Osteoporosis is by far the most common bone disease. It is characterised by reduced bone mineral density (BMD), micro-architectural deterioration of bone tissue and an increased risk of fracture.

The prevalence of osteoporosis and osteoporosis-related fractures increases markedly with age, reflecting the age-related decline in bone mass and the increased risk of falling in the elderly.

Fractures related to osteoporosis are a major public health problem in all developed countries, affecting up to 30% of women and 12% of men at some time in their life. In the UK alone, fractures affect over 250,000 individuals annually with treatment costs of about £1.4 million.

*Pathogenesis*

Post-menopausal osteoporosis occurs because of; low peak bone mass, accelerated bone loss after the menopause and with ageing or a combination of both factors.

In normal individuals, bone mass increases during skeletal growth to reach a peak between age 20-40 but falls thereafter. There is an accelerated phase of bone loss in women after the menopause as a result of oestrogen deficiency which causes uncoupling of bone resorption and bone formation, such that the amount of bone removed during the bone remodelling cycle slightly exceeds that which is replaced.

Bone mass and bone loss are regulated by a combination of genetic and environmental factors. Genetic factors play an important role, accounting for up to 80% of the population variance in peak bone mass and other determinants of fracture risk such as bone turnover and bone size. Environmental factors such as exercise and calcium intake during growth and adolescence are important in maximising peak bone mass and in regulating rates of post-menopausal bone loss.

Smoking has a detrimental effect on BMD and also associates with increased fracture risk, partly because female smokers have an earlier menopause than non-smokers.

Moderate amounts of alcohol do not appreciably influence the risk of osteoporosis, although alcoholism is a recognised cause of secondary osteoporosis.

Osteoporosis is less common in men than in women, and a secondary cause can be identified in about 50% of cases, most notably hypogonadism, corticosteroid use or alcoholism. The pathogenesis of osteoporosis secondary to hypogonadism in men is similar to that in post-menopausal osteoporosis, in that testosterone deficiency results in an increase in bone turnover and uncoupling of bone resorption from bone formation. No obvious cause can be identified in 50% of men with osteoporosis and it is likely that genetic factors play an important role in these cases.

Osteoporosis can occur as a complication of many diseases and drug treatments. In primary hyperparathyroidism, osteoporosis mainly occurs in post-menopausal women and here it appears that the high levels of PTH increase bone turnover and aggravate the uncoupling of bone resorption and bone formation which already occurs due to oestrogen deficiency.

A similar mechanism operates in thyrotoxicosis, driven by raised levels of thyroid hormones.

The mechanism in Cushing's disease is as described below for corticosteroid-induced osteoporosis.
Anorexia nervosa causes osteoporosis through several mechanisms including calcium deficiency, weight loss and hypogonadism, whereas malabsorption predisposes to osteoporosis through calcium deficiency and secondary hyperparathyroidism.

Inflammatory diseases cause osteoporosis by increasing bone resorption and suppressing bone formation through release of pro-inflammatory cytokines such as IL-1 and TNF, and similar mechanisms operate in certain types of cancer where a variety of bone-resorbing factors are released by the tumour, including TNF, lymphotoxin and parathyroid hormone-related protein (PTHrP).

Release of bone resorbing factors is also thought to underlie the pathogenesis of osteoporosis in Gaucher's disease and mastocytosis.

**Corticosteroid-Induced Osteoporosis**

Corticosteroid treatment is an important cause of osteoporosis, the risk of which is directly related to dose and duration of therapy. Although there is no 'safe' dose of corticosteroid, osteoporosis is less likely to occur in patients who are receiving inhaled glucocorticoids, short-term courses of steroids or prednisolone doses of less than 5 mg daily.

The risk becomes substantial when the dose of prednisolone exceeds 7.5 mg daily and is continued for more than 3 months.

Corticosteroids have adverse effects on several aspects of calcium metabolism. Intestinal calcium absorption is decreased and renal calcium excretion increased, leading to secondary hyperparathyroidism and increased bone turnover. This is combined with inhibition of bone formation due to a direct inhibitory effect on osteoblast activity and stimulation of osteoblast death through apoptosis.

The combination of all of these factors leads to rapid bone loss and a greatly increased risk of fracture.

**Clinical Features**

The clinical presentation of osteoporosis is with; fragility fractures, back pain, height loss and kyphosis although many patients are asymptomatic.

A common presentation is with radiological osteopenia in otherwise asymptomatic patients who are undergoing X-ray examination for trauma or another condition. The x-ray below shows a tibia with osteopenic appearances; the bony looks more radiolucent than normal.
Osteoporotic fractures can affect virtually any bone, but the most common sites are; the wrist (Colles fracture), spine (vertebral fracture) or femur (hip fracture). Patients suffering from a fragility fracture are often referred on for bone densitometry following a fragility fracture.

**Investigations and Diagnosis**

Measurements of bone mineral density (BMD) are necessary to make or exclude the diagnosis of osteoporosis. The preferred technology is dual energy X-ray absorptiometry (DXA) and the preferred measurement sites are the lumbar spine and hip.

Bone densitometers work on the principle that the calcium in bone attenuates passage of X-ray beams in proportion to the amount of mineral present. By comparing the degree of attenuation with known standards, BMD values can be estimated for various skeletal sites and the values are expressed in grams of hydroxyapatite per cm² of the area scanned.

In addition to giving absolute BMD values, DXA machines give results as 'T-scores' and 'Z-scores'. The T-score measures by how many standard deviations the patient's BMD value differs from that of a young healthy control.

