Osteoporosis: advances in assessment and drug therapy

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Definition
Osteoporosis can be defined as a systematic skeletal disorder characterised by low bone mass with micro-architectural deterioration of bone and a consequent increase in bone fragility and susceptibility to fracture.1 In 1994, the World Health Organization (WHO) defined osteoporosis in terms of bone mineral density (BMD). An individual was classified as having osteoporosis if their BMD was 2.5 standard deviations (SD) below the mean value in a young adult. Osteopaenia was defined by a BMD value that was more than 1 SD but less than 2.5 SD below the mean value in a young adult.2

Aetiology of osteoporosis
Although genetic factors account for 60–90% of variability in BMD, interaction with environmental and lifestyle factors such as diet, smoking, alcohol consumption and physical activity influence the level of BMD. At any given time, an individual’s BMD will be determined by their peak bone mass and subsequent bone loss. Peak bone mass in general is reached by the second or third decade. BMD will then plateau for a number of years before declining in later life. For women, bone loss is more marked in the first few years post menopause.

Consequences of osteoporosis
Osteoporosis predisposes to an increased risk of low trauma fracture, which increases with age for both men and women. In Caucasian populations, 1 in 2 women...
and 1 in 5 men aged >50 years will sustain a fragility fracture in their lifetime.\textsuperscript{3} Annually there are approximately 180,000 osteoporosis-related symptomatic fractures in England and Wales, of which 70,000 are hip fractures, 25,000 are clinically apparent vertebral fractures and 41,000 are wrist fractures.\textsuperscript{4} As only about one-third of vertebral fractures come to clinical attention, the true incidence is likely to be much higher.\textsuperscript{5} Although the vertebrae, hips and wrists are the commonest sites, other sites such as the humerus and ribs can be affected. The annual costs of osteoporosis are significant, estimated at £1.8 billion in 2000 and projected to reach £2.2 billion by 2020.\textsuperscript{6}

Both hip and vertebral fractures are associated with a significant mortality, and incidence increases exponentially with age for both men and woman.\textsuperscript{16} Hip fractures are associated with a 10–20% excess mortality in the first year following fracture, which is most marked in the first 6 months.\textsuperscript{9} This can be regarded as a complication of the fracture but is often due to co-existent co-morbidities. Up to 20% of patients require permanent nursing-home care following fracture.\textsuperscript{10}

Vertebral fractures occur commonly in the mid-thoracic spine (T7–T8) or at the thoracolumbar junction. In contrast to hip fractures, vertebral fractures are associated with a long-term increase in mortality,\textsuperscript{9} usually due to underlying co-morbidities. They also cause spinal deformity and pain with a resultant impairment of physical and mental function. A prior vertebral fracture is associated with a 4.4-fold increased risk of future vertebral fracture.\textsuperscript{11}

Wrist fracture incidence in women increases from the perimenopausal period until the mid-60s. For men, the incidence remains low until later life.\textsuperscript{12} Although not associated with an increased mortality, wrist fractures are linked with significant morbidity with up to 20% experiencing long-term complications, including reflex sympathetic dystrophy, malunion, neuropathy and secondary osteoarthritis.\textsuperscript{11} Wrist fractures are a warning for future fragility fractures, with a 1.7-fold increase in subsequent vertebral and 1.9-fold increase in subsequent hip fracture.\textsuperscript{11}

**Assessment of bone mineral density**

BMD is commonly measured by dual-energy x-ray absorptiometry (DEXA). A skeletal site, such as the hip, is exposed to two x-ray beams of differing intensity. This excludes the impact of surrounding soft tissue. The BMD is then derived by correcting for the area scanned, and expressed usually as g/cm\textsuperscript{2}. There is minimal radiation exposure and with lateral images DEXA may be able to accurately identify vertebral fractures (vertebral fracture assessment (VFA)). The results are expressed as T-scores (SD of BMD as compared with a young adult of similar gender and ethnicity) and Z-scores (SD of BMD as compared with an adult of similar age, gender and ethnicity).

However, as DEXA measures an areal rather than a true volumetric density, it overestimates BMD in large-boned individuals and underestimates in individuals with smaller bones. Areal BMD accounts for approximately two-thirds of bone strength variance. Other determinants of fracture risk such as bone structure and quality cannot be assessed by DEXA. Other limitations of DEXA include an inability to distinguish osteoporosis from osteomalacia. Furthermore, excess calcification, for example due to degenerative spinal disease, may produce high BMD measurements which lead to an underestimate of fracture risk.

