BEST PRACTICE

Osteoporosis

S P Tuck, R M Francis

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Osteoporosis is characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk. It is a common condition affecting one in three women and one in 12 men, resulting in substantial morbidity, excess mortality, and health and social services expenditure. It is therefore important to develop strategies to prevent and treat osteoporosis in both men and women. This paper reviews the pathogenesis of primary and secondary osteoporosis, as well as diagnosis, investigation, and management. This should include lifestyle changes to reduce bone loss and decrease the risk of falls, the identification and treatment of secondary causes of bone loss, and specific treatment for osteoporosis. Hormone replacement therapy, raloxifene, bisphosphonates, calcium and vitamin D, calcitonin, and parathyroid hormone have all been shown to improve bone density and decrease the risk of fracture in specific situations. It is important that treatment is tailored to the individual patient, to ensure compliance and optimise the potential benefits.

Osteoporosis is characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk.¹ Approximately, one in three women and one in 12 men will suffer an osteoporotic fracture at some point in their lives.² It has been estimated that 50 000 forearm fractures, 40 000 symptomatic vertebral fractures, and 60 000 hip fractures occur in the UK each year. These cause substantial morbidity, excess mortality, and health and social services expenditure. Up to 20% of all symptomatic vertebral fractures and 30% of hip fractures occur in men.³ Although, the incidence of forearm fracture is lower in males than females, men with forearm fractures are at increased risk of vertebral and hip fracture.⁴ Furthermore, men with distal forearm fracture have recently been shown to have lower bone mineral density (BMD) than age matched control subjects.⁵ It is therefore important to develop strategies to prevent and treat osteoporosis in men and women.

PATHOGENESIS OF OSTEOPOROSIS

Osteoporosis may be either primary (idiopathic) or secondary to one of a number of identifiable causes. In either case the end result is a low BMD. There is a strong inverse relationship between BMD and fracture risk, with a two to threefold

increase in fracture incidence for each standard deviation reduction in BMD.⁶ Other factors affect fracture risk independently of BMD, including bone turnover, trabecular architecture, skeletal geometry, postural instability, and propensity for falling. The BMD at any age is determined by the peak bone mass achieved, the subsequent rate of loss, and age at which that loss begins.

Peak bone mass

It has been estimated that genetic factors account for as much as 80% of the variance in peak bone mass, with the remainder being due to environmental factors, exercise, diet, and age at puberty.⁷⁻⁸ A variety of genes have been associated with BMD including vitamin D receptor, collagen 1 α 1, oestrogen receptor, insulin-like growth factor 1 (IGF-1) and IGF-1 binding protein.⁹ Intrauterine development has also been implicated as a factor in the peak bone mass achieved, as there is an association between birth weight, childhood growth rates, and peak BMD.¹⁰⁻¹¹

Bone loss

Involuntary bone loss starts between the ages of 35 and 45 in both sexes, but this is accelerated in the decade after the menopause in women. Bone loss then continues until the end of life in men and women.¹² Age related bone loss may be influenced by low body mass index, smoking, alcohol consumption, physical inactivity, impaired vitamin D production and metabolism, and secondary hyperparathyroidism.⁷⁻⁸

One of the causes of osteoporosis in women is the loss of sex steroids at the menopause, which leads to increased bone turnover and bone loss. Sex steroids also play an important part in the maintenance of bone density in men, as demonstrated by the rapid bone loss seen after castration.¹³ Up to 20% of men with symptomatic vertebral fractures and 50% of men with hip fractures are hypogonadal.¹⁴ Nevertheless, recent studies show that BMD and the prevalence of vertebral fracture in men are related to serum oestradiol, but not to serum testosterone.¹⁵⁻¹⁶ Furthermore, oestradiol appears to be the dominant sex hormone regulating bone resorption in men.¹⁷ It is therefore possible to produce a unified hypothesis of bone loss in men and women (fig 1). In this model intrauterine development, genetic and environmental factors interact to determine the peak bone mass. Declining sex

See end of article for authors' affiliations

Dr R M Francis,
Musculoskeletal Unit,
Freeman Hospital,
Newcastle upon Tyne,
NE7 7DN, UK;
RMFrancis@compuserve.com

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Figure 1 Unified model of bone loss after Riggs *et al.*⁸⁵

steroid concentrations, which have direct and indirect effects on bone turnover, influence the subsequent rate of bone loss.

