Introduction/Background
About one in two women and one in five men over 50 will fracture a bone because of osteoporosis. In recent years considerable advances have been made both in the identification of people at high risk of fracture and in the therapeutic options available for the treatment of osteoporosis.

Osteoporosis is characterised by the loss of bone mass and strength resulting in fragility fractures, particularly of the spine, hip, wrist, humerus and pelvis. Osteoporosis has probably existed throughout human history but only became a noticeable disease condition with the increase in human lifespan, since the risk of fractures increases steeply with age and most of those affected are over 75. Aside from the associated increase in morbidity and mortality, these fractures, particularly hip fractures, result in loss of independence for at least a third of people with osteoporosis. Vertebral fractures cause height loss, chronic pain, and difficulty in performing normal daily activities.

In general, age-related bone loss starts in the fourth or fifth decade of life and usually occurs as a result of increased bone breakdown by osteoclasts and decreased bone formation by osteoblasts. To summarise, skeletal fragility results from the following:

- Failure to produce a skeleton of optimal mass and strength during childhood growth
- Excessive bone resorption resulting in decreased bone mass and microarchitectural deterioration of the skeleton, and
- Inadequate bone formation in response to increased resorption during bone remodelling.

The role of oestrogen deficiency in bone loss in postmenopausal women is well-documented. In addition, vitamin D insufficiency and secondary hyperparathyroidism are common in elderly people and may also contribute to bone loss. Other possible factors contributing to bone loss include reduced physical activity with ageing and decreased production of insulin-like growth factors.

Genetic factors have a strong influence on peak bone mass, which is attained during the third decade of life and is an important determinant of the bone mass later in life. Nutrition, particularly calcium and vitamin D intake, hormonal status, and physical activity also influence peak bone mass.

Who is at risk of osteoporosis?
Lower peak bone mass, increased bone loss at the menopause, and greater longevity all confer a greater risk of osteoporosis in women than in men, and the disease is most commonly seen in postmenopausal women. Some of the risk factors for osteoporosis are at least partially independent of bone mineral density, whereas the effect of others is mediated solely through reduced bone mineral density (Table 1). Oral glucocorticoids, which are used in the elderly, are another cause of osteoporosis, and guidelines for the

### Abstract

Osteoporosis is characterised by the loss of bone mass and strength caused by complex interactions among local and systemic regulators of bone cell function. Osteoporosis is classified as a bone mineral density 2.5 or more standard deviations below normal peak bone mass—that is, a T score ≤ –2.5. The risk of osteoporosis is greater in women than in men and is most commonly seen in postmenopausal women resulting in fragility fractures, the risk of which increases steeply with age. Current treatments have demonstrated efficacy against vertebral and non-vertebral fractures although safety, tolerability, and cost are important considerations when choosing a therapy.

### Table 1: Risk factors for osteoporosis

<table>
<thead>
<tr>
<th>Partially independent risk factors for osteoporosis</th>
<th>Mediated solely through reduced bone mineral density</th>
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<tbody>
<tr>
<td>Age</td>
<td>Untreated hypogonadism</td>
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<tr>
<td>Previous fragility fracture</td>
<td>Malabsorption disorders</td>
</tr>
<tr>
<td>Maternal history of hip fracture</td>
<td>Endocrine disease</td>
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<td>Oral glucocorticoid therapy</td>
<td>Chronic renal disease</td>
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<td>Current smoking</td>
<td>Chronic liver disease</td>
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<td>Alcohol intake ≥ 3 units/day</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>Immobility</td>
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<tr>
<td>Body mass index ≤ 19</td>
<td>Drugs (aromatase inhibitors, androgen deprivation therapy)</td>
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<tr>
<td>Falls</td>
<td></td>
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</table>
prevention and management of glucocorticoid-induced osteoporosis should be adhered to.

How does osteoporosis present?
Osteoporosis often first presents as a clinically evident fracture. Any low trauma fracture, i.e. following a fall from standing height or less in someone aged over 45 should trigger the suspicion of osteoporosis. In other cases, osteoporosis may present as backache, height loss, spinal deformity, or radiological osteopaenia (low bone mass). Although most fractures due to osteoporosis present clinically, vertebral fractures may be asymptomatic in as many as two-thirds of patients. It is important to detect these fractures since they carry a high risk of further fractures in the spine and elsewhere.

The World Health Organization’s definition of osteoporosis is based on bone mineral density in the spine and proximal femur measured with dual energy x ray absorptiometry (DXA). Osteoporosis is classified as a bone mineral density 2.5 or more standard deviations below normal peak bone mass – that is, a T score ≤−2.5. 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 bone mineral density. This approach is in the form of an algorithm that enables the probability of a fracture to be calculated from clinical risk factors with or without bone mineral density values. People who have already had a fragility fracture are at greatly increased risk of sustaining a further fracture and pharmacological intervention should be started promptly in such cases.

Management
Falls have an important role in the pathogenesis of fragility fractures, particularly in frail and elderly people. Multiple medical and environmental factors increase the risk of falling and many of these are modifiable. In addition, lifestyle measures to improve bone health, such as maintaining adequate dietary calcium intake and normal vitamin D status should also be included. Appropriate levels of exercise should be recommended and smoking and alcohol abuse discouraged. Physiotherapy and pain relief are important in managing fractures.

Pharmacological interventions
Therapeutic options for osteoporosis have increased considerably over recent years. Current treatments include the bisphosphonates, strontium ranelate, raloxifene, hormone replacement therapy and parathyroid hormone peptides. Without head to head comparison trials with fracture end points, the efficacy of these drugs cannot be directly compared. Some, but not all, have proved efficacy against vertebral and non-vertebral fractures, including hip fractures and this is an important factor influencing choice. Safety, tolerability, and cost are also important considerations.