Nevertheless, BMD measured by DEXA can be used to predict future fracture. There is a doubling of fracture risk for each SD drop in BMD below the mean. The greatest predictive value is at the skeletal site at which BMD is measured. Therefore BMD measurement at the hip best predicts future hip fracture. However, measurement at one site can predict fracture risk at another. So for example, for each SD decrease in BMD at the hip there is a 2.6-fold increase in hip fracture risk but also a 1.4-fold and 1.8-fold increase in forearm and vertebral fracture risk respectively.\textsuperscript{14} Recommendations for requesting a DEXA scan are presented in Table 1.

**Secondary causes and further investigations for osteoporosis**

Approximately 50% of men and 20% of women will have a secondary underlying cause for their osteoporosis. (Table 2). Furthermore, other metabolic bone diseases such as osteomalacia and multiple myeloma mimic osteoporosis. History and examination and further investigations should aim to exclude such secondary causes (Table 3).

**Assessment of fracture risk and intervention thresholds**

In 1999, the Royal College of Physicians (RCP) published guidance whereby a T-score <-2.5 was used as a diagnostic and treatment threshold below which specific bone protective treatment was recommended.\textsuperscript{15} However, BMD measured by DEXA is a specific rather than a

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**TABLE 1. Indications for DEXA scan.**

- History of low trauma fracture
- Proven radiographic osteopaenia
- Current or planned oral corticosteroid use >3 months
- Aromatase inhibitors or gonadotropin-releasing hormone (GnRH) analogues
- Early menopause <45 years
- Women with history of untreated premenopausal amenorrhoea >6 months (not due to pregnancy)
- Diseases present known to be associated with osteoporosis [see Table 2]
- Family history of osteoporosis especially parental history of hip fracture
sensitive predictor for future fracture. Numerically, most low trauma fractures occur in the osteopaenic range. Furthermore, other independent risk factors, such as age, influence fracture risk. At the same T-score of -2.5, future fracture risk will lower for an individual aged 50 years as compared with 65 years.16

National Institute for Health and Clinical Excellence guidelines

Guidance for primary and secondary prevention for postmenopausal women was published by the National Institute for Health and Clinical Excellence (NICE)4,17 in 2008. These guidelines define intervention thresholds based on a combination of age, BMD, clinical risk factors and clinical indicators for low BMD (for primary prevention) (see Table 4). Alendronate is recommended as first line. If the patient is unable to take alendronate, e.g. due to intolerance or contraindication, alternative treatments are recommended only if there is a further reduction in BMD and/or presence of clinical risk factors. Raloxifene is not recommended for primary prevention. Teriparatide has been approved for secondary prevention, but is subject to stringent criteria due to its high cost. Patients aged ≥75 years can be treated without recourse to DEXA. NICE guidance does not apply to corticosteroid-associated osteoporosis or to men.

FRAX

In 2008, a fracture risk assessment tool (FRAX) supported by WHO was published. FRAX (http://www.shef.ac.uk/FRAX/)18 was developed using data from a number of population-based cohorts from around the world. It calculates 10-year risk for hip and major osteoporotic fracture based on a number of risk factors for both men and women aged 40–90 years (Table 5). Fracture risk can be calculated with or without BMD measurement, although using the former will give a more accurate assessment. FRAX does have a number of limitations. Only BMD measured at the femoral neck can be used to calculate future risk. Furthermore, FRAX cannot take into account a dose-response effect of risk factors. Therefore all doses of oral corticosteroids are treated equally and previous fracture is counted as 1, irrespective of the actual number. Finally, although a number of different diseases are known to increase osteoporotic and hence fracture risk, only rheumatoid arthritis is considered an independent risk factor as data regarding other diseases is considered too weak to be included.

TABLE 2. Secondary causes of osteoporosis.