Secondary osteoporosis

Osteoporosis can also be secondary to a large number of conditions. These include oral corticosteroids, hypogonadism, alcohol abuse, hyperthyroidism, skeletal metastases, multiple myeloma, and anticonvulsants. Up to 30% of women and 55% of men with symptomatic vertebral crush fractures have an underlying cause of secondary osteoporosis.^{18–19} Secondary osteoporosis may also be a risk factor for hip fracture.^{20–22}

Falls

A number of studies show that the risk of fracture is determined not only by BMD and other skeletal factors, but also non-skeletal factors associated with physical frailty and an increased risk of falls.^{21–23–24} A prospective study from Australia showed that the combination of low BMD and high body sway conferred a greater risk of fracture than either one alone.²⁴ The risk of hip fractures is also increased by conditions predisposing to falls, such as strokes, parkinsonism, dementia, vertigo, alcoholism, and visual impairment.^{25–26}

DIAGNOSIS OF OSTEOPOROSIS

The major end point of osteoporosis is fracture, especially distal forearm, vertebral, and hip. Historically, the diagnosis was made on the basis of a low trauma fracture, defined as a fall from standing height or less. As there is an inverse relationship between BMD and fracture risk methods have been developed to measure BMD using non-invasive techniques. The most widely used of these is dual energy x ray absorptiometry.

The World Health Organisation (WHO) has defined osteoporosis as a BMD 2.5 standard deviations or more below the mean value for young adults (T score <-2.5), whereas the term severe or established osteoporosis indicates that there has also been one or more fragility fractures.²⁷ The WHO defines osteopenia as a BMD T score between -1.0 and -2.5 . Although the WHO definition is useful for the diagnosis of osteoporosis, it does not necessarily represent a threshold for treatment. This is important as 70% of women above the age of 80 years have a T score of less than -2.5 , but only a proportion of these will sustain an osteoporotic fracture.²⁷ On the other hand, guidelines from the Royal College of Physicians suggest that treatment for osteoporosis should be considered in patients with a past history of fragility fracture and documented osteoporosis or osteopenia.²⁸

BMD can be measured at a number of sites, but the total hip is generally believed to be the most reliable for diagnostic purposes,²⁹ as it predicts femoral neck and trochanteric fractures, has the best precision, and there are adequate reference data for white men and women. There is no evidence that

Box 1: Indications for bone density measurement recommended by the Royal College of Physicians, where assessment would influence management³⁰

- Radiographic evidence of osteopenia and/or vertebral deformity.
- Previous fragility fracture.
- Prolonged corticosteroid therapy (prednisolone >7.5 mg daily for six months or more).
- Premature menopause (natural or surgical menopause before the age of 45 years).
- Prolonged secondary amenorrhoea (>1 year).
- Primary hypogonadism.
- Chronic disorders associated with osteoporosis.
- Maternal history of hip fracture.
- Low body mass index (<19 kg/m²).

population based bone density screening is effective at reducing fracture incidence, but BMD measurements have been advocated as part of a selective case finding strategy (box 1).

MANAGEMENT OF OSTEOPOROSIS

This should include the identification and treatment of underlying secondary causes of osteoporosis, lifestyle changes to reduce bone loss, prevention of falls, and specific treatment of osteoporosis. The Royal College of Physicians has published guidelines on the management of osteoporosis based on the grade of evidence available for each intervention.^{28–30} Grade A recommendations are based on randomised controlled trials. Grade B recommendations result from controlled studies without randomisation or epidemiological studies. Grade C evidence is based upon expert committee reports or the clinical experience of recognised authorities. The grading or recommendation takes no account of study size, the magnitude of the treatment effect, or the patient groups studied.

Investigations for secondary osteoporosis

Specific treatment of secondary causes of osteoporosis, such as male hypogonadism, primary hyperparathyroidism, and hyperthyroidism increases bone density by 10%–20%.^{31–33} It is therefore important that these conditions are sought from the medical history, physical examination, and appropriate investigation (table 1). Serum 25-hydroxyvitamin D (25-OHD) and intact parathyroid hormone 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 25-OHD and parathyroid hormone measurements are probably unnecessary if calcium and vitamin D supplementation is planned, as the results are unlikely to influence management. In individuals with unexplained osteoporosis and a history or investigations suggestive of malabsorption, tests for antiendomysial antibodies should be performed to exclude coeliac disease.

