Review

Acute and long-term management of patients with vertebral fractures

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Summary

Symptomatic vertebral fractures are associated with significant morbidity, excess mortality and health and social service expenditure. Up to 20% of patients with an incident vertebral fracture experience a further vertebral fracture within one year. It is therefore important that vertebral fractures are detected early, and treatment considered as soon as possible.

Only a third of vertebral fractures come to medical attention, where they typically present with acute back pain, but other presentations include loss of height and increasing kyphosis. Spine X-rays should then be performed to confirm the diagnosis and exclude other pathology.

Bone density measurements are not essential before starting treatment for osteoporosis in patients with low-trauma vertebral fractures, but may be useful to confirm osteoporosis when there is uncertainty about previous trauma. They may also aid in selecting the most appropriate therapy and monitoring response to treatment.

Up to 30% of women and 55% of men with symptomatic vertebral crush fractures have underlying secondary osteoporosis, where treatment may lead to large increases in bone density. These conditions should therefore be sought by medical history, physical examination and appropriate investigations.

The management of patients with acute vertebral fractures should include measures to reduce pain and improve mobility, as well as starting treatment for osteoporosis. Treatments have now been shown in randomized controlled trials to improve bone density and reduce the incidence of vertebral and non-vertebral fractures in patients with osteoporosis. Choice of treatment will depend on the underlying causes of bone loss, efficacy in any particular situation, cost, patient preference and the potential non-skeletal advantages and disadvantages.

Introduction

Osteoporosis has been defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. The three major osteoporotic fractures
are those of the forearm, vertebra and hip. Although hip fracture is generally considered to have the greatest personal and socioeconomic impact, it is now clear that vertebral fractures are also associated with significant morbidity, excess mortality and health and social service expenditure.\(^2,3\) Furthermore, there is an increased risk of further fractures in patients with vertebral fractures,\(^4,5\) so it is important that these are detected and treatment for osteoporosis considered as soon as possible. Having previously developed guidelines on the management of osteoporosis in patients with hip fractures,\(^6\) we now consider the acute and long-term management of patients with vertebral fractures.

Relevant papers on the treatment of osteoporosis were identified by performing MEDLINE and EMBASE searches of articles published up until the end of 2002, using the search strategy described previously.\(^7\) Our treatment recommendations are graded on the levels of evidence supporting their use. Grade A recommendations are based on randomized controlled trials; Grade B recommendations result from controlled studies without randomization, studies with a quasi-experimental design and epidemiological studies. Grade C recommendations are based on expert committee reports or the clinical experience of recognized authorities.\(^7\)

### Epidemiology of vertebral fractures

The incidence of vertebral fractures is difficult to quantify accurately, as only a third of patients come to medical attention after fracture.\(^8\) Nevertheless, the lifetime risk of symptomatic vertebral fracture for a 50-year-old White woman in the UK has been calculated to be 11\%, compared with 2\% for a 50-year-old man.\(^8\) The European Vertebral Osteoporosis Study (EVOS) shows that the overall prevalence of vertebral deformity increases in women from 5\% at the age of 50 years to 25\% at 75 years, whereas the corresponding figures for men are 10\% and 18\%.\(^9\) The higher prevalence of vertebral deformity in young men compared with women may be due to greater exposure to trauma.\(^10\) There is also a large variation in the prevalence of vertebral fractures across Europe, which may reflect differences in physical activity and other lifestyle factors.\(^9\)

Vertebral fractures have a major impact on a patient’s quality of life. The Study of Osteoporotic Fractures (SOF) assessed the effect of vertebral fractures in 7723 women aged >65 years.\(^11\) Impact on quality of life was assessed by changes in disability, pain and fear for the future. With every additional fracture, patients experienced a further deterioration in their quality of life. Back pain associated with vertebral fractures is one of the most important factors impairing quality of life. The EVOS study demonstrated that patients with three or more vertebral deformities were almost twice as likely to report back pain in the previous year, compared with subjects without deformity.\(^12\) A UK study in men has reported that in addition to back pain, loss of height and kyphosis, patients with symptomatic vertebral fractures experience poorer sleep, more emotional problems and poorer mobility than age-matched control subjects.\(^13\)

