REVIEW

Current and potential future drug treatments for osteoporosis

Sanjeev Patel

Osteoporosis is the most common metabolic bone disease in the developed world and is increasingly recognised as an important public health problem.¹ There is marked worldwide variation in its incidence. It is predicted that the incidence of hip fractures caused by osteoporosis will increase, particularly in developing countries.² The human burden of osteoporosis is considerable, with increased morbidity and mortality, especially following osteoporotic hip fractures.¹ The current financial burden is substantial, with estimated yearly costs of £750 million in the UK,¹ \$10 billion in the USA, and FF3.7 billion in France.³ The ability to measure bone mineral density and thereby monitor response to intervention has been vital in the development of pharmacological treatments. In this review I aim to discuss current issues surrounding the use of established and newly licensed drugs, as well as examining agents that are in the early stages of development.

Background

The cycle of bone resorption by osteoclasts followed by bone formation by osteoblasts is essential for modelling (resorption followed by formation at a distant skeletal site resulting in changes in architecture and growth), and remodelling (resorption followed by formation at the same skeleton site). In the first 20-25 years of life, bone mineral density increases with age until peak density is achieved. It then remains relatively constant until, in women, the menopause is reached, after which there is a phase of rapid oestrogen dependent bone loss for 5-10 years, and then a less rapid phase of age related bone loss. Prospective studies suggest that the latter may accelerate in the very old, particularly at the hip.⁴ In men there is no rapid phase of bone loss. Whether bone mineral density will decrease below the so called fracture threshold in later life is dependent on the absolute magnitude of peak density and subsequent rate of bone loss. Bone mineral density is highly correlated with bone strength (75-80% of variance in bone strength is explained by bone density)⁵ and at a given skeletal site it predicts future fracture risk. For every standard deviation by which bone mineral density is below peak bone mass, frac-

ture risk increases by a factor of 1.5 to 3.0.⁶ Other determinants of osteoporotic fracture are shown in table 1.

Drugs active on bone can be simplistically classified as those that inhibit bone resorption or those that stimulate bone formation (table 2). The effects of these drugs on bone mineral density are summarised in fig 1. Drugs that stimulate bone formation lead to a direct increase in bone mineral density, whereas those that inhibit bone resorption result in limited increases in bone mineral density by uncoupling bone turnover and allowing formation to continue in excess of resorption. This leads to an increase in bone mineral density due to filling in of the remodelling space (the remodelling transient).⁷ It has been suggested that beyond this increase (5-10%), there is little potential for further increases in density, giving rise to the term "the remodelling barrier".⁸ However, more recent evidence suggests that this may not be the case, and that bone mineral density may continue to increase beyond the first year of treatment with antiresorptive drugs.⁹ In addition, decreases in fractures do occur, partly due to increases in bone mineral density leading to increased bone strength as well as to a lower rate of trabecular perforation associated with reduced bone turnover.

Interventions aimed at decreasing fractures by influencing bone mineral density can either prevent low mineral density (by maximising peak density and decreasing rate of loss of bone in later life), or they can treat established low mineral density (osteoporosis). There are few data on pharmacological interventions capable of influencing peak bone mineral density, although prospective cohort studies are under way examining several variables including calcium supplements.^{10 11} In established osteoporosis, drugs that increase bone formation and mass are required; in practice, because of a

Table 1 Determinants of osteoporotic fracture

Bone mineral density
Gait and propensity to fall
Geometry (especially at the hip)
Bone dimensions
Bone "quality"
Bone architecture
? Trochanteric fat (padding)

Osteoporosis Unit,
Department of
Rheumatology, St
George's Hospital,
London SW17 0QT,
United Kingdom
S Patel

Correspondence to:
Dr Sanjeev Patel.