Lifestyle changes to reduce bone loss

All patients with osteoporosis and fractures should be given advice on lifestyle measures to decrease bone loss. These include eating a balanced diet rich in calcium, moderating tobacco and alcohol consumption, maintaining regular physical activity, and exposure to sunlight. Only exercise has grade A evidence for a beneficial effect on BMD, but there is grade B evidence that increasing dietary calcium intake and reducing tobacco consumption have beneficial effects on BMD and fracture risk (table 2).

Prevention of falls

Any patient who has a history of fractures and recurrent falls should undergo a falls assessment, to identify and modify intrinsic and extrinsic risk factors for falling. Intrinsic factors include poor vision, musculoskeletal and neurological disease

Table 1 Investigations for secondary osteoporosis

Investigation	Finding	Possible cause
Full blood count	Anaemia Macrocytosis	Neoplasia or malabsorption Alcohol abuse or malabsorption
Erythrocyte sedimentation rate	Raised erythrocyte sedimentation rate	Neoplasia
Biochemical profile	Hypercalcaemia Abnormal liver function Persistently high alkaline phosphatase	Hyperparathyroidism or neoplasia Alcohol abuse or liver disease Skeletal metastases or hyperparathyroidism
Thyroid function tests	Suppressed thyroid stimulating hormone; high thyroxine or triiodothyronine	Hyperthyroidism
Serum and urine immunoelectrophoresis (vertebral fractures)	Paraprotein band	Myeloma
Testosterone, sex hormone binding globulin, luteinising hormone, follicle stimulating hormone (in men)	Low testosterone or free testosterone index with abnormal gonadotrophins	Hypogonadism
Prostate specific antigen (in men)	Markedly raised levels	Skeletal metastases from prostate cancer

Table 2 The effect of lifestyle measures on bone density and the incidence of vertebral and hip fractures in the prevention of osteoporosis. Grading of recommendations adapted from Royal College of Physicians clinical guidelines for prevention and treatment of osteoporosis³⁰

	Bone density	Vertebral fractures	Hip fractures
Exercise	A	ND	B
Dietary calcium	B	B	B
↓ Smoking	B	B	B
↓ Alcohol	C	C	B

ND indicates that a beneficial effect on fracture incidence has not been demonstrated.

and medications, whereas extrinsic or environmental factors include trailing wires, loose carpets, and ill fitting footwear.

Evidence that falls assessment is worthwhile is provided by a randomised controlled trial in 301 elderly patients over 70 years, each with an apparent risk factor for falling.³⁴ Geriatric assessment with modification of risk factors reduced the rate of falls to 35% over 12 months, compared with 47% in those receiving the usual health care and social input. A more recent British study used similar interventions to evaluate their effectiveness in 397 community dwelling subjects over 65 years who had attended the accident and emergency department with a fall.³⁵ There was a significant 61% reduction in the risk of falls among the intervention group compared with the control group. However, neither study was sufficiently powered to detect a reduction in fracture incidence.

If falls cannot be prevented then the force of impact may be reduced by the use of hip protectors, which are incorporated into specially designed underwear. A Danish study of 665 elderly nursing home residents demonstrated over 50% reduction in hip fracture with hip protectors over 12 months.³⁶ Unfortunately, these garments are rather bulky and uncomfortable to wear and many older people find them unacceptable.³⁷ A systematic review of seven trials has recently been published, involving 3553 elderly people living in nursing homes, residential care, or supported at home.³⁸ This showed that 2.2%

of the participants allocated to hip protectors sustained a hip fracture, compared with 6.2% in the control group. Compliance was poor, especially in the long term. Furthermore, due to the large number of patients allocated by cluster randomisation, the reduction in fracture with hip protectors was not statistically significant.

