

Osteoporosis and its prevention

Osteoporosis is a “silent” disease that can result in severe morbidity and mortality once falls and fractures occur. In this first article of two, **Nuttan Tanna** discusses symptoms, risk factors and prevention

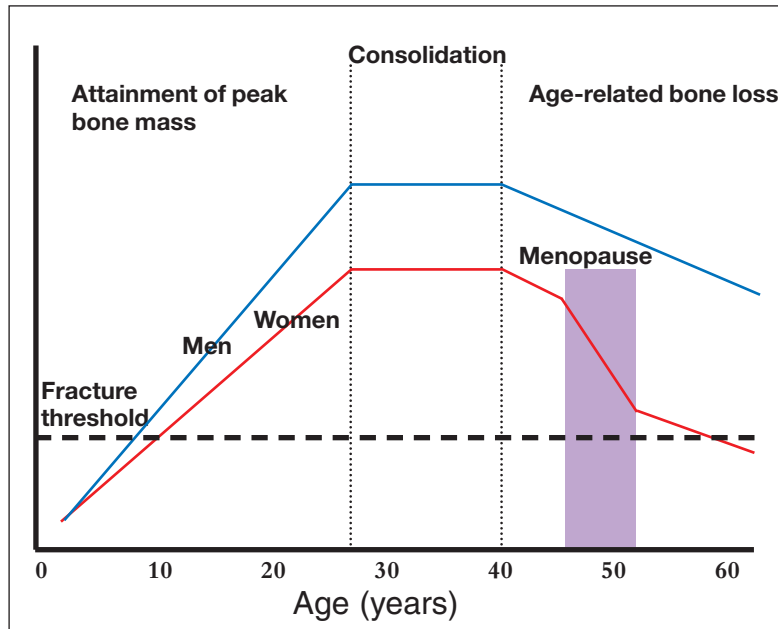


Figure 1: Age-related changes in bone mass

Bone density and its related property, bone strength, change considerably throughout life. Density increases during growth, continuing to rise even after growth in height stops. Peak bone mass is achieved between the ages of 25 and 40 years. The size and shape of each bone are genetically predetermined but are also influenced by endocrine factors, nutrition, physical forces and local growth factors (eg, bone morphogenetic proteins).

After skeletal maturity is reached, bone loss begins and persists until 85–90 years of age (research has not been undertaken for people aged over 90 years). Lifetime losses range from 20 to 30 per cent of peak mass for males and up to 50 per cent for females. Losses are attributable to a bone remodelling imbalance, which although minute at each remodelling locus (see p524), is cumulative. In women, oestrogen is one additional factor that determines and maintains bone mass density (BMD). Hypo-oestrogenic states (eg, anorexia nervosa and athletic amenorrhoea) are associated with low bone mass. A high bone mass is associated with parity and oral contraceptive use.

Overall, post-maturity losses amount to 0.25–1 per cent per year. Women experience an acceleration of bone loss to as much as 2–3 per cent each year, beginning in the perimenopausal period and continuing for around five years after menopause (see Figure 1). This acceleration stems from the decline in ovarian function and oestrogen production and perhaps also in the decreased production of other hormones, such as progesterone.

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Identify knowledge gaps

1. What factors affect bone loss?
2. What evidence-based measures can be taken to prevent osteoporosis?
3. How can pharmacists help prevent osteoporosis?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in “Plan and record”, (available at: www.rpsgb.org/education). This article relates to “common disease states” (see appendix 4 of “Plan and record”).

Osteoporosis

Osteoporosis is a progressive disease characterised by low bone mass, deterioration of bone structure and an increased likelihood of fracture. Fractures of the wrist, hip and spine are the most typical of osteoporotic fragility fractures, but fractures of other bones, such as the ribs, humeri and pelvis, are not uncommon.

Osteoporosis can be divided into two categories: primary and secondary. Primary osteoporosis is the more common form. It includes postmenopausal osteoporosis, age-related osteoporosis and idiopathic osteoporosis.

Age-related osteoporosis affects many individuals between the ages of 70 and 80 years. Patients typically present with a “dowager's hump” (kyphosis) due to vertebral collapse. This leads to other problems, including loss of height (it is not unusual for patients to lose between 10 and 20cm in height), bulging stomach due to loss of space under the ribs (in some severe cases, the rib cage can come to rest on the pelvic brim), a weak neck (the head falls forward), breathing difficulties, indigestion and gastro-oesophageal reflux, stress incontinence, back pain and mobility problems.