Accepted for publication
28 June 1996

Table 2 Current and potential future drug treatments for osteoporosis

Drugs which suppress bone resorption
 Hormone replacement† (oestrogens, progestagens, tibolone, tamoxifen and derivatives)
 Anabolic steroids†
 Bisphosphonates†
 Calcitonin†
 Calcium and vitamin D†
 Activated vitamin D†
 Ipriflavone†
 Integrin antagonists*
 Proton pump inhibitors*
 Amylin*

Drugs which simulate bone formation
 Fluoride†
 Bone growth factors
 Growth hormone
 Parathyroid hormone
 Parathyroid hormone receptor agonists (theoretical)*
 Vitamin D analogues*
 Zeolite A*
 Strontium salts

* Not tested on humans.

† Licenced in some countries.

Figure 1 Influence of various treatments on bone mass (see text for details).

lack of such agents (apart from fluoride) bone resorption inhibitors are used. However, it should be noted that increasing trabecular thickness by stimulating bone formation or inhibiting bone resorption does not reverse the

Figure 2 Schematic relations between bone mineral density, trabecular connectivity, and fracture risk. As bone mineral density decreases from normal (A) to moderate osteoporosis (B), where there is some disruption in trabecular connectivity, fracture risk increases. Treatment at B will restore bone mineral density and reduce fracture risk back to A. However, in severe osteoporosis (C), where bone mineral density is very low and trabecular connectivity is disrupted, treatment increases trabecular thickness and bone mineral density (D), but since trabecular connectivity is disrupted fracture risk is not substantially improved.

loss of trabecular connectivity that is seen in severe osteoporosis (fig 2).

Bone resorption inhibitors

HORMONE REPLACEMENT THERAPY (HRT)

Oestrogen replacement attenuates bone loss that occurs after the menopause and reduces osteoporotic fractures.⁵ Despite this, and a reduction in coronary heart disease and strokes, compliance is poor.¹² Reasons for this are multiple and include the need for monthly withdrawal bleeds (at least for non-continuous combined HRT) to prevent uterine cancer, anxiety regarding weight gain, breast tenderness, and more importantly concern regarding the increased risk of breast cancer. Previous meta-analyses have suggested a relative risk of 1.0 (no increased risk) to as high as 1.6 for breast cancer with HRT.¹² Recent studies do not seem to clarify this issue, showing either no increase in risk,¹³ to an increase in risk with longer duration of use and age.¹⁴ These differing results could be due to numerous factors including methodological design and differing HRT regimens studied in different populations.

Thus whether HRT is suitable for an individual is dependent on the aim of treatment and what is in practice a difficult risk-benefit analysis, with the patient's own views and preferences playing a substantial role. That is, treatment benefits such as relief of menopausal symptoms and reduction in cardiovascular disease and osteoporotic fractures have to be weighed against side effects, past medical and family history of cardiovascular disease, osteoporosis, and breast cancer, as well as other risk factors and patient preferences. For the female population, although more older women die of heart disease than of breast carcinoma, the beneficial effect of HRT on cardiovascular mortality may be negated by increased deaths from breast cancer. Definitive data may be provided by a long term prospective study examining the net health effects of HRT that is being carried out in the USA under the auspices of the Women's Health Initiative.

The timing and duration of HRT is also controversial. Maximum protection against osteoporosis would be provided by taking life-long HRT from the menopause, although this would have to be weighed against long term side effects, as discussed above. An alternative is to start HRT after a fracture, thus allowing easy identification of patients at risk who may comply with treatment. However, preventable fractures would occur with this strategy and there may be limited response due to extensive disruption of bone architecture. A third possibility is to start HRT many years after the menopause and to continue indefinitely thereafter. For example, starting HRT at the age of 70-75 years may be adequate intervention to reduce hip fracture rates, since the median age of hip fracture is 80 years and bone density at this site continues to decrease, although compliance in this age group is likely to be low and many individuals would have missed potential cardiovascular protection from HRT.

Obviously these strategies are not mutually exclusive and women of all ages can be offered HRT for the prevention and treatment of osteoporosis with appropriate counselling.

Various non-bleed HRT regimens are now available. These include continuous combined HRT preparations (combinations of oestrogens and progestogens) as well as tibolone.