There is also an increased mortality associated with vertebral crush fractures of about 18\% at 5 years, but this may be due to co-existing conditions associated with osteoporosis, rather than the fracture itself.\(^8\) An analysis of SOF data shows that mortality increases with the number of vertebral fractures.\(^2\)

It has been estimated that osteoporotic fractures cost £942 million annually in the UK, of which only £12 million is due to the acute cost of vertebral fractures.\(^3\) The social and economic cost of vertebral fractures may be substantially higher than this, because of the associated long-term morbidity. Patients with symptomatic vertebral fracture consult their GPs 14 times more often than do controls in the year following fracture,\(^3\) so are likely to continue to use health and social service resources at an increased rate.

Previous vertebral fractures increase the risk of further vertebral fracture. Women with one pre-existing vertebral deformity have a five-fold greater risk of further vertebral fracture.\(^4,14\) In a recent study, 20\% of postmenopausal osteoporotic women suffered a further vertebral fracture within one year of an incident vertebral fracture.\(^15\) Women with a previous vertebral fracture also have a 3.8-fold increased risk of hip fracture, compared with the background female population.\(^5\) This study also showed that the risk of hip fracture is highest in the first year following vertebral fracture.

### Pathogenesis of vertebral fractures

There is a strong inverse relationship between bone density and risk of vertebral fractures, with a 2.3-fold increase in vertebral fractures for each standard deviation reduction in spine bone density.\(^16\) Bone density, and therefore the risk of fracture at any age, is determined by peak bone mass, the age at which bone loss begins and the rate at which it...
progresses. Genetic factors account for as much as 80% of the variance in peak bone mass, whereas other potential determinants of bone mass at maturity include exercise, dietary calcium intake, smoking, alcohol consumption and age at puberty.\textsuperscript{17,18} Involutional bone loss starts between the ages of 35 and 40 in both sexes, but there is an acceleration of bone loss in the decade after the menopause in women. Overall, women lose 35–50% of trabecular and 25–30% of cortical bone mass with advancing age, whereas men lose 15–45% and 5–15%, respectively. Bone loss may also be influenced by low body weight, smoking, excess alcohol consumption, physical inactivity, impaired vitamin D production and metabolism and secondary hyperparathyroidism.\textsuperscript{17,18}

There are also a number of conditions that cause secondary osteoporosis. Up to 30% of women and 55% of men with symptomatic vertebral crush fractures have an underlying cause of secondary osteoporosis,\textsuperscript{19,20} such as oral steroid therapy, hypogonadism in men, alcohol abuse, hyperthyroidism, skeletal metastases and multiple myeloma.

Presentation of vertebral fractures

Vertebral fractures occur most commonly in the lower thoracic or upper lumbar spine\textsuperscript{8} and if symptomatic, typically present with severe pain of sudden onset. This may radiate anteriorly, mimicking chest or abdominal disease, or acute disc prolapse. The severe pain associated with symptomatic vertebral fractures usually persists for several weeks, before gradually improving.

Other presentations of vertebral fractures include loss of height and exaggeration of thoracic kyphosis. These patients may recall previous episodes of back pain, but skeletal deformity can occur without associated discomfort. Rare presentations of vertebral fracture include the cauda equina syndrome and paraparesis.

Patients with pre-existing chronic lung disease may pose a particular diagnostic and therapeutic challenge. If thoracic vertebral collapse occurs, the resulting loss of vital capacity will increase breathlessness. If these patients are treated with oral steroids for a presumed exacerbation of their chest disease, they may lose more bone, thereby increasing the risk of further fractures, and a vicious circle leading to respiratory failure can ensue. A lateral chest radiograph is valuable in this situation, as it may allow detection of fractures that might have been missed on a plain chest X-ray.

