11 Osteoporosis prevention and treatment

At a glance

- Encourage adequate calcium and vitamin D intake throughout life to ensure that maximum bone mineral density (BMD) is achieved.
- Weight-bearing exercise (30 minutes on most days) has been shown to help to maintain BMD.
- Monitor women taking multiple drugs and minimise those drugs known to cause a drop in BMD.
- Screen women at risk for osteoporosis, especially those with history of anorexia or premature ovarian insufficiency.
- All women with premature ovarian insufficiency should be on some form of hormone replacement until they are at least 50 years.
- Estrogen should be considered as a first line of therapy for the prevention and treatment of osteoporosis in women under 60 years.
- Exclude all secondary causes of osteoporosis before commencing treatment.
- Assess all women starting high-dose glucocorticoids for fracture risk and consider a bisphosphonate in women with high risk factors.
- Preventing osteoporosis in women at high risk requires a lifelong strategy and different treatment options are applicable at different phases of life.
- All women should be seen after a fragility fracture, commencing all over 75 years on a bisphosphonate and assessing those under 75 years with a dual-energy x-ray absorptiometry and fracture risk assessment score.
- Calcium and vitamin D supplements have no effect on fracture rates.

Lifetime risk

A woman's osteoporosis risk is determined largely by genetic factors but this risk is modified by her nutritional state and activity levels through childhood and early adulthood. Peak bone mass is usually acquired by the end of linear skeletal growth in the early to mid-20s, after which bones undergo a continual process of remodelling until the menopause, when bone resorption begins to outweigh new bone formation and bones lose strength. The higher the peak bone mass acquired in youth, the lower the risk of osteoporotic fracture in later life. A 10% increase of peak bone mass in children is estimated to reduce the risk of an osteoporotic fracture during adult life by 50%. In most women, the rates of bone mineral density loss appear to be highest during the year before until two years after the final menstrual period, with a small percentage of women being rapid bone losers, who may lose as much as 3–5% of bone mass per year.

Osteoporosis is becoming an increasing burden to the health service both in financial and human terms with one in three women over 50 years suffering a fragility fracture. One in six women will have a hip fracture and, of these, 20% will die within one month, 30% within one year and over 50% will no longer be able to live independently.

Diagnosis

Osteoporosis is diagnosed by the presence of a fragility fracture or by bone mineral density (BMD) assessment using dual-energy x-ray absorptiometry (DXA). A BMD that is 2.5 standard deviations (SD) or more below the mean BMD of a young adult reference population, which gives a T score of –2.5 or less, meets the criteria for a diagnosis of osteoporosis. Lowered bone mass giving a T score between –1.0 and –2.5 is defined as osteopenia. Women with T scores of less than –2.5 have the highest risk of fracture, although there are more fractures in patients with a T score between –1.0 and –2.5 because there are so many more patients in this category.

Bone turnover markers, such as C-terminal telopeptide of type 1 collagen, provide a more rapid response, indicating changes in bone turnover within one month, which is predictive of future changes in BMD. They are strongly suppressed by anti-resorptives depending on the potency of the drug. These bone turnover markers are increased after the menopause, corresponding to the increased bone resorption in this group. These markers may have future applications in predicting those women who are fast bone losers or non-responders to treatment but, currently, the markers have not been standardised for general use.

Quantitative ultrasound of the calcaneus (QUS) provides another modality for bone assessment. Its advantages are low cost, portability and lack of ionising radiation. QUS is a good predictor of osteoporotic fracture risk, although its sensitivity and specificity are not high enough for use as an alternative to DXA. It has a relatively high negative predictive value, so could be used to screen outpatients unlikely to have a BMD in the osteoporotic range. However, with a low positive predictive value, a diagnosis of osteoporosis using QUS would need to be confirmed with DXA.

Prevention

The best strategy for prevention of osteoporosis is by maximising peak bone mass and minimising the rate of bone loss. Maximum bone mineralisation can be aided by ensuring that girls maintain a diet that contains adequate protein and calcium and have enough exposure to sunlight for vitamin D formation. Maintaining a body mass index between 19–25 provides the best environment for regular menstrual cycles and, hence, adequate estrogen levels to ensure a healthy bone turnover.

