoporosis, for which it can be considered an alternative to HRT or bisphosphonates, particularly in younger patients. Regular monitoring of serum calcium is required because hypercalcaemia is a common adverse effect.

Formation-stimulating drugs

Drugs which stimulate bone formation are the subject of considerable research, but the only currently available agent is sodium fluoride. This drug may result in a 35% increase in BMD over four years, but can lead to dyspepsia and stress.
fractures. It is not widely used in the UK, but is popular in some other European countries.

Detection and treatment of secondary osteoporosis

The screening tests for primary causes are listed in Table 1. Partial recovery of bone mass is often achieved by treating these conditions.

Preventing fractures

- Preventing falls: predisposing factors (eg postural hypotension, drowsiness caused by drugs) should be eliminated. Patients should receive physiotherapy to improve their balance.
- Hip protectors, which are designed to absorb the impact of a fall on to the hip, have been shown to reduce the incidence of hip fracture among nursing home residents.
- Appropriate walking aids should be provided, and an environmental assessment made of patients' accommodation to eliminate hazards such as loose mats and cables.

Prevention of osteoporosis (Table 3)

Prevention of osteoporosis should aim to increase peak bone mass and reduce the subsequent rate of bone loss. HRT is the most effective preventive measure:
- Prophylactic treatment against bone loss should be targeted at postmenopausal women whose BMD at the lumbar spine or hip is more than 1 SD below the mean for their age.
- Women with BMD above the mean for young adults probably do not require HRT for prevention of osteoporosis.
- Women with intermediate BMDs may benefit from HRT if they lose bone at a faster than average rate. This may be determined from a repeat measurement of BMD after two years. In future, it may be possible to predict fast bone losers using biochemical markers of bone turnover.

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