Radiological assessment of vertebral fractures

The radiological features of vertebral fractures include end-plate deformity with a reduction in the mid-vertebral height (biconcavity), decrease in the anterior vertebral height (wedging) and reduction in the anterior and posterior vertebral height (compression).\textsuperscript{21} There is strong agreement between experienced radiologists in the assessment of vertebral fracture.\textsuperscript{22}

In epidemiological studies, measurements are made of the anterior, mid and posterior height of each vertebral body, which are then compared with the normal range for the individual vertebra. EVOS examined the relationship between morphometric vertebral deformities and BMD in 1429 men and 1610 women aged 50 years and above.\textsuperscript{23} Loss of anterior vertebral height alone, with normal mid-vertebral and posterior height, accounted for 26% of the documented vertebral deformities in men and 19% in women, but was related poorly to BMD in both sexes. Other vertebral deformities involving loss of mid-vertebral height (vertebral wedging and compression) were significantly related to low BMD.\textsuperscript{23} If spine X-rays show vertebral wedging with loss of anterior vertebral height only, degenerative arthritis should be suspected. Scheuermann’s disease may be associated with multiple deformities of this type.

Bone density measurement in patients with vertebral fractures

Where dual-energy X-ray absorptiometry (DXA) bone mineral density measurements (BMD) of the lumbar spine and femoral neck are not readily available, it is reasonable to start treatment for osteoporosis in patients with low-trauma vertebral fractures. Nevertheless, bone density measurements are useful to confirm the diagnosis of osteoporosis when there is uncertainty about the severity of previous trauma, to aid in the selection of the most appropriate therapy and to assess the efficacy of treatment.

About 50% of men and women with symptomatic vertebral fractures have evidence of osteoporosis (T score \(-2.5\)) on spine bone densitometry using the WHO criteria,\textsuperscript{24} whereas a further 40% have osteopenia (T score \(-1\) to \(-2.5\)).\textsuperscript{13,25} We usually consider treatment for osteoporosis in patients with an atraumatic vertebral fracture and a spine or hip bone density T score \(<-1.0\). If the spine and hip bone density measurements are both normal (T score \(>-1.0\)), we would suspect that vertebral fracture was due to antecedent trauma, unless...
there was a past history of other low trauma fractures.

Lumbar spine BMD measurements may be spuriously elevated in the presence of kyphosis, scoliosis, degenerative arthritis, spondylolisthesis, aortic calcification or vertebral fractures. This occurs more commonly in patients above the age of 65 years, where bone density measurement of the total hip or femoral neck may provide more useful information. Lateral spine BMD measurements exclude the spinous processes and posterior arches, so may improve the distinction between patients with osteoporotic fractures and normal subjects in this situation, but the precision is reduced.

Other investigations

In up to 30% of women and 55% of men with symptomatic vertebral crush fractures, there is an underlying cause of secondary osteoporosis, treatment of which may lead to large increases in bone density. These conditions should therefore be sought in all patients with vertebral fractures, by careful history, physical examination and appropriate investigation. Initial investigations should include full blood count, an inflammatory marker such as erythrocyte sedimentation rate (ESR), plasma viscosity (PV) or C-reactive protein (CRP), biochemical profile (urea, electrolytes, albumin, total protein and liver function tests), bone profile, serum calcium, phosphate and alkaline phosphatase and thyroid function tests. In patients with unexplained osteoporosis, anti-endomysial antibodies should be measured to look for coeliac disease, particularly if there is suspicion of malabsorption. Serum and urine electrophoresis should also be performed if the ESR, PV or CRP is elevated, or if there is concern about the possibility of myeloma. In men with vertebral fractures, serum testosterone, sex hormone binding globulin and gonadotrophins should also be measured, together with prostate specific antigen (PSA) if there are symptoms of prostatism or evidence of sclerosis on spine X-rays.

These investigations are usually normal in primary or postmenopausal osteoporosis, but unexplained anaemia, high ESR, PV or CRP raises the possibility of malignancy, whereas macrocytosis and abnormal liver function tests suggest alcohol abuse. Hypercalcaemia indicates possible primary hyperparathyroidism, myeloma or skeletal metastases, while hypocalcaemia, hypophosphataemia and raised alkaline phosphatase suggest a diagnosis of osteomalacia. Serum 25-hydroxyvitamin D (25OHD) and intact parathyroid hormone (PTH) measurements may be useful in excluding vitamin D deficiency and secondary hyperparathyroidism in patients with limited sunlight exposure, previous gastric resection, malabsorption or anticonvulsant treatment. Serum 25OHD and PTH measurements are probably unnecessary if calcium and vitamin D supplementation is planned, as the results are unlikely to influence management.