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Gastroenterological</th>
<th>Musculoskeletal</th>
<th>Drugs</th>
<th>Lifestyle</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>Inflammatory bowel disease</td>
<td>Rheumatoid arthritis</td>
<td>Oral corticosteroids</td>
<td>Alcohol ≥3 units per day</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Malabsorption states e.g. coeliac disease</td>
<td>Ankylosing spondylitis</td>
<td>Aromatase inhibitors</td>
<td>Current smoking</td>
<td>Prolonged immobility</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Chronic liver disease</td>
<td>Heparin</td>
<td>Low body mass index (&lt;19 kg/m²)</td>
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<td>Chronic renal disease</td>
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<tr>
<td>Hyperprolactinaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Organ transplantation</td>
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<tr>
<td>Osteomalacia</td>
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<tr>
<td>Cushing’s disease</td>
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<tr>
<td>Anorexia nervosa</td>
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TABLE 3. Additional investigations for osteoporosis and low trauma fracture.

- Full blood count
- Serum creatinine
- Liver transaminases
- Bone biochemistry
- Thyroid function tests
- Erythrocyte sedimentation rate or C-reactive protein

Other investigations if indicated:
- Protein immunoelectrophoresis and urinary Bence-Jones proteins
- Serum testosterone, sex hormone-binding globulin, follicle-stimulating hormone, luteinising hormone (in men)
- Serum prolactin
- Prostate-specific antigen
- Vitamin D
- Parathyroid hormone
- Endomysial and/or tissue transglutaminase antibodies (coeliac disease)
- 24-hour urinary cortisol/dexamethasone suppression test
- Urinary calcium excretion
- Lateral radiographs of lumbar and thoracic spine/DEXA-based vertebral imaging
- Isotope bone scan
National Osteoporosis Guideline Group

In 2009, guidelines were published by the National Osteoporosis Guideline Group (NOGG) based on opportunistic case-finding.19 These guidelines utilise future fracture risk calculated by FRAX and recommend treatment based on validated intervention thresholds not driven by cost. These are applicable to men aged ≥50 years and postmenopausal women. Following calculation of a 10-year fracture risk (hip and major osteoporotic fracture), treatment is recommended if the risk falls above the intervention threshold (high risk) or not recommended if it falls below (low risk). If risks are calculated without a BMD measurement, risk may fall into an intermediate category, in which case BMD measurement is recommended. Risk can be recalculated once BMD is available (Figure 1).

NOGG makes a number of other recommendations. For example, women with a prior low trauma fracture should be considered for treatment in any case, although BMD assessment may be appropriate, especially for younger women. Men aged ≥50 years and all postmenopausal women with a WHO risk factor or a body mass index (BMI) ≤19kg/m² should also be assessed for future fracture risk using FRAX. For those whose risk is considered to be low, further assessment is recommended at ≤5 years depending upon other clinical risk factors.

Specific drug treatment recommendations are simplified compared with NICE. For women, alendronate is recommended as the initial treatment. If alendronate cannot be taken, NOGG ranks other bisphosphonates, strontium ranelate and raloxifene equally. No further reduction in BMD is required to be eligible. Owing to its cost, teriparatide is reserved for those with very high risk, especially of vertebral fractures. Alendronate, risedronate, zoledronate and teriparatide are also approved for men.

Corticosteroid-induced osteoporosis

Corticosteroids are the most common cause of secondary osteoporosis and the most common iatrogenic cause.20 Initially bone loss is rapid, particularly in the first 12 months. This is thought to be related to excessive bone resorption, with subsequent slower bone loss due to impaired bone formation. Longer-term corticosteroid use increases the risk of myopathy and hence falls.

The risk of fracture with corticosteroids is greater than would be expected for a given BMD. The reasons for this are uncertain, but are likely to be related to structural changes not easily measured by DEXA. Corticosteroids primarily target sites rich in cancellous bone, increasing risk of fracture at the lumbar spine and proximal femur. The risk of fracture is increased by up to 75% within 3 months of initiation.20 Although fracture risk is dose-dependent, increased risk has been noted even at oral doses as low as 2.5 mg per day.21 There does not however seem to be a significant increased risk with inhaled steroids.22

The bone health of all patients who are likely to be on oral corticosteroids for >3 months should be assessed. The RCP published guidance recommending that all patients with a prevalent or incident low trauma fracture while on glucocorticoids or aged >65 years should be treated.23 For those ≤65 years, BMD assessment with DEXA was recommended with treatment threshold at a T-score ≤-1.5. Corticosteroid use of ≥5 mg for ≥3 months is a risk factor in FRAX. Other than this cut-off, dose or duration of treatment is not taken into account when calculating future fracture risks. At present alendronate, risedronate, zoledronate and teriparatide are all licensed treatments for corticosteroid-induced osteoporosis.