Tibolone

Tibolone, a synthetic steroid with weak oestrogenic, androgenic, and progestogenic properties, is licensed for the treatment of menopausal symptoms. It does not stimulate the endometrium or cause significant withdrawal bleeding.^{15,16} Two studies have shown that tibolone prevents rapid bone loss following the menopause. In one, 100 perimenopausal women were treated in a two year prospective double blind study comparing tibolone 2.5 mg per day with placebo.¹⁷ Metacarpal bone density showed no net loss in the tibolone group, whereas the placebo group decreased by 3.6% per year, which was a significant difference. More recently, a non-randomised two year study of 100 postmenopausal women showed that tibolone 2.5 mg per day increased bone mass by 2.5% at the lumbar spine and 3.5% at the femoral neck, compared to losses of 2.9% and 3.7% respectively for the placebo group ($P < 0.001$).¹⁸ Preliminary results from a further two year follow up (four years in total) suggests that tibolone continues to maintain bone mineral density.¹⁹ Patients with established osteoporosis have also been shown to benefit. In a small study of 38 women treated for two years, bone density at the lumbar spine increased by 4% per year compared to placebo ($P < 0.01$).²⁰ Recent studies appear to support these findings.^{21,22} However, fracture data are not available and the effects of tibolone on breast cancer rates and cardiovascular mortality are unknown. Nonetheless when results of further studies examining bone mineral density and fractures are available, tibolone may be a viable alternative to more standard HRT preparations.

Tissue specific oestrogens

In view of the difficulties with oestrogen supplementation described above, there is increasing interest in developing compounds that have tissue specific oestrogen activity. Ideally such a compound should preserve bone mineral density and decrease coronary heart disease without adversely affecting breast or uterine tissue. Potential candidates include tamoxifen, raloxifene, and droloxifene. Their

actions, as well as those of oestrogens and tibolone, are summarised in table 3.

Tamoxifen is a non-steroidal synthetic compound that has oestrogen agonist/antagonist effects, depending on the tissue and species.²³ The drug is widely used for the treatment of breast cancer and is undergoing primary prevention studies in high risk women. It preserves bone mass in animal models, but interpretation of its effects in women with breast cancer is confounded because of obvious or occult bony metastases.²⁴ Small but statistically significant increases in bone mineral density at the lumbar spine were found in tamoxifen treated patients (0.61% per year) compared to placebo (loss of 1% per year) in a recent two year placebo controlled study of 140 postmenopausal women with axillary node negative breast cancer.²⁴ This marginal beneficial effect of tamoxifen was confirmed in a two year randomised placebo controlled study of 65 postmenopausal women without breast cancer given 20 mg per day of tamoxifen or placebo.²⁵ Mean lumbar spine bone mineral density increased by 1.4% in the tamoxifen group over the period of the study compared to a loss of 0.7% with placebo. In another recent three year study of tamoxifen in women without breast cancer, bone mineral density in tamoxifen treated postmenopausal women increased at the lumbar spine (by 1.17% per year) and total hip region (by 1.71% per year) compared to placebo ($P < 0.005$).²⁶ Premenopausal women were also treated in this study, with contrasting results, in that the premenopausal tamoxifen group actually lost bone by 1.44% per year at the lumbar spine compared to placebo ($P < 0.001$). Statistically non-significant bone loss occurred at the hip. The authors comment that this discrepancy between premenopausal and postmenopausal women suggests that in those with premenopausal levels of oestrogen, the net effect of tamoxifen is antioestrogenic to the skeleton.

Reductions in rates of myocardial infarction in women with breast cancer treated with tamoxifen have also been noted,²⁷ but given that bone mineral density changes are minimal, that uterine stimulation occurs with treatment,²⁸ and that menopausal symptoms are not ameliorated, it is doubtful whether tamoxifen will ever be used in the treatment of osteoporosis.