If the above investigations suggest the possibility of malignancy, further assessment may then include bone marrow examination, isotope bone scan or MRI scan. It is important to appreciate that osteoporotic vertebral fractures are associated with increased uptake on isotope bone scan, which usually persists for over a year. The increased uptake on isotope bone scan with skeletal metastases is generally more extensive, as it includes both the spine and appendicular skeleton. It is likely that as access to MRI scans improves, they will be used more frequently in the assessment of vertebral fractures.

Acute management of vertebral fractures

There is currently no consensus as to the best management of the acute painful vertebral fracture, and little published work on the subject. We have therefore developed a pragmatic algorithm for the acute management of symptomatic vertebral fracture, which is shown in Figure 1. Traditional management has concentrated on analgesia, rest with physical support such as a brace or corset, and subsequent gradual mobilization within the limits of pain. The use of a corset should no longer be advocated, as it immobilizes the spine, thereby aggravating bone loss and wasting of the muscles around the spine. A balance has to be found between relieving pain sufficiently to allow rapid remobilization, but avoiding the potential adverse effects of strong analgesics such as opiates and opioids, to which elderly people are particularly susceptible. Non-steroidal anti-inflammatory drugs may help but have significant toxicity, though newer agents such as COX2 inhibitors may be safer. Physical treatments such as transcutaneous electrical nerve stimulation (TENS) may help in the short term and also in the chronic situation. Intercostal nerve blocks may also help in the management of acute pain, particularly if other measures prove ineffective.

Other specific bone active treatments are now used more frequently in the acute management of vertebral fractures. These include subcutaneous, intranasal or rectal calcitonin (Grade A) and
intravenous bisphosphonates such as pamidronate or clodronate (Grade B). In a double-blind, placebo-controlled trial in 56 patients with acute vertebral fracture, IM salmon calcitonin 100 IU daily led to a greater reduction in pain intensity. A subsequent randomized controlled trial in 32 men and 68 women with acute vertebral fracture showed that intranasal calcitonin 200 IU daily for 28 days was more effective than placebo at decreasing pain and improving mobility. A review article identified eight trials between 1966 and 1998, and found that calcitonin given nasally or subcutaneously was strongly analgesic within 2 weeks. The beneficial effect persisted for at least 4 months, without serious side effects. Two recent studies have reported the use of intravenous bisphosphonates in patients after acute vertebral fracture. One demonstrated significant pain relief with clodronate when compared to paracetamol alone, whereas the other reported improvement in pain in a series of five patients whose symptoms had not responded to a combination of analgesics including opiates. Further studies are required to confirm the benefits of calcitonin and bisphosphonates in patients with acute vertebral fracture, but it is worthwhile considering these agents in such patients admitted to hospital with back pain.

Vertebroplasty

Percutaneous vertebroplasty is an interventional radiological technique that involves the injection of bone cement, usually polymethylmethacrylate, into a cervical, thoracic or lumbar vertebra for the relief of pain, and for strengthening of the bone. Initially introduced for the treatment of malignant causes of vertebral collapse, its use has been extended to include cases of osteoporotic vertebral collapse, particularly when conventional forms of treatment have proved unsuccessful.

Experience with the technique is limited, and a recent review could only find two uncontrolled prospective studies and a variety of case reports. Significant pain relief was apparent within 1–2 days after injection in up to 80% of all patients treated, with a similar improvement in mobility. Relief of symptoms can last from several months to several years. Complications of the technique appear to be uncommon, but include leakage of bone cement into the paravertebral tissues, compression of spinal nerve roots and pulmonary embolism.

Patients being considered for vertebroplasty should satisfy the following criteria: severe pain and loss of mobility that has not been relieved by conventional medical therapy; other causes of pain have been excluded by appropriate investigations including CT or MRI and the affected vertebra should not be significantly destroyed and should retain at least one third of its original height.

It has recently been proposed that isotope bone scan has a predictive effect in choosing those patients most likely to benefit from vertebroplasty. Patients with osteoporotic vertebral collapse often have multiple fractures, which are a mixture of old, and new lesions. Only those lesions showing increased activity on the bone scan should be selected for treatment.
No progression of deformity has been noted in the treated vertebrae in any of the reported series. However, it has been suggested that there is a slight but significantly increased risk of vertebral fracture in the vicinity of a cemented vertebra.35

In summary, vertebroplasty appears to be a safe and effective treatment for the relief of pain in those patients who do not respond to conservative medical treatment (Grade C). However, experience with the technique is still limited, and it has not yet been fully evaluated by a large-scale prospective clinical study.