Treatment of osteoporosis

Treatments for osteoporosis can be divided into antiresorptive and anabolic agents. Antiresorptive agents decrease bone resorption and, because of the transient uncoupling of bone turnover, result in a modest increase in BMD of between 5% and 10%, predominantly in the first year of treatment. In contrast, anabolic agents can increase BMD by up to 50%.³⁹

In studies of the treatment of osteoporosis, oestrogen, raloxifene, bisphosphonates, calcitonin, calcium, and vitamin D and parathyroid hormone have all been shown in randomised controlled trials to have a beneficial effect on BMD. The effect of these treatments on fracture incidence is also shown in table 3.

Hormone replacement therapy (HRT)

A number of small controlled trials show that HRT prevents the rapid bone loss that occurs at the menopause.³⁰ A recent five

Table 3 The effect of drug treatment on the incidence of vertebral, non-vertebral, and hip fractures. Grading of recommendations adapted from the updated Royal College of Physicians clinical guidelines for prevention and treatment of osteoporosis²⁸

	BMD	Spine	Non-vertebral	Hip
Oestrogen	A	A	A	B
Raloxifene	A	A	ND	ND
Etidronate	A	A	B	B
Alendronate	A	A	A	A
Risedronate	A	A	A	A
Calcitonin	A	A	B	B
Calcium + vitamin D	A	ND	A	A
Parathyroid hormone	A	A	A	ND

ND indicates that a beneficial effect on fracture incidence has not been demonstrated.

year randomised controlled trial in 464 postmenopausal women shows that HRT reduces the risk of non-vertebral fractures by 71%.⁴⁰ Unfortunately, the benefit of previous long term HRT on bone density decreases progressively once treatment is stopped and may be lost completely by the age of 75 years.⁴¹

An alternative approach is to use HRT in older women or those with established osteoporosis, where the reduction in fracture risk may be apparent earlier. Small studies in older women with established osteoporosis (subject number 40 and 78, with mean age 65 and 68 years respectively) show that HRT increases spine bone density by about 5%.^{42, 43} One of these studies also shows a reduction in vertebral fracture incidence of 60%.⁴³

Meta-analyses have been performed of 13 randomised controlled trials of the effects of HRT on vertebral fractures⁴⁴ and 22 randomised controlled trials on non-vertebral fractures.⁴⁵ Overall, there was a 33% reduction in vertebral fracture and a 27% reduction 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.

Raloxifene

Raloxifene (Evista) is a selective oestrogen receptor modulator, with agonist actions on the skeleton, but antagonistic effects on the breast and endometrium. In the MORE (Multiple Outcomes of Raloxifene Evaluation) study of 7705 postmenopausal women aged 31–80 years with osteoporosis, raloxifene increased lumbar spine and femoral neck BMD by 2%–3%, reduced the risk of vertebral fractures by 30%–50%, and decreased the incidence of breast cancer.^{46, 47} There is no evidence that raloxifene decreases the incidence of non-vertebral fractures.

Bisphosphonates

These are analogues of naturally occurring pyrophosphate, which although poorly absorbed from the bowel, localise 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.

Two studies of cyclical etidronate (Didronel PMO) in women aged up to 75 years with established osteoporosis (involving 66 and 423 women respectively), showed an increase in spine bone density of 5% and a reduction in the incidence of further vertebral fractures of about 60%.^{48–50} There are no interventional studies investigating the effect of etidronate on hip fracture incidence, but epidemiological data suggest that it decreases hip fractures by 44% in women over the age of 76 years.⁵¹

In a randomised controlled trial in 994 women with osteoporosis aged between 45 and 80 years, alendronate (Fosamax) increased bone density by up to 8.8% at the lumbar spine and 5.9% at the femoral neck.⁵² This study also showed a 48% reduction in the proportion of women with new vertebral fractures. The Fracture Intervention Trial in 2027 women (aged 55–81 years) with low hip bone density and at least one vertebral fracture, showed that alendronate significantly increased forearm, spine, and femoral neck BMD and decreased the incidence of fractures at these sites by about 50%.⁵³ In a further 4432 women with low hip bone density but no prevalent vertebral fracture, taking part in the clinical fracture arm of the Fracture Intervention Trial, alendronate decreased the incidence of vertebral deformation by 44%.⁵⁴ This second part of the Fracture Intervention Trial showed no overall reduction in clinical fractures with alendronate, although there was a significant reduction in women with baseline femoral neck BMD T score <–2.5.⁵⁴ Alendronate is now available as daily 10 mg and weekly 70 mg preparations, which are equally effective in decreasing bone turnover and increasing BMD.⁵⁵