Raloxifene, a benzothiopyrene derivative, has antioestrogenic activity on uterine and breast cancer cells but an oestrogenic effect on the skeleton.^{29,30} In ovariectomised rats, raloxifene is as effective as oestrogen in maintaining trabecular bone volume³¹ and bone strength and density.^{32,33} Uterine hypertrophy did not occur with raloxifene, and reductions in cholesterol levels were found, similar to the action of oestrogen.^{30,31,34}

Droloxifene, another mixed oestrogen antagonist/agonist, is under clinical development for treatment of advanced breast carcinoma. Like raloxifene, droloxifene has an oestrogenic effect on bone but an antioestrogenic effect on the uterus. Droloxifene prevents

Table 3 Actions of oestrogens and mixed oestrogen agonists/antagonists

Agent	Skeletal benefits?	Cardiovascular benefits?	Alleviates menopausal symptoms?	Increased breast cancer risk?	Withdrawal bleeding/Increases uterine cancer?
Oestrogens	Yes	Yes	Yes	Probably	Yes
Tibolone	Yes	↓ cholesterol	Yes	?	No
Tamoxifen	Yes	Yes	No	No	Yes
Raloxifene	Yes	↓ cholesterol	?	No	No
Droloxifene	Yes	↓ cholesterol	?	No	No

bone loss in ovariectomised rats,^{35 36} reduces serum cholesterol,³⁶ and has no effect on uterine weight.^{35 36}

The results of clinical studies currently in progress will be vital in assessing the potential of raloxifene and droloxifene as alternatives to standard oestrogen replacement regimens.

Progestogens

There is uncertainty about the effects of progestogens on bone metabolism, partly due to the fact that different progestogens have differing effects. Thus C19 derivatives such as norethisterone acetate have significant oestrogenic and androgenic properties compared to C21 derivatives such as medroxyprogesterone and dydrogesterone. Biochemical markers suggest that both derivatives inhibit bone resorption, although the data for C21 derivatives are limited. Norethisterone was shown to increase distal forearm bone mineral density in 44 postmenopausal women, in whom the hormone was well tolerated.³⁷ In addition, continuous combined oestrogen/norethisterone may result in a larger increment of bone mineral density compared to continuous oestrogen with sequential norethisterone (taken for 10 days of a cycle).³⁸ However, norethisterone used alone has detrimental effects on serum lipids,³⁹ although the situation is less clear when combined with an oestrogen.⁴⁰ Medroxyprogesterone given alone does not seem to protect against bone loss in postmenopausal women,⁴¹ although a recent study suggests that when given with oestrogen it enhances the increase in vertebral bone mineral density seen with oestrogen alone.⁴² Currently it seems that progestogens alone are not suitable in osteoporosis for the majority of individuals, although continuous combined oestrogen/progestogen preparations may have an increasing role since withdrawal bleeding is minimal in the long term, with significant increases in bone mineral density.⁴³

BISPHOSPHONATES

Although first synthesised almost a 100 years ago, and used in treating Paget's disease for 20–25 years, the bisphosphonates have only been shown to be of potential benefit in osteoporosis in the last decade. Table 4 shows some of the bisphosphonates that are licensed or undergoing investigation for the treatment

of osteoporosis. The chemical structure and pharmacology of bisphosphonates have been reviewed recently.⁴⁴

Etidronate

The two landmark studies of bisphosphonates in osteoporosis treatment were those of cyclical etidronate in the treatment of established vertebral osteoporosis (defined by the presence of one but not more than four vertebral fractures) by Watts *et al.*,⁴⁵ who studied 429 women over two years, and Storm *et al.*,⁴⁶ who studied 66 women over three years. Both were much criticised on numerous grounds including lack of adequate power to demonstrate vertebral fracture reduction (the primary end point was change in bone mineral density) as well as the semiquantitative assessment of vertebral deformity in both studies, rather than actual measurement, and the 40% drop out rate in the smaller study by Storm *et al.*⁴⁷ A two year extension of the original Watts study (with 357 patients continuing double blind treatment in year 3 and 277 patients receiving open label treatment in year 4) has been reported.⁴⁸ Gains in bone mineral density with cyclical etidronate reported from the original study persisted after the third year, but the anticipated improvement in vertebral fracture incidence in the first two years of the study did not achieve overall statistical significance in the third year, except when posthoc analysis was carried out in women with bone mineral density below the 50th centile at baseline. Despite these criticisms, cyclical etidronate has been licensed in several countries, although not in the United States. Data for non-vertebral fracture reduction are lacking although increases in bone mineral density at the hip have been found.⁴⁸ Since these studies, preliminary reports suggest that cyclical etidronate can reduce early postmenopausal bone loss⁴⁹ and be potentially useful in preventing steroid associated osteoporosis.⁵⁰