Bisphosphonates
Bisphosphonates slow the rate at which bone is dissolved. Large randomised clinical trials have shown that the bisphosphonates reduce the risk of vertebral and hip fractures.

Several bisphosphonates are available, namely alendronic acid (Fosamax®, Fosavance® (with vitamin D)), risedronate (Actonel®) and zoledronic acid (Aclasta®). The oral bisphosphonates (alendronate and risedronate) are treatments for established postmenopausal osteoporosis, male osteoporosis and glucocorticoid-induced osteoporosis. Zoledronic acid is a relatively new option for treatment of postmenopausal osteoporosis and requires a single intravenous infusion once a year.

Bisphosphonates are generally well tolerated but the most common side effects associated with these treatments are digestive in nature, such as indigestion, diarrhoea, constipation and abdominal pain. Oral bisphosphonates must be taken fasting, with a full glass of water, and the individual must be upright and stay sitting or standing without taking food or drink for the next 30-60 minutes. Patients should receive supplemental vitamin D and calcium if dietary intake is insufficient.

Strontium ranelate
Strontium ranelate (Protos®), a sachet mixed with water and taken daily, has a dual action of increasing bone formation as well as decreasing bone breakdown and has been shown to reduce the risk of spinal, non-vertebral and hip fractures. It is indicated for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and peripheral fractures, including the hip.

Adverse events are generally mild and include diarrhoea and headache. The spectrum of anti-fracture efficacy of strontium ranelate makes it an ideal first-line treatment. Patients should receive supplemental vitamin D and calcium if dietary intake is insufficient.

Raloxifene
Raloxifene (Evista®) is a selective oestrogen receptor modulator (SERM) used to both prevent and treat osteoporosis in postmenopausal women. It stimulates bone growth just as oestrogen does, but has an anti-oestrogenic effect on the uterus and on breast tissue, reducing the risk of developing breast cancer. Raloxifene reduces the risk of vertebral fractures, but has not been shown to prevent fractures at other sites. It does not relieve vasomotor symptoms associated with the menopause. Side effects include hot flushes, leg cramps, and a threefold increase in the relative risk of venous thromboembolism, which means that it is contraindicated in anyone with a history of deep vein thrombosis (DVT).

Hormone replacement therapy (HRT)
The pros and cons of HRT are many, and are the subject of much debate. HRT is thought to be of most benefit for
preventing osteoporosis if it is started early in menopause and is taken for at least five years. However, long-term use increases the risk of side effects. Briefly, HRT has been associated with an increased risk of breast cancer, endometrial cancer, thrombosis, stroke and heart disease. However, as well as preventing osteoporosis, HRT reduces the symptoms of the menopause, which can be very distressing for some women, and is also associated with a reduced risk of bowel cancer.

Generally HRT is not usually recommended as a first choice of therapy for long-term prevention of osteoporosis in women who are over 50 years of age, as there are other medicines available that do not carry the risks associated with HRT. Nonetheless, HRT remains an option for women over 50 at risk of fractures for whom these other medicines are not suitable. HRT is a suitable option for women who have had an early menopause. However, in this case HRT should only be used for treating menopausal symptoms and preventing osteoporosis until the age of 50, after which time other medicines may be more suitable.

There are also a few quite specialised and not commonly used treatments, namely calcitonin, calcitriol and teriparatide.

Calcitonin (Miacalcic®) is a hormone involved in the regulation of bone turnover. It is given by injection or nasal spray and is used for postmenopausal osteoporosis when treatment with bisphosphonates, strontium or raloxifene is unsuitable. It can relieve pain when used following a collapsed vertebra, but has a number of potential side effects, including allergic reactions.

Calcitriol (Rocaltril®) is a vitamin D-like compound that can be used in osteoporosis following the menopause or in situations where osteoporosis has been caused by steroid drugs. Studies of the effect of calcitriol on bone loss and fractures have produced conflicting results; however it has been shown to reduce the risk of spinal fractures but not hip fractures.

Teriparatide (Forteo®) is used for the treatment of osteoporosis in postmenopausal women and in men with an increased risk of fracture. It works by increasing the formation of bone and is given by daily injection under the skin, using an injection pen. It has been shown to reduce the incidence of spinal but not hip fractures.

Calcium and vitamin D supplements should be prescribed with most treatments for osteoporosis since the evidence base for their efficacy in preventing fractures is derived from studies in which calcium and vitamin D were routinely administered.

Conclusion

Continuance with osteoporosis treatments needs to be improved and possible approaches include better patient education and the use of intermittent dosing regimens, such as once weekly oral bisphosphonate therapy or once-yearly intravenous therapy with zoledronic acid.

Many hormones (PTH, vitamin D, oestrogen) and growth factors (IGF-1, TNF, RANKL) regulate the activity of osteoblasts and osteoclasts. Denosumab, a human monoclonal antibody against RANKL, decreases bone turnover and increases bone mass in both lumbar spine and hip using a dose of 60 mg every 6 months. The decreases in bone turnover markers are similar to or greater than the most potent bisphosphonates. Increases in bone mineral density are at least as large as those achieved with bisphosphonates. Studies evaluating the effect of denosumab on fracture risk are in progress and the drug is currently under review by the FDA.

Other areas of research into new treatments include the use oral calcimimetic drugs that stimulate intermittent production of parathyroid hormone, selective oestrogen receptor modulators with mixed oestrogenic and anti-oestrogenic effects and inhibitors of sclerostin, a protein produced by bone that is a negative regulator of bone formation, and its signalling pathway.

References:
3. Rutherford D. Prevention and treatment of osteoporosis www.netdoctor.co.uk