Risedronate (Actonel) has been shown to be effective in the management of postmenopausal osteoporosis.^{56, 57} The Vertebral Efficacy with Risedronate Therapy Study Group in America⁵⁶ and Europe and Australia⁵⁷ showed a significant increase in BMD compared with placebo of 5%–6% at the lumbar spine, 1.6%–3.1% at the femoral neck, and 3.3%–6.4% at the femoral trochanter over three years.^{56, 57} There was also a significant 41%–49% reduction in the incidence of new vertebral fractures and 33%–39% decrease in non-vertebral fractures in women treated with risedronate compared with placebo.^{56, 57}

McClung *et al* studied 5445 women age 70–79 years with low BMD and 3886 women over 80 years with at least one clinical risk fracture for hip fracture, who were randomised to receive either risedronate or placebo.⁵⁸ The incidence of hip fracture in women with low BMD taking risedronate (1.9%) was 40% lower than in those on placebo (3.2%). In contrast, there was no significant reduction in fracture risk with risedronate in the older women recruited on the basis of a clinical risk factor for hip fracture. These data, together with those from the Fracture Intervention Trial of alendronate,⁵⁴ suggest that BMD measurements are useful in identifying patients who would benefit from bisphosphonate treatment.

Calcium and vitamin D

Calcium supplementation may prevent bone loss in older men and women,⁵⁹ but there is no convincing evidence that it decreases the risk of fracture in patients with osteoporosis. The results of vitamin D supplementation studies are also inconsistent.^{60, 61} There is therefore little evidence to support the use of either calcium or vitamin D alone. In contrast, combined calcium and vitamin D supplementation may be useful in the management of frail elderly patients with osteoporosis, as vitamin D deficiency and secondary hyperparathyroidism are common in this situation. A French study of 3270 women (mean age 84 years) living in nursing homes and apartment blocks for the elderly used 800 IU of vitamin D₃ and 1.2 g of elemental calcium daily. This regimen decreased parathyroid hormone levels, increased femoral neck BMD, and reduced the risk of hip fracture by 27%.^{62, 63} A smaller study of 389 elderly men and women (mean age of 70 years) living at home demonstrated that 700 IU of vitamin D₃ and 500 mg of elemental calcium daily had a modest beneficial effect on BMD and decreased the incidence of non-vertebral fracture by 54%.⁶⁴

Calcitonin

Calcitonin is a potent antiresorptive agent, with a rapid but short lived effect on osteoclast function. Early studies in postmenopausal women with osteoporosis showed small increases in BMD and a reduction in vertebral fractures with calcitonin.^{65, 66} The PROOF (Prevent Recurrence of Osteoporotic Fractures) Study investigated the effects of five years' intranasal calcitonin in 1255 women with osteoporosis. Treatment with calcitonin resulted in a modest increase in BMD. Although the 200 IU dose significantly reduced the risk of new vertebral fractures by 33%, the decrease in fractures with 100 and 400 IU was not statistically significant.⁶⁷ A recent review of 14 trials of parenteral and intranasal calcitonin involving a total of 1309 men and women showed a 57% reduction in fracture compared with placebo (55% for vertebral and 66% for non-vertebral).⁶⁸

Parenteral calcitonin (Calsynar) is expensive (table 4) and the cheaper intranasal form (Miacalcic) has only recently become available in the UK, as a result of which calcitonin has only rarely been used for long term treatment. Nevertheless, short courses of calcitonin are useful in the management of the pain associated with acute osteoporotic fractures. In a randomised controlled trial of 100 men and women with acute vertebral crush fractures, 200 IU daily of nasal salmon calcitonin for 28 days decreased pain and resulted in earlier mobilisation compared with placebo.⁶⁹

Table 4 The annual cost of drug treatment for osteoporosis. Data derived from the *British National Formulary*, March 2002. The annual cost of Calsynar is based on the dose of 100 IU daily for 10 days every four weeks, as used by Rico *et al*⁶⁶