Exercise should be incorporated into daily living from a young age; ideally, 30 minutes on most days of the week. Muscles and bones respond when they are stressed, as happens with weight-bearing or impact exercises, which play an important role in building and maintaining bone strength, improving balance and preventing falls. Smoking and high alcohol intake should be discouraged, as both reduce bone density.

There is general agreement that population screening is not cost effective but all health professionals should undertake opportunistic case finding within their practice and should assess fracture risk in any postmenopausal women seen with clinical risk factors. The 2012 National Institute for Health and Care Excellence (NICE) guidance suggested estimating the 10-year absolute risk of fracture in all women over 65 years.[1] Women who have an independent clinical risk factor for fracture should have their risk estimated at age 50–65 years. The recognised clinical risk factors for osteoporosis are listed in Box 11.1.

The drop in BMD seen with glucocorticoid use appears to be dose dependent and cumulative. It is greatest in the first 6–12 months of treatment, so patients should be assessed and treated early. A woman who is starting high-dose prednisolone (over 7.5 mg/day), who is known to have a BMD lower than –1.5 SD mean BMD or who has had a previous fragility fracture should be started on a bisphosphonate at commencement of steroids. Women at a lower risk should have a risk assessment before starting steroids together with other clinical information to decide on the need for treatment.

Box 11.1

Clinical risk factors for osteoporosis

- Increasing age
- History of parental hip fracture (gives a two-fold increased risk of hip fracture)
- Low body mass index (< 18.5 kg/m^2) or previous anorexia
- Previous fragility fracture
- Current smoking
- Alcohol intake of 3 units/day or higher
- Secondary causes of osteoporosis; for example:
  - Rheumatoid arthritis
  - Untreated hypogonadism
  - Prolonged immobility
  - Organ transplantation
  - Type 1 diabetes
  - Hyperthyroidism
  - Gastrointestinal disease
  - Chronic liver disease
  - Chronic obstructive pulmonary disease
- Current or past glucocorticoid treatment for 3 months or longer
- Drugs known to decrease bone mineral density (e.g., aromatase inhibitors, proton pump inhibitors, selective serotonin reuptake inhibitors, thiazolidinediones and anticonvulsants)

Risk assessment

The National Osteoporosis Guideline Group (NOGG) has produced guidelines on the management of fracture risk,[2] which uses FRAX® (Centre for Metabolic Bone Diseases, University of Sheffield), an online calculator validated for patients aged 40–90 years.[3] FRAX calculates the patient's 10-year risk of hip and major osteoporotic fracture, which then links to the NOGG guidance to obtain advice on appropriate management (Figure 11.1). The NOGG guideline advice is that:

- Postmenopausal women with a prior fragility fracture should be considered for treatment without the need for further risk assessment, although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women.