**TABLE 4. NICE clinical risk factors for fracture and clinical indicators for low bone mineral density (BMD).**

<table>
<thead>
<tr>
<th>Independent clinical risk factors for fracture</th>
<th>Clinical indicators for low BMD</th>
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<tbody>
<tr>
<td>• Parental history of hip fracture</td>
<td>• Low body mass index (BMI) (&lt;22 kg/m²)</td>
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<tr>
<td>• Alcohol intake of ≥4 units per day</td>
<td>• Prolonged immobility</td>
</tr>
<tr>
<td>• Rheumatoid arthritis</td>
<td>• Untreated premature menopause</td>
</tr>
<tr>
<td></td>
<td>• Medical conditions e.g. Crohn’s disease, ankylosing spondylitis</td>
</tr>
</tbody>
</table>

**TABLE 5. Risk factors used in FRAX.** *(Reproduced from the FRAX website with permission of the International Osteoporosis Foundation.)*

- Age
- Gender
- Weight
- Height
- Previous fracture
- Parental history of hip fracture
- Current smoker
- Current oral corticosteroid use of ≥5 mg per day for ≥3 months
- Rheumatoid arthritis
- Other secondary causes of osteoporosis
- Alcohol ≥3 units per day
- Femoral neck bone mineral density (BMD)

*FRAX* is a sophisticated risk assessment instrument, developed by the University of Sheffield in association with the World Health Organization. It uses risk factors in addition to DEXA measurements for improved fracture risk estimation. It is a useful tool to aid clinical decision-making about the use of pharmacologic therapies in patients with low bone mass. The International Osteoporosis Foundation supports the maintenance and development of FRAX.*
Management of osteoporosis

General measures

A review of lifestyle factors that improve bone strength and reduce the risk of falling should be undertaken. Advice regarding stopping smoking, avoiding excess alcohol and caffeine and encouraging weight-bearing activity should be given. Falls risk assessment should be undertaken and referral to a specific falls clinic should be considered. Prolonged immobility should be avoided.

Older patients are more likely to be vitamin D, calcium and protein deficient. A healthy diet is important to maintain the musculoskeletal system. Indeed, correcting poor protein intake has been shown to improve hip fracture outcomes with fewer complications such as bed sores and infection.

Calcium and vitamin D

Calcium and vitamin D reduce secondary hyperparathyroidism, improving bone strength. Furthermore, they also reduce the risk of falling by improving muscle strength and reducing body sway. Efficacy in reducing hip and non-vertebral fractures in elderly nursing-home residents was shown in a landmark study: following 18 months of supplementation with 1.2 g calcium and 800 iu of vitamin D3 per day, the numbers of hip fractures were 43% lower and non-vertebral fractures 32% lower compared with placebo.

Other studies tend to confirm that vitamin D in combination with calcium reduces non-vertebral fracture risk. A Cochrane analysis of 45 studies found that this combination reduced hip fracture risk by 16%, the greatest reduction being seen in subjects in institutionalised care. There was no reduction with vitamin D alone. Fracture prevention with vitamin D seems to be dose-dependent, with a meta-analysis looking at the efficacy of supplementation in patients ≥65 years finding no benefit with ≤400 iu per day whereas a dose of 482–770 iu per day reduced non-vertebral fracture by 20% and hip fracture by 18%.

There is no evidence that calcium alone has any anti-fracture efficacy. Furthermore, given recent concerns regarding calcium supplementation and myocardial infarction, calcium supplementation alone for osteoporosis is not indicated.

Bisphosphonates

Bisphosphonates inhibit osteoclast activity and recruitment and promote osteoclast apoptosis, inhibiting bone resorption and so increasing BMD. Both oral (alendronate, risedronate, ibandronate) and intravenous (ibandronate, zoledronate) preparations are available.

Oral bisphosphonates are associated with upper gastrointestinal side-effects and so the intravenous route may be more attractive for some, albeit more expensive. Alendronate, risedronate and zoledronate have been shown to reduce both hip and vertebral fracture risk. Ibandronate has been shown to reduce vertebral fracture but non-vertebral fracture reduction was only demonstrated in a post hoc analysis among high-risk groups (femoral neck BMD <−3.0).