The Z-score measures by how many standard deviations the BMD deviates from that of an aged-matched control. Osteoporosis is diagnosed when the T-score value falls to -2.5 or below (shaded orange in the figure), whereas T-score values that lie between -1.0 and -2.5 are defined as being in the osteopenic range (shaded beige in the figure). Values of BMD above -1.0 are regarded as normal.

If the diagnosis of osteoporosis is confirmed by bone densitometry, a history should be taken to identify predisposing causes such as early menopause, excessive alcohol intake, smoking and corticosteroid therapy.
Physical examination should include a search for endocrine disease (thyrotoxicosis, Cushing's disease, hypogonadism), neoplasia (evidence of weight loss, lymphadenopathy) and inflammatory disease.

Routine biochemical and haematological screens should include; serum calcium and phosphate, thyroid function tests, immunoglobulins and ESR.

Additional investigations such as serum vitamin D and PTH measurement may be required if there is reason to suspect vitamin D deficiency or primary hyperparathyroidism. Levels of sex hormones and gonadotrophins should be measured in men with osteoporosis and in amenorrhoeic women below 50. Transiliac bone biopsy is only required in patients with early-onset osteoporosis of unknown cause or when coexisting osteomalacia is suspected.

**Treatment**

Individuals with normal BMD can be reassured, whereas patients with osteopenia should be given advice on lifestyle factors such as smoking (stop), alcohol (limit to < 20 U/week), dietary calcium (aim for 1500 mg daily) and exercise (encourage).

Osteopenic patients with BMD values between -2.0 and -2.5 should be offered a repeat BMD measurement in 2-3 years.

Specific anti-osteoporosis treatment should be considered in patients with BMD values in the osteoporotic range, especially those who have a previous history of fragility fractures.

**Bisphosphonates**

Bisphosphonates are currently the market-leading drugs for osteoporosis. They are synthetic analogues of pyrophosphate that adsorb on to bone surfaces and become incorporated within bone matrix. When osteoclasts resorb bone that contains bisphosphonate, the drug is released within the cell, where it inhibits signalling pathways that are essential for osteoclast function.

Bisphosphonate therapy results in a decrease in bone resorption, but bone formation is also suppressed because of coupling between these processes in the bone remodelling cycle. The suppression of bone resorption acts to prevent bone loss, however, and allows mineralisation of existing bone to increase. Patients who are treated with bisphosphonates usually experience a gradual increase in BMD of about 5-8% with a plateau about 2 years after commencing therapy.

Bisphosphonates are poorly absorbed from the gastrointestinal tract and should be taken on an empty stomach with plain water only, avoiding food for 45-60 minutes after administration. Upper gastrointestinal upset can occur, especially with aminobisphosphonates such as alendronate and risedronate. These drugs should be used with caution in patients with gastro-oesophageal reflux disease, and avoided in patients with oesophageal stricture or achalasia.

**Hormone Replacement Therapy (HRT)**

HRT with oestrogen and progestagens prevents post-menopausal bone loss and reduces the risk of osteoporotic fractures. The use of HRT as a treatment for osteoporosis has diminished in recent years following publication of the large Women's Health Initiative study which showed that long-term HRT increased the risk of breast cancer, thromboembolic disease, stroke and cardiovascular disease.

These risks are lower with oestrogen-only HRT in women who have had a hysterectomy, but even in this group HRT is regarded as second-line treatment because safer alternatives are available.

Testosterone is indicated for men with osteoporosis who have hypogonadism.
Calcium and Vitamin D Supplements

Are generally used as an adjunct to other treatments. Calcium is typically given in doses of 500-1000 mg daily. Vitamin D supplements in doses of 400-800 U daily.

When given as monotherapy, calcium and vitamin D supplements have been shown to prevent fragility fractures in elderly institutionalised patients with vitamin D deficiency, but they do not seem to be effective at preventing fractures in other patient groups.

Calcitonin

Calcitonin is an osteoclast inhibitor which is effective in preventing post-menopausal bone loss and in the secondary prevention of vertebral fractures in patients with established osteoporosis. However, the effects are not as robust as those of the aminobisphosphonates and there is doubt concerning calcitonin’s effectiveness in preventing non-vertebral fractures.

There is evidence that calcitonin has analgesic properties and may be helpful in reducing the pain of acute vertebral fracture when given by subcutaneous or intramuscular injection (100-200 U daily).

Parathyroid Hormone (PTH)

PTH is an effective treatment for osteoporosis and works by stimulating bone formation. The beneficial effects of PTH on the skeleton are thought to depend on its intermittent mode of administration which results in peaks and troughs of circulating hormone. This contrasts with the situation in primary hyperparathyroidism where there is a sustained elevation in PTH which causes bone loss and can result in an increased risk of osteoporosis.

The formulation currently available is the 1-34 fragment amino acid (teriparatide), given by single daily subcutaneous injection of 20 μg over a 12-18-month period. Teriparatide increases BMD by 10% or more in osteoporotic subjects and reduces the risk of both vertebral and non-vertebral fractures. It is also effective in male osteoporosis and corticosteroid-induced osteoporosis.

Teriparatide has been successfully combined with HRT but administration of bisphosphonate therapy prior to or during teriparatide treatment has been shown to blunt the anabolic effect. Because of its high cost, teriparatide is currently reserved for patients with severe osteoporosis or those who have not responded adequately to other therapies.