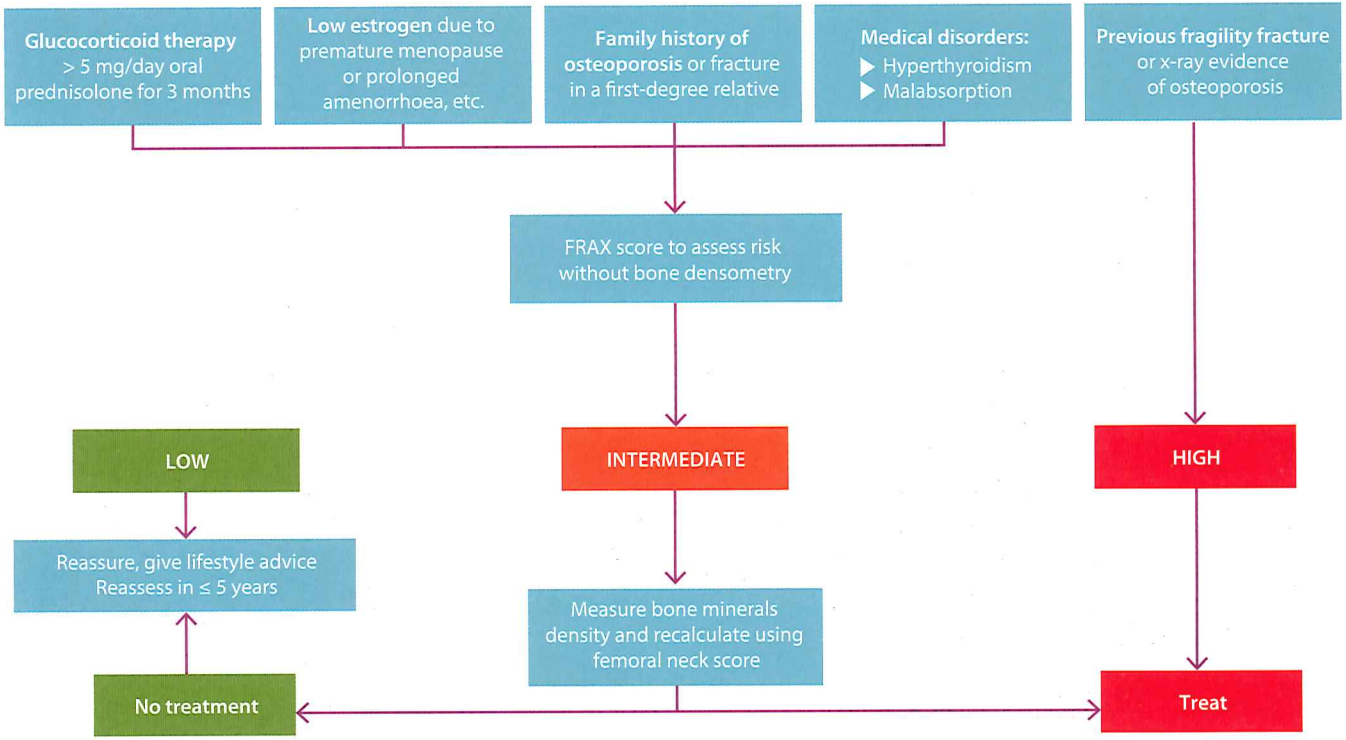

Figure 11.1 Management of menopausal women with clincial risk factors for osteoporosis

- Assessment using the FRAX tool should be undertaken in all postmenopausal women without fracture but with a clinical risk factor or a body mass index less than 19 kg/m^2. Following the assessment of fracture risk using FRAX, the patient may be classified to be at low, intermediate or high risk:

  1 Low risk – reassure and offer lifestyle advice (sunlight exposure for vitamin D and advice on calcium-rich foods, exercise, smoking cessation and alcohol reduction). Reassess in five years or sooner, depending on the clinical context.
  2 Intermediate risk – measure BMD, as this increases the accuracy, and recalculate the fracture risk to determine whether an individual's risk lies above or below the intervention threshold.
  3 High risk – can be considered for treatment without the need for BMD, although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women.

  Before instigating treatment, further assessments should be made to exclude other underlying causes of the low BMD, to ensure that the woman is suitable for treatment (Box 11.2).

Box 11.2

Assessment of secondary causes of osteoporosis

- Full history and clinical examination
- Full blood count, erythrocyte sedimentation rate or C-reactive protein
- Serum calcium, phosphate
- Parathyroid hormone (if calcium levels abnormal)
- Renal function
- Liver function and transaminases
- Thyroid function
- 25-hydroxyvitamin D levels

Plus, as necessary:

- DXA
- Myeloma screen: protein electrophoresis and urinary Bence-Jones proteins
- Coeliac screen: tissue transglutaminase antibodies

Treatment of women at increased risk of osteoporotic fracture

The treatment of postmenopausal women at increased risk of osteoporotic fracture consists of lifestyle measures, including diet, weight-bearing exercise, smoking cessation, counselling on falls prevention and avoidance of heavy alcohol use. Additional pharmacological agents may be used for those deemed to be at increased risk. The agent used will depend on the age of the woman, the level of risk and her overall health.

Calcium and vitamin D supplements

Women who are getting adequate calcium from dietary intake alone may not wish to take additional calcium supplements. There has been some controversy around the effects of calcium supplements resulting from a meta-analysis which showed that the risk of coronary heart disease was increased by 31% in those women taking calcium supplements.[4] The validity of this study has been questioned, however, by a 2014 meta-analysis from an Australian research group, who observed no relationship between calcium supplementation, with and without vitamin D, and coronary heart disease risk in more than 63,500 elderly women.[5]