Drug	Cost (£)
Premarin 0.625 mg	38.72
Prempak C	70.74
Premique	108.06
Evista	257.57
Didronel PMO	162.22
Fosamax	301.39
Risedronate	284.66
Calsynar	1032.44
Miacalcic	547.24
Calcichew D ₃ Forte	69.35

Parathyroid hormone

Parathyroid hormone is released from the parathyroid glands and its physiological role is to maintain normal circulating calcium levels. Parathyroid hormone stimulates both bone formation and resorption, leading to increased or decreased BMD, depending on the mode of administration.⁷⁰ Continuous infusion causes persistent elevation of parathyroid hormone and results in greater resorption than formation, leading to bone loss. In contrast, daily injections lead to only transient peaks in serum parathyroid hormone, resulting in greater bone formation and an increase in BMD.

Early studies using human parathyroid hormone (1–34) were undertaken in the 1970s and showed large increases in BMD.⁷¹ Large trials have only become possible with the development of recombinant human parathyroid hormone (1–34): rhPTH (1–34). In a study of 1637 postmenopausal women with osteoporosis, patients were randomised to receive either rhPTH (1–34) or placebo subcutaneous injections for two years, together with calcium and vitamin D.⁷² Treatment with rhPTH (1–34) 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 drug is currently not licensed for the treatment of osteoporosis in the UK.

Treatment of osteoporosis in men

There are few studies examining the treatment of osteoporosis in men. However, there are data to support the use of bisphosphonates, calcium and vitamin D, testosterone, and rhPTH (1–34). Calcitriol has also been studied, but has not been found to have any effect on BMD or fracture incidence.⁷³

Observational studies in men with idiopathic and secondary osteoporosis suggest that intermittent cyclical etidronate therapy increases BMD at the lumbar spine by 5%–10%, with smaller increases at the hip.⁷⁴ It would appear that cyclical etidronate has comparable effects on bone density in men and women, but the effect on fracture incidence in men remains unclear.

A recent randomised controlled trial examined the effect of 10 mg alendronate (Fosamax) daily in 241 men with osteoporosis aged between 31 and 87 years, 37% of whom were hypogonadal. It showed a mean increase in BMD of 7.1% at the lumbar spine and 2.5% at the femoral neck, compared with changes in the control group of 1.8% and –0.1% respectively.⁷⁵ There were similar increases in BMD in eugonadal and hypogonadal men treated with alendronate. The incidence of new radiological vertebral fractures was also significantly reduced compared with placebo. Similar results were reported in another randomised controlled trial in 134 men with primary osteoporosis.⁷⁶ The daily preparation of alendronate has now been licensed in the UK for treatment of osteoporosis in men.

As mentioned earlier, calcium and vitamin D supplementation has been shown to increase BMD and decrease non-vertebral fractures in men and women aged above 65 years.⁶⁴ Subanalysis of the results for the men in this study showed a significant improvement in BMD with calcium and vitamin D, but no reduction in fractures was demonstrated.

In addition to improving bone density in men with hypogonadal osteoporosis,³¹ testosterone may increase spine bone density in eugonadal men with vertebral fractures. An uncontrolled study of testosterone treatment in 21 eugonadal men with vertebral osteoporosis showed a significant increase in spine bone density of 5% in six months, although no change in hip bone density was seen.⁷⁷ A randomised controlled cross-over study in 15 men on long term corticosteroid treatment showed an increase in spine bone density of 5% after 12 months' treatment with testosterone, while no change was observed during the control period of 12 months' observation.⁷⁸

Another anabolic agent which may be useful in men with osteoporosis is human parathyroid hormone. In a small randomised controlled trial of rhPTH (1–34) 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.⁷⁹ Preliminary results of another study in 437 osteoporotic men, showed an increase in BMD and a 50% reduction in new vertebral fractures with rhPTH (1–34).⁸⁰

Choice of treatment in the individual patient

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, and patient preference. 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.

A number of factors may influence compliance and tolerability. Conventional HRT causes regular vaginal bleeding in 90% of women. Although continuous combined oestrogen/progestogen preparations offer the prospect of the benefits of HRT without the need for regular bleeds, these may cause spotting in the early months of treatment. The use of HRT is also associated with an increased risk of venous thromboembolism. HRT is likely to cause breast tenderness in older women, who may also be concerned about the risk of breast cancer with prolonged HRT.