**Treatment of osteoporosis**

All patients with vertebral fractures should be given general advice on lifestyle measures to decrease further bone loss, including eating a balanced diet rich in calcium, stopping smoking, moderating alcohol consumption and, if possible, maintaining regular physical activity and exposure to sunlight. Calcium and vitamin D supplementation may be necessary in patients with low dietary calcium or those likely to have vitamin D deficiency because of limited sunlight exposure. In patients with a past history of recurrent falls, measures should be taken to reduce the incidence of falls.36 Consideration should also be given to the use of external hip protectors, which may decrease the risk of hip fractures in frail or institutionalized elderly people.37

Treatments for osteoporosis may be classified into antiresorptive and anabolic agents. Antiresorptive agents cause a transient uncoupling of resorption and formation, leading to a modest increase in bone density of 5–10%. A number of these treatments have also been shown to reduce the incidence of fractures (Table 1). Anabolic agents such as sodium fluoride and teriparatide (recombinant human PTH 1–34) lead to larger increases in bone density, but only teriparatide has been shown to decrease fracture incidence.

Underlying causes of secondary osteoporosis should be treated where possible, as long-term treatment of patients with male hypogonadism, primary hyperparathyroidism and hyperthyroidism increases bone density by between 10% and 20%.38–40 Although one would anticipate that this would decrease the risk of further fractures, this remains unproven.

The Royal College of Physicians and the Bone and Tooth Society of Great Britain have published updated guidelines on the prevention and treatment of osteoporosis.7 Their conclusions about the efficacy of different treatments in decreasing the risk of fractures are shown in Table 1. Although the grading of the strength of the recommendations based on study design is clearly useful, this takes no account of study size, the magnitude of the treatment effect and the patient groups studied. It is therefore important to consider these issues.

**Hormone replacement therapy**

Hormone replacement therapy (HRT) was previously regarded as the gold standard for the prevention and treatment of osteoporosis, but few interventional studies have examined the effect of HRT on fracture incidence. In a five-year randomized controlled trial in 464 postmenopausal women, HRT reduced the risk of non-vertebral fractures by 71%.41 In small studies in older women with established osteoporosis (subject numbers 40 and 78, with mean ages 65 and 68 years, respectively), HRT increased spine bone density by about 5%.42,43 One of these studies also showed a reduction in vertebral fracture incidence of 60%.43 Recent meta-analyses have been performed of randomized controlled trials of the effects of HRT on vertebral and non-vertebral fractures.44,45 Overall, there was a 33% reduction in vertebral fracture and a 27% decrease in non-vertebral fracture with HRT. There was an attenuated response with advancing age, such that the risk reduction of 12% was not statistically significant above the age of 60 years.

The results of the Women’s Health Initiative (WHI) Study of HRT have recently been published.46 This involved 16,608 postmenopausal

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**Table 1** The effect of drug treatment on the incidence of vertebral, non-vertebral and hip fractures

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<thead>
<tr>
<th>Drug</th>
<th>Vertebral fractures</th>
<th>Non-vertebral fractures</th>
<th>Hip fractures</th>
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<tbody>
<tr>
<td>HRT</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>A</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Etidronate</td>
<td>A</td>
<td>B</td>
<td>B</td>
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<tr>
<td>Alendronate</td>
<td>A</td>
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<td>Risedronate</td>
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<td>Calcitriol</td>
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<td>A</td>
<td>ND</td>
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<tr>
<td>Teriparatide</td>
<td>A</td>
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<td>ND</td>
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</tbody>
</table>