Some doubts still remain as to the extent and significance of osteomalacia with cyclical etidronate. The cyclic regimen was adopted to minimise the risk of osteomalacia that results from continuous etidronate use, with preliminary reports of quantitative bone histomorphometry after six to seven years of use suggesting that significant osteomalacia does not occur.⁵¹ However, these data have yet to be fully reported and peer reviewed, and a

Table 4 Bisphosphonate compounds under investigation or licenced (approximately ranked according to increasing potency to inhibit bone resorption)

Generic name	Chemical name	Company/companies
Etidronate*	(1-hydroxyethylidene)bisphosphonate	Procter & Gamble
Clodronate*	(dichloromethylene)bisphosphonate	Boehringer Ingelheim/Boehringer Mannheim
Tiludronate*	[[[4-chlorophenyl]thio]-methylene]bisphosphonate	Sanofi
Pamidronate*	(3-amino-1-hydroxypropylidene)bisphosphonate	Ciba-Geigy
Neridronate	(6-amino-1-hydroxyhexylidene)bisphosphonate	Shire
Alendronate*	(4-amino-1-hydroxybutylidene)bisphosphonate	Merck
Mildronate†	[3-(dimethylamino)-1-hydroxypropylidene]bisphosphonate	Gador
BB-1053	[1-hydroxy-3-(1-pyrrolidinyl)-propylidene]bisphosphonate	Pharmacia/Leo
Cimadronate (YM 175)	[(Cycloheptylamino)-methylene]bisphosphonate	Yamanouchi
Risedronate*	[1-hydroxy-2-(3-pyridinyl)-ethylidene]bisphosphonate	Procter & Gamble
Ibandronate (BM 21.0955)	[1-hydroxy-3-(methylpentyl-amino)propylidene]bisphosphonate	Boehringer Mannheim
Zoledronate CGP 42,446	[1-hydroxy-2-(1-imidazol-1-yl)ethylidene]bisphosphonate	Ciba-Geigy

* Bisphosphonates investigated in humans for the treatment of osteoporosis.

Cyclical etidronate (Didronel PMO) and alendronate (Fosamax) are licenced in some countries.

† Previously dimethyl pamidronate.

question mark remains, since other workers have shown both focal and general osteomalacia after four years of treatment.⁵² Newer more potent bisphosphonates do not show the osteomalacic potential of etidronate, so continuous use is possible.

Alendronate

Alendronate has recently gained a licence for the treatment of osteoporosis in postmenopausal women in several countries. Dose ranging studies (5–40 mg) have shown that the optimal dose is 10 mg per day.^{9–53} In established postmenopausal osteoporosis (defined as lumbar spine bone mineral density < -2.5 SD below the mean for young premenopausal women), alendronate increased mean bone mineral density at the lumbar spine and femoral neck by 7.2% and 5.3% respectively from baseline in a two year study of 188 women.⁹ In a larger three year study of 516 osteoporotic women (again defined as lumbar spine bone mineral density < -2.5 SD below the mean for young premenopausal women) mean increases from baseline of 4.9% to 7.8% were found at the lumbar spine and 2.9% to 4.8% at the femoral neck, the variation reflecting different dose groups.⁵³ Similar findings have been reported in a third study of alendronate and bone mineral density, although the definition of osteoporosis was slightly different (lumbar spine bone mineral density < -2.0 SD below the mean for young premenopausal women).⁵⁴ Consistent with the increase in bone mineral density has been the demonstration of decreased rates of vertebral fractures in a report examining pooled data from several studies of varying alendronate doses.⁵⁵ A total of 994 women was assessed over three years, with a vertebral fracture rate of 3.2% in the alendronate group compared to 6.2% in the placebo group ($P = 0.03$). There were also reductions in the progression of vertebral deformities as well as reduced loss of height with alendronate treatment. Importantly, a trend was noted for a reduction in non-vertebral fractures. Recently, the results from the 2027 women in the vertebral deformity limb of the fracture intervention trial have been presented,⁵⁶ and seem to confirm that alendronate reduces vertebral fractures and hip fractures compared to placebo. These data have not been published as yet and hence have not been critically reviewed.