An alternative to HRT is raloxifene, but this may aggravate hot flushes, particularly in women close to the menopause. Although raloxifene decreases the incidence of breast cancer, it is associated with an increased risk of venous thromboembolism.

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.

In addition to improving BMD, calcium and vitamin D may decrease body sway and reduce the risk of falls in older people. Calcium and vitamin D supplements are generally well tolerated, but they may cause gastrointestinal symptoms.

The annual cost of treatment for osteoporosis varies widely (table 4). It is therefore appropriate to reserve the more expensive treatments for patients with a high risk of fracture; as indicated by low BMD and/or past history of osteoporotic fractures. Intranasal calcitonin could be reserved for those patients who have failed other treatments either due to lack of response or intolerance.

A schematic representation of the management of osteoporosis is provided in fig 2. All individuals should be advised on a good diet, regular exercise, discontinuing smoking, moderating alcohol consumption, and maintaining regular exposure to sunlight. In younger postmenopausal women with

Figure 2 Schematic representation of the management of osteoporosis.

osteoporosis, the treatment choice is HRT or raloxifene. In women who are unable or unwilling to take HRT or in older patients, bisphosphonates are probably most appropriate. In the frail elderly, calcium and vitamin D supplementation would appear to be the treatment of choice. In patients with a past history of recurrent falls, measures should be taken to reduce the incidence of falls. Consideration should also be given to the use of external hip protectors.

A significant proportion of men with osteoporosis have underlying secondary causes, which should be sought and treated when possible. In terms of specific treatments then the first choice must be a bisphosphonate, with the best evidence currently being for alendronate.

Monitoring of treatment

Approximately 10%–15% of patients fail to respond to treatment.⁸¹ Therefore, at least one repeat dual energy x ray absorptiometry scan is recommended to confirm treatment response. This is usually best done after two years of treatment as it takes this long for response to antiresorptives to exceed the least significant change in BMD. Furthermore, the BMD may fall in the first year of treatment only to increase in the second year: a phenomenon known as regression to the mean.⁸² The most sensitive site for monitoring is the lumbar spine.⁸¹ This is because it contains a high proportion of trabecular bone, which responds rapidly to treatment and can be scanned with reasonable accuracy (precision approximately 1%).

The use of BMD to assess response has disadvantages. It takes two years before lack of response is noted and the use of the spine can be affected by degenerative changes, especially in patients over 65. An alternative is to use bone turnover markers, which have a maximum suppression in the order of 50% within three months of starting therapy.⁸³ This would allow earlier identification of non-responders. Bone turnover markers exhibit diurnal and day to day variation and are influenced by many other factors.⁸⁴ Sample collection may also be inconvenient, requiring timed morning urines, venepuncture without haemolysis, and storage at -70°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 and research studies.⁸⁴

CONCLUSIONS

This article reviews the evidence of the efficacy of the different treatments available for patients with osteoporosis. The increasing range of options allows treatment to be better matched to the individual situation. Where necessary, alternatives can be substituted if the patient proves intolerant of or unresponsive to the first choice. There is also growing evidence that a number of treatments are effective in men with osteoporosis. The advent of new anabolic therapies and their use in combination with antiresorptive agents, raises the possibility of reversing low BMD in osteoporosis. Ideally, patients at high risk of fracture should be identified early and

treated by a combination of lifestyle changes, correction of secondary causes of osteoporosis, and specific treatments to improve bone density and decrease fracture risk.

ADDENDUM

A recent large scale study of the use of HRT in 16 608 postmenopausal women has been published (*JAMA* 2002;**288**:321–33). This demonstrated 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, but these benefits were outweighed by an increase in cardiovascular events, strokes, pulmonary emboli, and breast cancers. There was, however, no overall increase in mortality. The risks were increased by longer duration of use. Also many of the patients were elderly and had pre-existing cardiovascular and thrombotic risk factors.

Authors' affiliations

S P Tuck, Musculoskeletal Unit, Freeman Hospital, Newcastle upon Tyne
R M Francis, University of Newcastle upon Tyne and Freeman Hospital, Newcastle upon Tyne.

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