Zoledronate is the most potent of the available bisphosphonates, with highest affinity for bone, and is the only intravenous drug that has demonstrated anti-fracture efficacy in randomised controlled trials (RCTs). In the HORIZON Pivotal Fracture Trial, an annual infusion of zoledronate 5 mg reduced vertebral and hip fracture incidence by 70% and 40% respectively over 3 years. A further study also found a significant reduction in mortality in patients given zoledronate within 90 days of a hip fracture during the 1.9 years of follow-up.
Duration of therapy
The optimal duration of bisphosphonate use remains unclear. The Fracture Intervention Trial Long-term Extension (FLEX) study examined the outcomes of continued treatment after 5 years on alendronate: subjects continuing treatment for a further 5 years were compared with placebo. Stopping treatment was associated with a decline in hip and lumbar spine BMD over the following 5 years compared with those who continued but mean BMD levels remained at or above the pre-treatment levels from 10 years earlier. There was an increase in the incidence of clinical vertebral fractures in those stopping treatment. However, non-vertebral fracture risk was not significantly different between the two groups.37 Therefore on the basis of this study a cessation of alendronate could be considered after 5 years, although those with a high risk of vertebral fracture may benefit by continuing.

Osteonecrosis of the jaw
Bisphosphonates have been linked to an increase in osteonecrosis of the jaw (ONJ), defined as an area of exposed bone in the maxillofacial region for >8 weeks. It can be associated with pain (although approximately one-third are painless), swelling, ulceration, sinus formation and tooth-loosening. Other risk factors include malignancy, chemotherapy, local trauma (including invasive dental procedures), steroid use and infection.

The prevalence of ONJ is unknown, with a lack of prospective data, but the incidence is higher in malignant disease where there is more frequent use of intravenous bisphosphonates with a shorter duration between treatments and hence a higher cumulative dose. In this population, the estimated incidence is between 1% and 15% and seems related to dose and duration of treatment.38 By contrast, the incidence in osteoporosis, where much lower doses are used, is much lower and has been estimated at between 1 in 10,000 and 1 in 100,000 person years of exposure.38 In the HORIZON Pivotal Fracture Trial study of zoledronate, a 3-year study that recruited almost 8000 patients, only 1 case in each of the treatment and placebo arms was noted.34

From a pragmatic point of view, good oral hygiene including regular dental assessments should be encouraged, especially if other risk factors are present, and it would be prudent for any planned invasive dental procedures to be completed before starting a bisphosphonate. Should ONJ develop, bisphosphonates should be stopped, although there is no evidence to suggest that this would improve the long-term prognosis. Furthermore, there is no evidence that short-term withdrawal of bisphosphonates in those already established on treatment reduces the risk of developing ONJ if invasive dental procedures are undertaken subsequently.

Atrial fibrillation
An association between bisphosphonates and atrial fibrillation (AF) was first observed in the HORIZON Pivotal Fracture Trial of zoledronate (1.3% of zoledronate users vs 0.5% controls; p<0.001).34 A non-significant increase in AF was also seen in the alendronate Fracture Intervention Trial.39 However no similar relationship has been found in the risedronate studies.

Other data have suggested a link. In a cohort of 719 women derived from a healthcare delivery system in Washington State, Heckbert examined outcomes in women who had ever been exposed to alendronate and found an increased risk of AF (hazard ratio (HR) 1.86; 95% confidence interval (CI) 1.09–3.15).40 However, the risk with alendronate was higher in patients on statins and with diabetes mellitus and the number of cases was small. By contrast, two large population studies (from Denmark and the UK) comprising several thousand women have not confirmed an association.41,42 Therefore there seems to be only a small increased risk of developing AF with bisphosphonates, with benefits of treatment outweighing risks. The picture is complicated as patients who are more likely to need bisphosphonates are also more likely to develop AF for other reasons, i.e. the elderly.