Grading of recommendations adapted from the updated Royal College of Physicians Clinical Guidelines for Prevention and Treatment of Osteoporosis, although data on teriparatide were not available when this was published. ND, beneficial effect on fracture incidence has not been demonstrated.
women in the US, of whom 8506 were treated with conjugated equine oestrogens and medroxyprogesterone acetate. This study was recently halted, when the Data Monitoring and Safety Committee concluded that this showed that the risks of HRT outweighed the potential benefits. This was the first randomized controlled trial to demonstrate a significant reduction in hip fractures (34%), vertebral fractures (34%) and other osteoporotic fractures (23%) with HRT. There was also a decrease in colorectal cancers of 37%, but these benefits were outweighed by an increase of 29% in cardiovascular events, 41% in strokes and 26% in breast cancer.46

**Tibolone**

Tibolone (Livial) has weak oestrogenic, progestogenic and androgenic actions. A study in 107 osteoporotic women with a mean age of 63 years shows that tibolone increases bone density,47 but there is no information on its effect on fracture incidence. Tibolone is only licensed for the prevention of osteoporosis, but may be useful in the management of established osteoporosis, when women are unwilling or unable to take other treatments.

**Raloxifene**

Raloxifene (Evista) is a selective oestrogen receptor modulator (SERM), which has oestrogen agonist actions on the skeleton and lipid profile, but acts as an oestrogen antagonist on the breast and endometrium. In the MORE (Multiple Outcome of Raloxifene Evaluation) Study of 7705 postmenopausal women aged 31–80 years with osteoporosis, three years of treatment with raloxifene increased lumbar spine and femoral neck bone density by 2–3%, reduced the risk of vertebral fractures by 30–50% and decreased the incidence of breast cancer by 76%.48,49 Raloxifene also reduced the incidence of clinical vertebral fractures in the MORE Study within one year of starting treatment.50 There is no evidence yet that raloxifene decreases the incidence of non-vertebral fractures.48 In contrast to the situation with HRT, raloxifene does not increase the risk of cardiovascular disease, but has been shown to decrease the incidence of cardiac events in patients at high risk of cardiovascular disease.51

**Bisphosphonates**

These are analogues of naturally occurring pyrophosphate, which although poorly absorbed from the bowel, localize preferentially in bone, where they bind to hydroxyapatite crystals. Bisphosphonates decrease bone resorption by reducing osteoclast recruitment and function. As bisphosphonates persist in the skeleton for many months, their duration of action is prolonged beyond the period of administration.

In two studies in women aged up to 75 years with established osteoporosis (involving 66 and 423 women, respectively), cyclical etidronate (Didronel PMO) increased spine bone density by 5% and reduced the incidence of further vertebral fractures by about 60%.52–54 Cyclical etidronate also increased femoral neck bone density by 2% compared with the control group,54 but there are no interventional studies investigating the effect of treatment on hip fracture incidence.

In a three-year randomized controlled trial in 994 women with osteoporosis aged between 45 and 80 years, continuous alendronate (Fosamax) increased bone density by up to 8.8% at the lumbar spine and 5.9% at the femoral neck.55 This study also showed a 48% reduction in the proportion of women with new vertebral fracture. The three-year Fracture Intervention Trial of alendronate recruited 2027 women (aged 55–81 years) with low hip bone density and at least one vertebral fracture. Here alendronate significantly increased bone density in the forearm, spine and femoral neck and decreased the incidence of fractures at these sites by 48%, 55% and 51%, respectively.56 Pooled analysis from 3658 women with osteoporosis enrolled into the Vertebral and Clinical Fracture Arms of the Fracture Intervention Trial showed a significant reduction in clinical vertebral fractures after only 12 months’ treatment with alendronate.57 Another study in 359 women with osteoporosis aged between 60 and 85 years, showed no attenuation of the beneficial effect of alendronate on bone density with advancing age.58

Risedronate (Actonel) has been shown in two large three-year randomized controlled trials involving 2458 and 1226 postmenopausal women with osteoporosis to increase lumbar spine and femoral neck bone density, and to decrease the incidence of vertebral and non-vertebral fractures by 41–49% and 33–39%, respectively.59,60 A significant reduction in vertebral fractures of 65% and 61%, respectively, was observed after the first year of treatment with risedronate.59,60 Another randomized controlled trial in 9331 women showed that risedronate decreased the risk of hip fractures by 40% in those with low bone density and by 60% if vertebral fractures were also present at baseline.61

Bisphosphonates are also effective in preventing bone loss in men and women on long-term oral corticosteroids.62,63 These studies also provide evidence that bisphosphonates may reduce the
incidence of vertebral fractures in patients with corticosteroid-induced osteoporosis. Weekly preparations of alendronate and risedronate are now available, which have effects on BMD and the biochemical markers of bone turnover comparable to their equivalent daily preparations. Many patients appear to find weekly bisphosphonate treatment more convenient than daily administration.