Alendronate may also be beneficial in preventing bone loss in early postmenopausal women,⁵⁷ and a large multicentre study of over 1600 women is now under way with the objective of examining the efficacy of alendronate in the prevention of postmenopausal bone loss compared to placebo and HRT.⁵⁸ Preliminary reports of bone histomorphometry show that alendronate decreases bone turnover in a dose dependent manner and does not impair mineralisation.⁵⁹ As would be expected with bisphosphonate compounds, side effects are predominantly gastrointestinal, with recent reports of severe erosive oesophagitis prompting the manufacturers to emphasise that the drug should be taken with a adequate amount of

plain water and that patients should not lie down following ingestion (see revised data sheet).

Although all the studies of alendronate in established osteoporosis used calcium supplements (500 mg per day) in the placebo as well as alendronate treated groups, the data sheet for treatment of osteoporosis is for alendronate alone and is rather vague about the need for calcium supplementation, suggesting simply that all patients should have "adequate dietary calcium". Not all patients are likely to require calcium supplements, although there are difficulties in assessing pretreatment intake, as discussed below.

Since alendronate has been available, most clinicians have inevitably had to compare alendronate and etidronate. Alendronate is undoubtedly more potent than etidronate, but there are no data to indicate superiority in terms of fracture reduction. Moreover, although it is tempting to compare percentage changes in bone density reported in the studies of these compounds, this approach is unreliable because of different baseline bone mineral density values in the study populations, as well as different definitions of osteoporosis as entry criteria (the presence of vertebral fractures in the etidronate studies^{45–46} as opposed to low bone mineral density for alendronate^{9–53–54–55}). Further comparisons of the two compounds are shown in table 5. Important differences are the possibility of prolonged increases in bone mineral density,⁹ and potential for reduction in non-vertebral fractures with alendronate, although on a cost per day basis alendronate (with calcium) is twice as expensive as etidronate in the United Kingdom.

Other bisphosphonates

Several other bisphosphonates are in phase II-III development. Preliminary data in early postmenopausal women indicate that *risedronate* (5 mg/d or cyclically) is effective in preserving bone mass,⁶⁰ and does not adversely influence bone histomorphometry.⁶¹ Studies of cyclical *clodronate*, both oral and intravenous, have shown improvements in lumbar spine bone mineral density in women with postmenopausal osteoporosis compared to placebo.^{62–64} These studies have either been of small numbers of patients^{62–63} or not adequately randomised,⁶⁴ although larger studies are planned or ongoing.⁶⁵ Similarly *pamidronate* also increases lumbar spine bone mineral density,⁶⁶ although again the studies are relatively limited. Also there is concern about erosive oesophagitis with oral pamidronate, which seems to be a feature of aminobisphosphonates (see alendronate).