Exact mechanisms also remain unclear. Although it is possible that zoledronate increases production of pro-inflammatory cytokines and induces transient hypocalcaemia, in the HORIZON Pivotal Fracture Trial study most cases occurred a number of months later, which makes these reasons less likely.34

Oesophageal cancer
Upper gastrointestinal complaints are common with oral bisphosphonates, with an increased risk of oesophagitis, particularly when the correct advice regarding administration is not followed. Concerns regarding oesophageal cancer risk have been raised. In 2009, the Food and Drug Administration reported 23 cases in the USA (median time to diagnosis 2.1 years, range 0.5–10 years) and 31 cases from Europe and Japan (median time to diagnosis 1.3 years, range 0.3–8 years), with all available oral bisphosphonates implicated.43

Subsequently two studies analysing data from the same General Practice Research Database produced conflicting reports. One found that oral bisphosphonates prescribed ≥10 times, or for about 5 years, nearly doubled the risk,44 while another found no increased risk.45 Differences could be explained by differences in study length (the positive study was longer) and/or sample size (the positive study was larger), although neither study validated diagnoses using medical records, nor provided data as to whether the drugs were taken correctly.46 Although the overall incidence of oesophageal cancer is likely to be low, it would be prudent to consider alternatives in the presence of pre-malignant lesions, such as Barrett’s oesophagus.

Atypical subtrochanteric fractures
A consequence of bisphosphonate-induced bone turnover suppression is the impairment of normal bone repair, resulting in reduced bone strength that potentially increases the risk of fracture. The proximal femoral...
shaft is subject to high stresses and so is more susceptible to minor trauma. Atypical subtrochanteric fractures that have distinct radiographic features characterised by cortical thickening and are transverse or oblique in nature have been reported with long-term bisphosphonate use. Such fractures usually require surgical fixation. A case report suggests that teriparatide may promote fracture healing.47

A study of over 200,000 women aged ≥68 years found that bisphosphonate use for ≥5 years more than doubled the risk of hospitalisation for subtrochanteric or femoral shaft fractures compared with transient (<100 days) bisphosphonate use (adjusted odds ratio (OR) 2.74; 95% CI 1.2–6.02).48 The absolute risk, however, was low. A further study identified over 12,000 women aged ≥55 years who had a femoral fracture in 2008 and of whom 59 had an atypical subtrochanteric or femoral shaft fracture.49 The age-adjusted relative risk (RR) was 47.3% (95% CI 25.5–87.3); the multivariable OR was 33.3 (95% CI 14.3–77.8). The risk was independent of systemic corticosteroid use or other drugs with bone effects and independent of age and other co-morbidities. Again, the absolute risk was low with the number needed to harm (NNH) for one case of atypical fracture estimated to be 2000 per year of bisphosphonate use. The risk increased with duration of use and fell after drug withdrawal.

These studies contrasted with data from a re-analysis of three bisphosphonate RCTs (two of alendronate and one of zoledronate) which found 12 atypical fractures in 10 patients among 14,195 women and no association with bisphosphonate use. However, the authors acknowledged that the study was underpowered to make any definitive conclusions.50

In 2011 the European Medicines Agency recommended that the product information for all bisphosphonates should be updated to include a warning about this risk and advised doctors to periodically review bisphosphonate therapy, particularly after 5 years of use.51 In addition it was emphasised that the condition may be bilateral and that patients should be reminded to report any pain, weakness or discomfort in the thigh or groin area as this may be due to fracture.

**Hormone replacement therapy**

Oestrogen inhibits bone resorption and so reduced availability, as is the case post menopause, results in increased bone loss. Hormone replacement therapy (HRT) has been shown to reduce fracture risk. The Women’s Health Initiative (WHI), a large randomised placebo-controlled trial of hormone replacement in postmenopausal women, found a significant reduction in hip (RR 0.66; 95% CI 0.45–0.98) and vertebral fracture (RR 0.66; 95% CI 0.44–0.98) after a mean follow-up of 5.2 years.52 However, the study also raised concerns regarding cardiovascular disease and breast cancer risk which in turn have influenced prescribing habits.