Idiopathic osteoporosis can affect young or middle-aged men and premenopausal women. Testosterone deficiency exists in about 30 per

Panel 1: Glucocorticoid-induced osteoporosis

At pharmacological doses, glucocorticoids inhibit osteoblast activity (see p524). In 2002, the Royal College of Physicians produced "Glucocorticoid-induced osteoporosis—guidelines for prevention and treatment". These evidence-based guidelines are particularly useful for health professionals involved in overseeing the care of patients on glucocorticoid treatment. They include patient information, and an easy to follow algorithm that helps assessment of a patient's risk of osteoporosis and diagnosis. The National Institute for Healthcare and Clinical Excellence guidance for primary prevention of osteoporotic fragility fractures due to be published in 2006 will include updated guidance for glucocorticoid-induced osteoporosis.

cent of men with spinal osteoporosis and there is a significant risk of hip fractures in elderly men.

In secondary osteoporosis, an identifiable agent or disease process causes bone loss. Chronic conditions recognised as causes of osteoporosis include hyperthyroidism, hyperparathyroidism, diabetes mellitus, amenorrhoea, anorexia nervosa, hyperprolactinaemia, neoplastic disease, coeliac disease, inflammatory bowel disease, alcoholism and rheumatoid arthritis. Drugs that can cause secondary osteoporosis include glucocorticoids (see Panel 1), anticonvulsants and heparin.

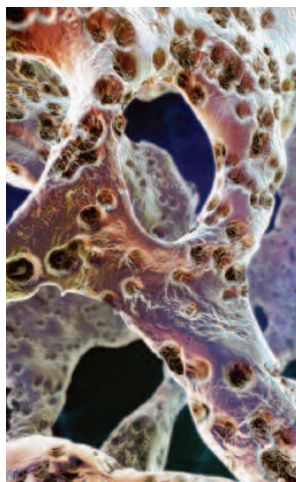
Social and economic implications It is estimated that in 2002, 8.1 per cent of women in the UK had osteoporosis (around 2.6 million women in England and Wales). Prevalence increases markedly with age after menopause, and about 50 per cent of women aged 80 years or over have osteoporosis.

The annual incidence of osteoporotic fractures, including recurrent fractures, is at least 180,000 but it is also known that between 50 and 70 per cent of vertebral fractures do not come to clinical attention. The annual cost of these fractures to the NHS is estimated to be over £1.8 billion and is rising. By the age of 50, the lifetime risk of osteoporotic fracture is around 40 per cent in Caucasian women and 13 per cent in men. With an ageing UK population, it is estimated that the number of osteoporotic fractures over the next 50 years will double.

Up to the age of 65 years, most fractures are of the forearm. After this, the risk of hip fractures rises exponentially and, for vertebral fractures, the rise is linear with age. Hip fractures alone account for more than 20 per cent of orthopaedic bed occupancy.

As well as severe pain, fractures can result in significant disability and considerable morbidity. After sustaining a hip fracture, many patients are unable to walk or perform other activities of daily living and are unable to continue to live independently. After hip fracture, between 25 and 50 per cent of patients become less independent—many require residential or nursing care. Mortality after a hip fracture is around 10–20 per cent.

Risk factors Although 85 per cent of population variance in BMD is attributable to genetic factors, osteoporosis is a multi-factorial disorder. Causal factors can be traced in



Osteoporotic bone

epidemiological investigations by identifying risk factors associated with an increased incidence of either low BMD or non-traumatic fractures. Risk factors are listed in Panel 2. Demonstration of actual causality requires experimental evidence that a factor produces bone loss and its removal halts the loss. Oestrogen deficiency and long-term corticosteroid therapy have been experimentally established as causal risk factors.

Primary prevention

Various strategies are available for primary prevention of osteoporosis, that is intervention before substantial bone loss has occurred. Population-wide primary prevention measures mainly involve providing health education and these interventions are relatively inexpensive to make.

Lifestyle advice Lifestyle interventions include maintaining a healthy balanced diet, with adequate calcium and vitamin D intake. Up to 40 per cent of adult skeletal mass is accrued during adolescence so calcium and vitamin D intake are particularly important at this time.