Analysis of part of the Women's Health Initiative study in 2013 showed that women taking HRT together with calcium (1000 mg/day) and vitamin D (400 iu/day) supplements had greater bone protection than those taking HRT alone.[6] This study also noted an increase in renal calculi with vitamin D and calcium supplements and no effect on risk of cardiovascular disease. Meta-analyses of large randomised controlled trials (RCTs) of calcium and vitamin D supplementation in over 50,000 adults have concluded that calcium has a small effect on BMD at a year, with no clinically significant effect on fracture. In patients with very low vitamin D levels, supplements will prevent osteomalacia, otherwise vitamin D supplements have shown no skeletal or non-skeletal effects. Only one small randomised trial of calcium and vitamin D supplementation in frail elderly women with low dietary calcium and vitamin D deficiency who are institutionalised showed significant reductions in hip fracture risk of 23%.[7] The results from this population group are not reproducible in other cohorts. Hence, the advice to postmenopausal women with osteoporosis remains that they should take adequate supplementary calcium (generally 500–1000 mg/day) to ensure that their total calcium intake (diet plus supplements) approximates 1200 mg/day (Table 11.1).

Sufficient vitamin D is necessary for the intestinal absorption of calcium and phosphate. Low vitamin D levels are associated with impaired calcium absorption and a compensatory rise in parathyroid

Table 11.1

Calcium content of typical foods

Food	Calcium content (mg)
Milk:	
Full-fat (250 ml)	295
Semi-skimmed (250 ml)	300
Skimmed (250 ml)	305
Low-fat yogurt (100 g)	150
Cheddar cheese (50 g)	360
Boiled spinach (100 g)	159
Brazil nuts (100 g)	170
Tinned salmon (100 g)	93
Tofu (100 g)	480

hormone, which results in excessive bone resorption and a decrease in BMD. The optimal dietary vitamin D intake is not known, but around 800–1000 units per day is recommended in postmenopausal women with osteoporosis. Only 10% of vitamin D comes from dietary sources (oily fish, liver, egg yolks), with supplementation from fortified breads and cereals; 95% of vitamin D is generated in the skin by photosynthesis from ultraviolet sunlight. Fair-skinned people need 20–30 minutes of exposure of the forearms and face at midday two or three times a week in summer for adequate synthesis. In northern latitudes, the skin is unable to form vitamin D in the winter, so low levels of vitamin D are seen in the winter months in those groups that get insufficient sun exposure in the summer months (elderly, dark-skinned and ethnic minority groups who cover their skin) who fail to build up adequate reserves in their adipose tissue. A UK study found 90% of middle-aged adults had vitamin D levels under 40 nmol/l in winter.[8] The concept of what constitutes a normal range to maintain optimum health is still uncertain but the generally accepted norms are that over 70 nmol/l is replete, 40–70 nmol/l is insufficient and under 40 nmol/l is deficient.

Testing for vitamin D deficiency has become substantially more common in general practice, yet there remains uncertainty over who to test, what the results mean (for example, are they related to the patient's symptoms or to an illness) and what to do with the results. A 2014

systematic review looked at papers studying the association between vitamin D status and ill health and the role of supplements.[9] It concluded that there are moderate associations between low vitamin D levels and a range of non-skeletal disorders (cardiovascular disease, depression, dementia, diabetes, infectious disease, multiple sclerosis, weight gain, declining muscle strength and all-cause mortality). However, many of these conditions involve inflammatory processes, which themselves reduce vitamin D levels. Vitamin D supplementation has not been shown to improve outcomes, suggesting that low vitamin D levels may be a consequence rather than a cause of ill health. However, the 2016 advice from Public Health England is that all adults and children over the age of one should consider taking a daily supplement containing 10 µg vitamin D, particularly during autumn and winter. People who have a higher risk of vitamin D deficiency are advised to take a supplement all year round. A review by the Scientific Advisory Committee on Nutrition concluded that these at-risk groups include pregnant women and women who are breastfeeding, people over 65 years and those whose skin has little or no exposure to the sun, such as those in care homes or people who cover their skin when they are outside.[10] People with dark skin, from African, African-Caribbean and South Asian backgrounds, may also not get enough vitamin D from sunlight in the summer. These groups should consider taking a supplement all year round as well.