More recent data has cast some doubt on the initial findings. The oestrogen-only arm did not show an increased breast cancer incidence after 7 years of follow-up.53 Furthermore, a subgroup analysis found that healthy individuals aged 50–59 years using HRT had no increased risk of coronary heart disease.54 The National Osteoporosis Society (NOS) published a Position Statement in 2010 recommending that HRT should be continued at least until the age of 50 years in women who experience an early menopause and could be considered as a treatment for osteoporosis for postmenopausal women aged <60 years who do not have risk factors for breast cancer, heart disease, stroke or venous thromboembolism if the benefits outweigh the other risks.55

**Selective oestrogen receptor modulators**

Selective oestrogen receptor modulators (SERMs) act as oestrogen agonists at certain target sites and antagonists at others. Raloxifene acts as a bone agonist and has been shown to reduce vertebral fractures by a magnitude of 30–50%.56 A reduction in hip fracture incidence was not shown. Data on non-vertebral fractures have only been positive in post hoc analysis in women with prevalent vertebral fractures.57 Raloxifene has been shown to be as effective in reducing risk of invasive breast cancer as tamoxifen, although does have a non-significant higher risk of non-invasive breast cancer.58

**Strontium ranelate**

Strontium ranelate has a dual mode of action increasing bone formation and reducing bone resorption due to direct effects on both osteoblasts and osteoclasts. An RCT showed that strontium ranelate reduced new vertebral fractures by 41% over a 3-year period with a reduction of 49% within the first 12 months.59 A 36% reduction of hip fracture was found in post hoc analysis in women aged ≥74 years with a femoral neck BMD T-score ≤-3.0.60 Strontium ranelate has seen to be effective at reducing fracture risk in populations not routinely studied. A study specifically determining the effect on elderly patients aged 80–100 years found a 32% and 31% reduction in vertebral and non-vertebral fractures respectively over a 3-year period.61 In women with lumbar spine osteopaenia with and without prevalent vertebral fractures, strontium ranelate reduced vertebral fracture risk.62

Adverse events associated with strontium ranelate include headaches, nausea and diarrhoea, especially in the first 3 months of treatment. There appears to be an increase in venous thromboembolism. There have been reported cases of the DRESS syndrome, characterised by severe systemic symptoms and eosinophilia, again occurring early on in treatment.

**Parathyroid hormone**

Intermittent exposure to parathyroid hormone (PTH) promotes bone formation through direct effects on osteoblasts, i.e. is anabolic. This is in contrast to the catabolic effects associated with continuous exposure to supraphysiological levels, e.g. in primary or secondary hyperparathyroidism. Teriparatide has been shown to reduce the risk of vertebral and non-vertebral fracture risk.63 The effects of teriparatide persist for up to
30 months after stopping.\textsuperscript{64} Teriparatide is given as a daily subcutaneous injection and the treatment course is for 24 months; at present repeat courses are not recommended. Although there is no evidence of synergy when teriparatide is combined with alendronate,\textsuperscript{65} the administration of a bisphosphonate once the treatment course of teriparatide has been completed is recommended as it maintains or even potentiates the skeletal benefits accrued.\textsuperscript{66} Due to its high costs, teriparatide is primarily limited to those with severe osteoporosis with multiple fractures.

**Denosumab**

RANKL (NF-\( \kappa \)b ligand) expressed on osteoblasts activates RANK expressed on osteoclasts, promoting osteoclast differentiation, proliferation, activation and survival. Denosumab is a fully human monoclonal antibody against RANKL inhibiting the binding of RANKL with RANK on osteoclasts and hence bone resorption.

In a randomised placebo-controlled trial, 7868 women with postmenopausal osteoporosis of whom 24\% had pre-existing vertebral fractures were given subcutaneous denosumab 60 mg every 6 months.\textsuperscript{67} After 3 years, denusomab reduced the risk of new radiographic vertebral fractures by \( 68\% \) \( \text{-} \text{clinical vertebral fractures by } 69\% \), hip fractures by \( 40\% \) and non-vertebral fractures by \( 20\% \). The risk of cancer or infection was similar between treatment and placebo groups. However, incidence of eczema (3.0\% vs 1.7\%) and cellulitis, including erysipelas (0.3\% vs <0.1\%) was significantly higher than placebo. In the follow-up, only 1 patient developed ONJ and this was after dental extraction.

A further randomised placebo-controlled trial assessed efficacy in men on androgen-ablation therapy for prostate cancer with denosumab given over a 24-month period. Denosumab increased BMD at the lumbar spine, total hip and distal third of the radius but also significantly reduced the incidence of new vertebral fractures by \( 62\% \) at 36 months compared with placebo.\textsuperscript{68}

Denosumab has a number of advantages compared with bisphosphonates. Given the route of administration adherence is more likely and gastrointestinal adverse events less likely, and, unlike intravenous preparations, it can be given easily in a primary care setting. Furthermore, denosumab is not incorporated in bone, its effects are rapidly reversed and it has a short half-life. This makes it safer with regard to adverse events. Doses do not need to be adjusted due to renal impairment, although patients with creatinine clearance <30 ml/min or on chronic haemodialysis are at greater risk of developing hypocalcaemia.