Calcitonin
Calcitonin is a potent antiresorptive agent, with a rapid but short lived effect on osteoclast function. A study in 60 postmenopausal women with vertebral fractures (mean age 68 years) demonstrated that cyclical IM calcitonin (100IU daily) and oral calcium supplements (500mg elemental calcium daily) for 10 days every 4 weeks, decreased the incidence of vertebral fractures by 60% over 2 years, compared with an increase in 35% in a group receiving calcium alone. The Prevent Recurrence Of Osteoporotic Fractures (PROOF) study, in 1255 women with established osteoporosis, showed only marginal benefits on bone density with 5 years of treatment with calcitonin. Although there was a 36% reduction in new vertebral fractures with doses of 200IU calcitonin daily, there was no significant decrease in fractures with 100 or 400IU/day.

Calcium and vitamin D
There is a high prevalence of vitamin D insufficiency in active community-dwelling elderly with osteoporosis. Although calcium and vitamin D supplementation improves bone density and decreases the incidence of hip and non-vertebral fractures in institutionalized elderly women and older men and women living in the community, there is no definite evidence that it is effective in patients with established osteoporosis, or that it decreases the incidence of vertebral fractures.

Calcitriol
Patients with established osteoporosis have lower calcium absorption than do age-matched controls. Malabsorption of calcium in osteoporosis can be overcome by pharmacological doses of vitamin D or by low doses of the vitamin D metabolites, providing a rationale for the use of calcitriol. A three year study comparing calcitriol with calcium supplementation in 622 women with vertebral fractures (mean age 64 years) showed a significantly lower incidence of new vertebral fractures with calcitriol, but this was due to an increase in fracture rate with calcium rather than a reduction with calcitriol. The potential risk of hypercalcaemia and the need for regular monitoring of serum calcium and renal function limit the use of calcitriol in the management of osteoporosis.

Teriparatide
Teriparatide (Forsteo), which became available in the UK in 2003, is the first anabolic treatment for osteoporosis that has been shown to decrease fracture incidence. In a study of 1637 postmenopausal women with osteoporosis, patients were randomized to receive either teriparatide or placebo subcutaneous injections for 2 years, together with calcium and vitamin D. Treatment with teriparatide for a median of 20 months increased BMD by 9–13% more in the lumbar spine and 3–6% more in the femoral neck than the placebo preparation. There was also a 65% reduction in new vertebral fractures, and a 53% reduction in non-vertebral fractures. The anti-fracture efficacy of teriparatide appears to be largely independent of age, initial BMD and the presence or absence of prevalent vertebral fractures.

Treatment of osteoporosis in men
There are few studies examining the treatment of osteoporosis in men. Observational studies in men with idiopathic and secondary osteoporosis suggest that intermittent cyclical etidronate therapy increases bone density at the lumbar by 5–10%, with smaller increases at the hip. It would therefore appear that cyclical etidronate has comparable effects on bone density in men and women, although the effect on fracture incidence in men remains unclear.

In a recent randomized controlled trial in 241 men with osteoporosis aged between 31 and 87 years, 36% of whom were hypogonadal, alendronate increased bone density at the lumbar spine by 5.3% and femoral neck by 2.6%, compared with the control group. Alendronate also decreased the incidence of vertebral fractures and decreased height loss. In a small study in 28 men with osteoporosis, nasal calcitonin 200IU daily for 12 months increased lumbar spine BMD by 4.7% compared with controls, but resulted in no significant change in BMD at the proximal femur. As mentioned earlier, calcium and vitamin D supplementation reduced the incidence of non-vertebral fractures in men and women aged above 65 years living in the community. In a small study of teriparatide in 23 men aged 30–68 years, BMD increased by 13.5% in the lumbar spine and by 2.9% at the femoral neck over 18 months.
osteoporotic men, showed significant increases in lumbar spine and femoral neck after a median of 11 months of treatment with teriparatide.\textsuperscript{78}

**Choice of treatment**

In considering the choice of treatment in the individual patient, a number of factors are important. These include the underlying pathogenesis of bone loss, evidence of efficacy in any particular situation, the cost of treatment, tolerability, patient preference and the potential non-skeletal advantages and disadvantages of treatment (Table 2). It is therefore probably inappropriate to consider HRT in the absence of oestrogen deficiency, or calcium and vitamin D supplementation in women at the menopause who are likely to be vitamin-D-replete.