Calcium The bioavailability of calcium is increased by potassium (good sources are meat and fish). It is reduced by oxalates (found in green leafy vegetables), phytates (found in grains), high salt content and sulphur amino acid metabolites. The National Osteoporosis Society (NOS) has produced a patient information leaflet on calcium (available at: www.nos.org.uk/InfoSheets/CALCIUM.pdf). Current NOS guidelines recommend 700mg calcium daily for people over the age of 19 years, ideally from dietary sources. This is based on the reference nutrient intake for the UK population, set by the Committee on the Medical Aspects of Food and Nutrition Policy. Between the ages of 11 to 18 years, a higher

Panel 2: Risk factors for primary osteoporosis

- Age (osteoblast function, calcium absorption, and PTH and calcitonin levels decrease with age)
- Being female
- Being Caucasian
- Having a small body frame
- Menopause
- Family history—individuals with maternal history of hip fracture should be assessed. Genes implicated in development of osteoporosis include vitamin D receptor genes, oestrogen receptor genes, type 1 α 1 collagen, transforming growth factor- β 1 and insulin-like growth factor genes.
- Lifestyle (eg, limited physical exercise, cigarette smoking and high alcohol intake—the last two are toxic to bone cells)
- Poor nutrition (a balanced protein and carbohydrate intake is as important as adequate calcium intake)

NICE guidance

Guidance from the National Institute for Health and Clinical Excellence on the primary prevention of osteoporotic fragility fractures is scheduled to be published in February 2006. It will include guidance on osteoporosis screening techniques and cost-effective screening approaches. Currently, a high-risk case screening approach is used by some organisations. Often, patients are identified opportunistically. Many organisations do not have guidelines in place and there is a wide variation in services that are available.

NICE guidelines for assessing risk and preventing falls were published in 2004 and include an algorithm to illustrate an ideal patient care pathway. The guidelines advocate the dovetailing of falls and specialist osteoporosis services to improve care delivery.

intake, ranging between 800mg and 1000mg daily may be necessary.

Vitamin D Vitamin D is a hormone, synthesised from 7-dehydrocholesterol by skin cells during exposure to ultraviolet light. It undergoes a two-step activation process — 25-hydroxylation in the liver and 1 α -hydroxylation in the kidney — to 1 α ,25-dihydroxycholecalciferol. The activation of vitamin D is controlled by PTH phosphatase and, perhaps, by calcium and other factors that regulate 1 α -hydroxylase.

It is possible that vitamin D deficiency contributes to fractures both by increasing bone fragility and by impairing muscle strength, which increases the likelihood of falls in elderly people. If significant, vitamin D deficiency can lead to secondary hyperparathyroidism and a serum PTH is a sensitive pointer to sub-nutrition. Vitamin D deficiency is noted in Asians in the UK and in older people. Long-term dietary treatment has been shown to lead to normal bone density in patients with evidence of vitamin D deficiency. Oily fish is one commonly consumed food that is a good source of vitamin D. Examples include salmon, mackerel and sardines.

The World Health Organization has graded the evidence base for various lifestyle interventions with respect to reducing or increasing the risk of osteoporotic fractures. Mild to moderate alcohol intake has beneficial effects on bone mass at both hip and spine, whereas high intake is associated with reduced BMD and accelerated bone loss. The level of what constitutes appropriate drinking and the impact of different alcohol products is being debated. Excessive alcohol intake also increases risks for cardiovascular disease and breast cancer and, therefore, drinking should not be promoted as being good for bone health. Other controllable determinants include:

- High caffeine intake — increases risk of hip fracture
- Low vegetable intake — vegetables, particularly onions, have beneficial effects on bone metabolism (animal studies)
- Smoking — a meta-analysis of 29 cross-sectional studies reported a cumulative effect of smoking on reductions in BMD and increases in hip fracture risk with age
- Lack of physical activity — weight bearing exercise has been shown to have a

positive effect on BMD in children and adolescents and duration and intensity of training correlates with BMD in gymnasts and athletes. However, excessive exercise has a negative effect on BMD (eg, in females excessive exercise causes delayed puberty and amenorrhoea, leading to low BMD).