NICE has approved denosumab for both primary and secondary prevention of osteoporosis prevention in postmenopausal women.\textsuperscript{69} The criteria are summarised in Table 6. It is also licensed for the treatment of bone loss associated with hormone ablation in prostate cancer in men at increased risk of fractures.

**Novel treatments**

Cathepsin K is a lysosomal protease that is expressed by osteoclasts and plays a central role in osteoclast-mediated bone degradation. By inhibiting cathepsin K, bone formation is preserved but resorption prevented. Odanacatib is a highly selective cathepsin K inhibitor currently under investigation. In a phase 2 study oral odanacatib, at a dose of 50 mg weekly, increased lumbar spine and total hip BMD by 5.7\% and 4.1\% respectively compared with placebo after 24 months.\textsuperscript{70} Adverse events were similar to placebo. The anti-fracture efficacy is now currently being assessed.

src kinase is expressed on osteoclasts and mediates several pathways regulating osteoclast activity. In a phase 1 study of healthy men an src kinase inhibitor, saracatinib, dose-dependently reduced bone resorption markers after 25 days.\textsuperscript{71}

\begin{table}[h]
\centering
\caption{NICE recommendations for denosumab.\textsuperscript{69}}
\begin{tabular}{llll}
\hline
\textbf{Primary prevention} & & & \\
Women unable to comply with or who have a contraindication to alendronate and either risedronate or etidronate & & & \\
\hline
\textbf{Age (years)} & \textbf{No risk factor*} & \textbf{1 risk factor*} & \textbf{2 risk factors*} \\
\hline
65–69 & Not recommended & \( T \leq -4.5 \) & \( T \leq -4.0 \) \\
70–74 & \( T \leq -4.5 \) & \( T \leq -4.0 \) & \( T \leq -3.5 \) \\
\geq75 & \( T \leq -4.0 \) & \( T \leq -4.0 \) & \( T \leq -3.0 \) \\
\hline
\textbf{* Risk factors: parental history of hip fracture, alcohol intake of \( \geq 4 \) units per day, and rheumatoid arthritis} & & & \\
\textbf{Secondary prevention} & & & \\
\textbullet Increased risk of fragility fracture & & & \\
\textbullet Unable to comply with alendronate and either risedronate or etidronate & & & \\
\textbullet Contraindication to alendronate and either risedronate or etidronate & & & \\
\end{tabular}
\end{table}
Osteoporosis is a common problem and is associated with considerable morbidity and mortality. Whereas previously bone mineral density measurements alone have been used to determine treatment thresholds, both NICE and FRAX/NOGG take into account other independent risk factors when determining risk of future fracture. Assessment of potentially treatable underlying causes should be undertaken.

Bisphosphonates remain the initial drugs of choice. However, concerns such as osteonecrosis of the jaw, atrial fibrillation, oesophageal cancer and atypical femoral fractures have been raised, particularly with longer-term use. Drug holidays may be a way of obviating this risk. Newer treatments with novel mechanisms of action are now becoming available. Denosumab, a biologic agent, is effective at reducing low trauma fracture. With time, with a better understanding of bone biology, additional targeted agents are likely to become available.

References


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**STarT Back – one size doesn’t fit all**

The Keele STarT Back approach developed by the Arthritis Research UK Primary Care Centre uses a simple clinical tool to stratify patients according to their risk of developing chronic back pain and then direct them towards treatment appropriate to their level of risk. The results recently published in *The Lancet* show that this approach both gives better outcomes for patients and is more cost-effective.

[www.keele.ac.uk/sbst/](http://www.keele.ac.uk/sbst/)

In connection with this, Keele is hosting a free conference on **17 April 2012** with workshops for clinicians and commissioners:

**Implementing stratified care for back pain**

**Implications for commissioning**

[www.keele.ac.uk/sbst/training](http://www.keele.ac.uk/sbst/training)
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