HRT remains a treatment option for younger (<60 years) postmenopausal women with vertebral fractures, particularly if they have climacteric symptoms. Although the WHI Study suggests that the risks of HRT outweigh the benefits in normal postmenopausal women,\textsuperscript{46} the balance of risks and benefits may be different in women with established osteoporosis, where the risk of fracture is higher. Raloxifene is an appropriate treatment for younger women with vertebral fractures, but should be avoided in women within 1–2 years of the menopause, where it may aggravate hot flushes. Raloxifene may also be less appropriate in older women who are at high risk of hip and other non-vertebral fractures.

Bisphosphonates have complex instructions for administration, which may preclude their use in unsupervised patients with cognitive impairment. Alendronate in particular should be avoided in patients with oesophageal and upper gastrointestinal disorders. As the anti-fracture efficacy of calcitonin is less well documented than that of HRT, raloxifene and bisphosphonates, it should be used in patients unable to tolerate other treatments or in the acute management of painful vertebral fractures.

As calcium and vitamin D supplementation has not been shown to reduce the incidence of vertebral fractures, it should generally not be used alone in the management of patients with vertebral fractures. Nevertheless, calcium and vitamin D may be used as an adjunct to other treatments, particularly in older patients with vitamin D insufficiency and secondary hyperparathyroidism.

Teriparatide is likely to be particularly useful in the management of patients with severe osteoporosis, those who have had a number of previous fractures, and individuals who have failed to respond to antiresorptive treatments.

**Monitoring of treatment**

As between 10–15% of patients fail to respond to treatment, it has been suggested that at least one repeat DXA scan is performed.\textsuperscript{79} This should probably be performed after at least 2 years of treatment, as it takes this long for the response to antiresorptive treatments to exceed the least significant change in BMD. Furthermore, the BMD may appear to fall in the first year of treatment, only to increase over a longer period of observation.\textsuperscript{80}

An alternative approach for the monitoring of response to treatment is to use the biochemical markers of bone turnover, which decrease by up to 50% within 3 months of starting treatment therapy.\textsuperscript{81} Unfortunately, these markers exhibit diurnal and day-to-day variation and are influenced by many other factors. Sample collection may also be inconvenient, requiring timed morning urines, venepuncture without haemolysis and storage at \(-70\,^\circ C\) in some cases. In view of these difficulties, it is currently recommended that the use of bone turnover markers is confined to specialist centres.

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**Table 2** The non-skeletal advantages and disadvantages of the main treatments for osteoporosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT</td>
<td>↓Hot flushes, ↓colon cancer</td>
<td>Bleeds, breast cancer, heart disease, venous thromboembolism</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>↓Breast cancer, no bleed</td>
<td>Hot flushes, venous thromboembolism</td>
</tr>
<tr>
<td>Etidronate</td>
<td>No extra-skeletal benefits</td>
<td>Gastrointestinal side-effects</td>
</tr>
<tr>
<td>Alendronate</td>
<td>No extra-skeletal benefits</td>
<td>Gastrointestinal side-effects ± oesophagitis</td>
</tr>
<tr>
<td>Risedronate</td>
<td>No extra-skeletal benefits</td>
<td>Gastrointestinal side-effects</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Analgesic effect</td>
<td>Nausea, vomiting, diarrhoea</td>
</tr>
<tr>
<td>Calcium and vitamin D</td>
<td>↓Sway, ↓falls</td>
<td>Bowel symptoms</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>↓Improve muscle function</td>
<td>Monitoring for hypercalcaemia</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>No extra-skeletal benefits</td>
<td>Mild hypercalcaemia, nausea, headaches</td>
</tr>
</tbody>
</table>
**Acknowledgements**

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**References**