Obesity protects against bone loss because there is increased loading stress to the spine. In females, there can be increased conversion of adrenal androgens to oestrogens, which are then stored in fatty or adipose tissue. However obesity has adverse effects on other biological systems, especially the cardiovascular system. Therefore, weight-bearing exercise and a healthy balanced diet that supports an acceptable body mass index makes up lifestyle advice that should be given to the population.

Prophylaxis Preventive therapy is recommended for women who have gone through a premature menopause, individuals on long term glucocorticoid therapy, and for those with a previous fragility fracture. Drugs licensed for prophylaxis (including bisphosphonates and hormone replacement therapies) and newer treatments are discussed in a further article.

There is some evidence that thiazide diuretics may protect against osteoporosis, reducing age-related bone loss by decreasing urinary calcium excretion. However it is reported that this protective effect is lost within four months of stopping thiazide treatment.

Pharmacy services for osteoporosis

The National Osteoporosis Society has submitted a proposal for the inclusion of osteoporosis care within the new general medical services contract in the next financial year. It argues that inclusion is a much needed driver for delivery of improved quality services for patients with osteoporosis in the UK.

Pharmacists can play a role in the management of patients with osteoporosis beyond dispensing and its related counselling. Many primary care organisations are setting up falls services with multidisciplinary care offered within secondary and primary care sectors and across the interface. Pharmacists have a role in supporting medication management within these multidisciplinary teams.

In addition, pharmacists with prescribing qualifications can offer patients improved access and further choice for medication support. The National Service Framework for Older People recommends annual medication reviews for people over 75 years of age who take more than four medicines. Pharmacists performing reviews can check for compliance with bone-sparing therapy and assess current drug profiles for medicines that could increase the risk of a fall. Provision of lifestyle advice can also support self care.

Some pharmacists are involved in the development of area-wide osteoporosis guidelines and patient pathways as well as audits to demonstrate a high level of patient care delivery.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Provide lifestyle advice for optimal bone health to the next three women who ask you about menopausal symptoms.
2. Look out for the NICE guidance on osteoporosis due in February 2006 and incorporate it into your practice.
3. Make sure that the next elderly woman who asks for advice on back pain and has risk factors for osteoporosis is investigated for osteoporotic vertebral fracture