Estrogen-based treatments

HRT has been shown to be effective in preserving bone density and in reducing the risk of spine, hip and other osteoporotic fractures in women over 50 years. It acts as an anti-resorptive agent by reducing osteoclast numbers and function and may possibly also increase bone formation by osteoblast stimulation. A significant fracture reduction is seen after more than two years of treatment and some studies indicate that this benefit may persist for several years after stopping longer-term HRT use. HRT, together with strontium ranelate , are the only drugs with RCT evidence of effectiveness in women with osteopenia. In the Fracture Intervention Trial, alendronate did not show a reduction in fracture risk in osteopenia, making HRT a better choice in these women.[11]

The bone-protective effect of estrogen is dose and duration related and the bone-preserving effect of HRT declines after discontinuation of treatment. The standard doses of HRT used for symptom relief are considered bone conserving but studies have shown that lower doses (for example, 1 mg 17β estradiol, 0.3 mg conjugated estrogen) or a 25 µg patch to be effective. Studies have shown that the use of HRT even for a few

years around the menopause may provide a long-term protective effect many years after stopping HRT.

Tibolone is a synthetic compound with estrogenic, progestogenic and androgenic properties, which acts on the skeleton in a similar manner to HRT, reducing vertebral and non-vertebral fractures, although with no significant reduction in hip fractures. Its use is associated with a small but significant increased risk of stroke but there is no effect on venous thromboembolism. Although there is no increase in breast density seen with tibolone use, there was an increased recurrence risk among breast cancer survivors seen in the LIBERATE trial.[12] It is an effective alternative to HRT but the overall risks are broadly similar to oral HRT.

Guidance on the use of HRT in the prevention and treatment of osteoporosis has been updated with both the British Menopause Society (BMS) and the National Osteoporosis Society (NOS) issuing position statements:

- Advice should be given to menopausal women regarding lifestyle modification and bone health. This should include information on a balanced diet, adequate calcium and vitamin D intake, exercise, smoking cessation as well as avoidance of excessive alcohol intake (BMS).
- Explain to women that the baseline population risk of fragility fracture for women around menopausal age in the UK is low and varies from one woman to another, but that their risk of fragility fracture is decreased while taking HRT (NICE).
- HRT should be considered the first-line therapeutic intervention for the prevention and treatment of osteoporosis in women with premature ovarian insufficiency and symptomatic menopausal women below 60 years of age (BMS).
- Women who have experienced an early menopause (whether natural or surgically induced) should be recommended HRT until at least the normal age of the menopause (around 50 years). This will help to reduce bone loss and to avoid the symptoms and other complications of prolonged estrogen deficiency (BMS).
- For postmenopausal women below the age of 60 years who do not have risk factors for breast cancer, heart disease, stroke or venous thromboembolism, the risks associated with HRT are low. For these women, HRT can be considered as a first-line treatment for osteoporosis, providing that the beneficial effects on fracture risk reduction outweigh any adverse risks for that individual (BMS).
- In women up to the age of 60 years who are using HRT for relief of menopausal symptoms, it is accepted that the HRT benefit normally

exceeds risk irrespective of the potential bone effect, which will be an additional benefit (BMS).
- Initiating HRT after the age of 60 years for the sole purpose of the prevention of osteoporotic fractures is not recommended (BMS).
- HRT is an effective treatment for menopausal symptoms, which also offers protection against fractures at both hip and spine. For the large proportion of women affected by osteoporosis, who are over the age of 60 years, HRT is not considered a suitable treatment for osteoporosis. However, in the under 60 years age group, HRT still has a role to play in the management of osteoporosis (NOS).

Women with osteoporosis, or who are at high risk of developing osteoporosis, need lifelong management. Using HRT through their 50s, with bisphosphonate, as the risks associated with HRT rise, would seem to be a reasonable regimen in well-counselled women.

Non-estrogen-based treatments

Bisphosphonates

The bisphosphonates (alendronate, risedronate and ibandronate) are used in fracture prevention and treatment of osteoporosis and also for the prevention of corticosteroid-induced osteoporosis. Alendronate is available as a generic drug and is the cheapest bisphosphonate, so should be used first. In the Fracture Intervention Trial, alendronate therapy increased femoral neck BMD by 4.1% and spine BMD by 6.2% and reduced the risk of vertebral fracture by approximately 50% and hip and wrist fractures by approximately 30% in women with osteoporosis.[13] Risedronate has also been shown to reduce vertebral and non-vertebral fractures. Ibandronate reduces vertebral but not non-vertebral fractures by 50%, and is available in a monthly oral dosing regimen or a three-monthly intravenous bolus. Zoledronic acid is administered via intravenous infusion over 15 minutes annually, so provides an alternative option for individuals who cannot tolerate oral bisphosphonates or who find the yearly dosing regimen more convenient.

All bisphosphonates are poorly absorbed from the gastrointestinal tract (only 5–10% of the administered dose) and must be given on an empty stomach. The principal adverse effect of bisphosphonates is irritation of the upper gastrointestinal tract, so patients should remain upright for 30 minutes after the dose. Bisphosphonates should not be given to patients with active upper gastrointestinal disease and treatment should be changed to another bisphosphonate or discontinued in patients who develop any symptoms of

oesophagitis. The oesophageal irritation will not respond to a proton pump inhibitor and the addition of these drugs is associated with a reduction in the effectiveness of bisphosphonates and an increased risk of fracture.

Bisphosphonates are chemical analogues of naturally occurring pyrophosphates, thus allowing them to be integrated into the skeleton, remaining there for longer than 12 years, inhibiting osteoclast-mediated bone loss. This raises concerns about their potential effects on the fetal skeleton, so bisphosphonates are not advised in women of childbearing age. Equally, as the very long-term risks remain unknown, they are best avoided where possible in women aged under 60 years.

Most of the RCTs involving bisphosphonates have used calcium and vitamin D supplements, and we have no comparative trials to show that their fracture outcomes are enhanced by supplements. Studies of alendronate and zolendronate showed no effect on BMD with additional calcium supplements. As long as patients have adequate dietary calcium and vitamin D levels, co-prescription of supplements is probably not necessary (Table 11.2).

Table 11.2

Treatments for osteoporosis and levels of evidence for fracture prevention at spine and hip when given with calcium and vitamin D supplements

Bisphosphonate	Spine	Hip
Etidronate	A	B
Alendronate	A	A
Risedronate	A	A
Ibandronate	A	ND
Zoledronic acid	A	A
Calcitriol	A	ND
Calcitonin	A	B
Estrogen	A	A
Raloxifene	A	ND
Strontium ranelate	A	A
Parathyroid hormone peptides	A	ND

A = meta-analysis of RCTs or from at least one RCT or at least one well-designed, controlled study without randomisation; B = from at least one other type of well-designed quasi-experimental study or well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, or case–control studies; ND = not demonstrated

An increased risk of osteonecrosis of the jaw has been seen with longer duration of exposure. This adverse effect is mainly limited to high-dose intravenous use in cancer or immune-suppressed patients and those with pre-existing dental disease. The incidence with low-dose bisphosphonates is 1–69 in 100,000 patient years. However, it is prudent to advise a dental check-up before commencing a bisphosphonate and on maintaining dental hygiene while taking the drug.

The HORIZON Pivotal Fracture Trial found that the number of patients who had an arrhythmia, including serious atrial fibrillation, was greater in the zolendronate compared with placebo group. This potential association has not been reproduced in other such trials, suggesting the risk of atrial fibrillation from oral bisphosphonates is small, although there may be a greater potential risk with intravenous bisphosphonates.[14] The benefits of fracture prevention for an individual must be balanced against their potential risk of atrial fibrillation, with caution when considering intravenous bisphosphonates for women with serious underlying heart disease or a history of atrial fibrillation.

The suppression of bone remodelling with bisphosphonate use over seven years has also led to an increase in atypical transverse femoral fractures of around 5 in 10,000 patient years. This is thought to occur secondary to impaired healing of smaller stress fractures. Patients may present with dull aching pain in the groin or thighs prior to fracturing, so they should be investigated early with x-rays of both femurs, as fractures can be bilateral.

There is currently no consensus on how long to continue bisphosphonate therapy. Having a drug holiday after five years to allow increased bone turnover and normal skeletal repair may be reasonable for women who have a stable BMD with no prevalent vertebral fractures and who are at low risk for fracture in the near future. The FLEX study showed that discontinuation of alendronate after five years did not result in increased fracture risk, despite a small drop in BMD and rise in bone turnover markers.[15] However, in high-risk patients (BMD under –2.5 or prevalent vertebral fractures), giving a further five years of alendronate was associated with over 50% fewer non-vertebral fractures. Predictors of future fracture after discontinuation of treatment are: age over 75 years, BMD at discontinuation, smoking, fractures occurring during treatment, prevalent vertebral fractures and body mass index. The length of the drug holiday should be decided based on the patient's response to initial treatment and their current fracture risk. When the T score falls below –2.5, treatment should be resumed.