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

Bone biology

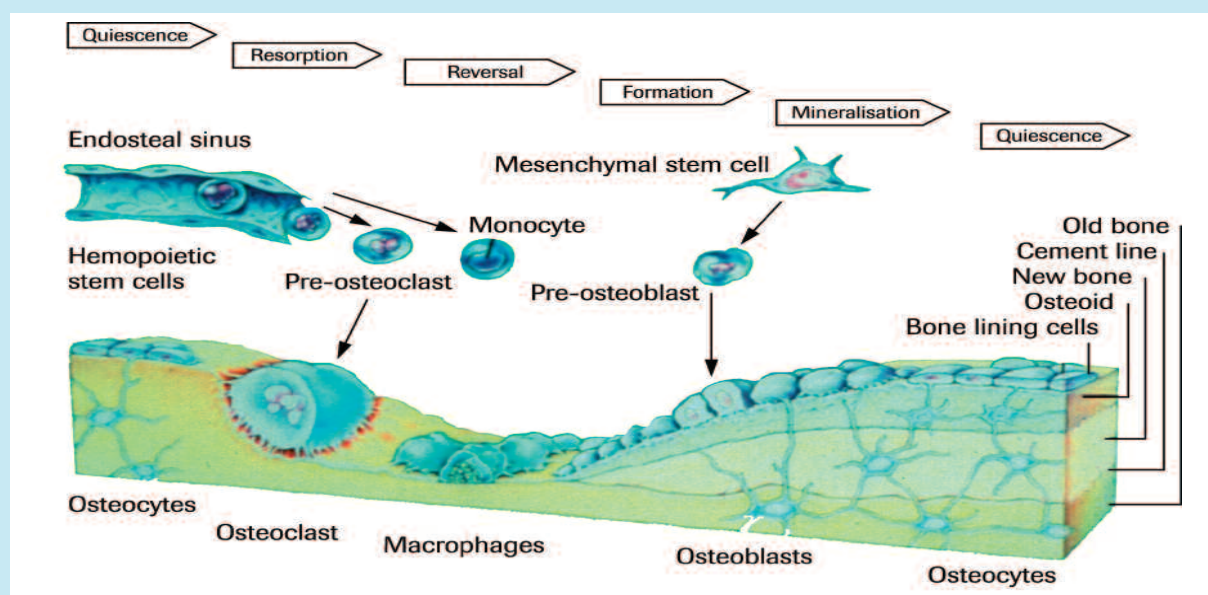


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The remodelling cycle

The skeleton supports the body, protects vital organs, anchors muscles and stores homeostatically active minerals, principally calcium. Bones vary in structure according to their specific functions. Eighty per cent of bone is compact (as in the skull), and the rest is cancellous, as predominates in the vertebrae. Bone matrix comprises collagen and mucopolysaccharides and is mineralised, consisting mainly of hydroxyapatite. The mineral phase gives compressive strength and rigidity but it is the fibrous organic matrix that gives bone its resistance to tractional and torsional forces. The strength-to-weight ratio of bone is related to this integrated composition as well as to the microscopic arrangement of collagen fibres within the bone.

In addition to collagen, matrix proteins of special interest are osteocalcin, osteonectin and phosphoproteins. Research is under way to assess their mechanisms of action and use in diagnostic tests. Bone tissue also contains stimulators of bone cell proliferation and proteins that promote differentiation to expedite fracture repair and bone remodelling.

Bone remodelling Bone is a living tissue. All bone undergoes continuous turnover, although compact bone does so more slowly than cancellous bone. Teams of osteoclasts and osteoblasts, termed "remodelling units", work together to resorb a microscopic amount of bone tissue and repair it. The process of remodelling allows for the repair of microdamage and the release of calcium into the circulation to satisfy homeostatic demands.

The remodelling cycle begins with activation — a change in the local environment to bring osteoclasts to the bone surface. This occurs when remodelling stimuli (eg, hormones or physical forces, such as weight bearing exercise) affect dormant cells that line bone surfaces. Underlying bone surfaces containing chemicals that attract osteoclasts from within the bone are exposed. The osteoclasts attach to the surface by a specialised fimbriated organelle and proceed to resorb bone mineral and organic matrix with the release of acid and proteolytic enzymes.

Once a resorption cavity is formed, osteoblasts fill the excavated area with calcifiable matrix. Some osteoblasts are internalised in the

newly formed matrix and become osteocytes. These cells maintain contact with each other and with surface osteoblasts via a canalicular system, which provides an enormous surface area for mineral exchange.

Resorption and formation occur in close obligatory sequence and have an impact on bone quality and the amount of bone preserved. An entire remodelling cycle, from activation to complete repair takes about 100 days. Remodelling occurs at internal sites such as cortical, endosteal, or trabecular bone surfaces. Other surfaces, such as periosteal surfaces, do not remodel vigorously, except at sites of tendons.

Activators of bone remodelling and hence of resorption, include parathyroid hormone (PTH), E-series prostaglandins, 1,25-dihydroxycholecalciferol (the active metabolite of vitamin D) and thyroid hormone. Inhibitors of bone resorption include interferons, calcitonin and oestrogens.

Agents that enhance osteoblast activity (ie, stimulate bone growth) include bone-derived growth factors, insulin, somatomedins, prostaglandins (at low concentrations) and, possibly, testosterone and progesterone. Injury can promote local prostaglandin production so can also enhance osteoblast activity. 1,25-Dihydroxycholecalciferol may also have an anabolic effect on osteoblasts.

Calcium About 99 per cent of total body calcium is deposited in bone. The remainder is distributed between the extracellular fluid and intracellular compartments. The concentration of calcium ions in the blood is precisely regulated by feedback mechanisms acting through the parathyroid glands. Decreases in blood calcium can result from reduced intake, reduced intestinal absorption and enhanced urinary loss.

When blood calcium levels are decreased, parathyroid hormone (PTH) is secreted. This promotes bone resorption and the renal tube reabsorption of calcium. PTH is also responsible for enhancing the activity of renal 1 α -hydroxylase, the enzyme responsible for converting vitamin D to its active form. This results in enhanced intestinal calcium absorption. Normalisation of blood calcium levels suppresses PTH secretion.

Further reading

To understand the pathophysiology and therapeutics of osteoporosis and find out about advances made in service provision pharmacists may find the following references of interest:

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- World Health Organization scientific group. *Prevention and management of osteoporosis*. Geneva: WHO; 2003.
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