Strontium ranelate

Strontium ranelate appears to decrease bone resorption while sustaining bone formation, thus reducing vertebral and hip fractures. Like calcium, strontium is an alkaline earth element and becomes incorporated into the skeleton, so causing a significant overestimation of BMD. The adverse effects of strontium are diarrhoea and a less than 1% increased risk of venous thromboembolism and nervous system disorders (headaches, seizures, memory loss and disturbance in consciousness). An RCT involving 7500 postmenopausal women with osteoporosis has shown an increased risk of myocardial infarction in women taking strontium (relative risk 1.6; 95% confidence interval 1.07–2.38). The European Medicines Agency Committee has recommended that the use of strontium is restricted to the treatment of severe osteoporosis in women at high-risk of osteoporosis with no cardiac problems or uncontrolled hypertension. All women should have an assessment of their cardiovascular risk pretreatment and every 6–12 months during treatment.

Selective estrogen receptor modulators

Raloxifene is a selective estrogen receptor modulator (SERM), which reduces vertebral fractures only, by 30–50%. It has estrogenic actions in bone and anti-estrogenic actions in the endometrium and breast tissue, reducing the risk of breast cancer to the same extent as tamoxifen. Adverse effects include hot flushes, arthralgia, calf cramps and a lowering of blood lipids. It was postulated that this could be cardioprotective; however, the Raloxifene Use for the Heart (RUTH) study found that raloxifene did not reduce the risk of coronary heart disease in women over 60 years and that it increased the risk of fatal stroke and venous thromboembolism.[16] Owing to the weak anti-resorptive effects of raloxifene, its use should be reserved for those women who cannot tolerate bisphosphonates or for women with osteoporosis and increased risk of breast cancer. It is not recommended by NICE for the primary prevention of fracture.

Bazedoxifene is another SERM that is available for the prevention and treatment of postmenopausal osteoporosis with similar efficacy to raloxifene, decreasing vertebral and non-vertebral fractures by 42%, breast protective effects and also a similar adverse-effect profile.

Duavive® (Merck, Sharpe & Dohme), is a new tissue-selective estrogen complex produced by combining 0.45mg conjugated estrogens with 20 mg of the SERM bazedoxifene. It is effective in alleviating menopausal symptoms, rapidly inducing amenorrhoea, giving endometrial protection

and increasing bone density. It is now licensed for the treatment of estrogen deficiency symptoms in postmenopausal women with an intact uterus who are over 12 months since their last period and for whom treatment with progestin-containing therapy is not appropriate.

Teriparatide

Recombinant 1–34 parathyroid hormone, given as a subcutaneous daily injection, reduces vertebral and non-vertebral fractures in postmenopausal women with osteoporosis. As they are much more costly than other options, they are reserved for women with severe osteoporosis who are unable to tolerate or are unresponsive to other treatments. It can be given for 24 months in severe osteoporosis, reverting to a bisphosphonate once BMD has improved. The bisphosphonates, estrogens and SERMs are all anti-resorptive agents, which slow bone turnover by decreasing bone resorption. In contrast, parathyroid hormone enhances bone turnover by stimulating osteoblasts to produce greater bone formation, which is evident within the first month of treatment and peaks six to nine months after initiation once the osteoclasts become activated in response.

Denosumab

Denosumab is a monoclonal antibody against the receptor activator of nuclear factor κ-B ligand (RANKL), which acts to increase osteoclast function. Denosumab binds to the RANKL receptor, reducing osteoclast function. Administered via subcutaneous injection every six months, it has been shown to improve bone mineral density and to reduce the incidence of new vertebral, hip, and non-vertebral fractures in postmenopausal women. Its suppression of bone remodelling is more potent than bisphosphonates and it already shares some of their long-term consequences, such as osteonecrosis of the jaw and atypical femoral fractures, although its effect on bone wears off faster than bisphosphonates on stopping treatment. RANKL is also involved with the immune system and the immune suppression seen with denosumab use has been associated with an increase in skin and urinary tract infections and endocarditis.

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