Despite the encouraging results from studies of bisphosphonates in osteoporosis several issues remain to be considered. These include the long term effects of bisphosphonates on the skeleton, particularly with respect to bone turnover and strength. Related to this is the safe duration of treatment, particularly with alendronate and now with etidronate, which has had the previous three year limit of use

Table 5 Summary of actions of various drug treatments for osteoporosis (for details see text)

Agent	Etidronate (Didronel)	Alendronate (Fosamax)	Calcitriol (Rocaltrol)	Calcium & vitamin D	Calcitonin	Ipriflavone	Fluoride
Licensed indication	PMO (vertebral)	PMO	PMO	—	—	—	—
Duration of treatment	Was licensed for 3 years, now unlimited	Not limited	Not limited	—	—	—	2–4 years
LS BMD	Yes	Yes	Yes	Yes	Yes	Yes	Yes
↓Vert fractures	Probably (see text)	Yes	Possibly (see text)	?	Possibly	No data	Yes
Hip BMD	Yes	Yes	Yes	Yes	?	No data	Probably
↓Hip fractures	No data	Probably	No data	Yes	?	No data	Insufficient data
Side effects	GI disturbances	GI disturbances	Hypercalcaemia	None	Nausea, vomiting, flushing	Negligible	Mainly GI
Regimen	Cyclical etidronate (400 mg/day for 14 days) with calcium carbonate (500 mg/day for 76 days)	Alendronate 10 mg/day	Calcitriol 0.5 µg/day	Calcium 1.2 g/day Cholecalciferol 800 IU/day	Variable according to preparation	600 mg/day	Variable according to preparation
Calcium supplementation	Included	Not included	Not included	Included	Not included	Not included	Not included in most preparations
UK cost (30 days)	£13.40 (Didronel PMO)	£27.56 (£30.85 with 500 mg/day calcium carbonate as Calciheiw)	£12.93	Calciheiw D3 Forte (two tabs per day is nearest to above doses) (£9.90)	Available but not licenced	Not available	Not available

removed. Also, definitive data for hip fracture are not yet available, which is a crucial area given the greater clinical and financial burden of fractures at this site. Careful long term follow up studies will be required to assess these issues.

CALCITONIN

Calcitonin has been shown to increase bone mineral density, particularly at the spine, with some evidence that it reduces hip and vertebral fracture rate.⁶⁷ The major current area of interest is the development of alternative routes of administration for use in osteoporosis, avoiding the need for intramuscular or subcutaneous preparations. To this end numerous studies have examined nasal and rectal preparations and have shown varying degrees of efficacy.^{67–68} Nasal preparations have a licence for the treatment of osteoporosis in some European countries and Japan, although there are doubts about efficacy because of poor bioavailability. A new oral formulation is being developed and undergoing phase II testing. However, given these difficulties as well as limited efficacy and the occurrence of significant side-effects it is unlikely that calcitonin will gain widespread acceptance for the treatment of osteoporosis. On the positive side, calcitonin has been used since the early 1960s in Paget's disease of bone and there are no long term adverse consequences known.⁶⁹ Moreover, analgesic effects are well documented,⁷⁰ although, given the cost, it would be reasonable to use more standard analgesic preparations in the first instance.

CALCIUM AND VITAMIN D

The role of calcium and vitamin D in the management of osteoporosis has been a subject of much debate. From balance studies we know that calcium, like iron, has a threshold effect where, above a certain level of intake, no bone accumulation occurs⁷¹ (analogous to iron intake and haemoglobin). This is important since in theory an intake just above this threshold will lead to maximal skeletal retention. In addition the role of calcium, and the

recommended daily intake, is likely to be different according to the phase of skeletal development (childhood, young adult, perimenopausal, and elderly).^{71–72} Thus calcium supplementation has been shown to increase bone mineral density in prepubertal children compared to placebo (although the effect during the teenage years is still unclear), with preliminary results of prospective cohort studies suggesting a potentially beneficial effect on peak bone mineral density.⁷³ Calcium supplementation around the menopause also has some benefit with respect to bone mineral density, although not as much as oestrogen replacement.⁷¹ In older people, the data for calcium are unclear, although those with low calcium intakes may possibly benefit. In a recent four year study examining the effect of calcium supplementation (1 g) in approximately 80 women who were 9–10 years (mean) postmenopausal, a significant decrease in the rate of bone loss at multiple skeletal sites was found compared to placebo.⁷⁴ Differences between previous studies may relate to differences in dosages of calcium used, in baseline calcium and vitamin D intake, the site of the skeleton examined, physical activity, and possibly genetic differences such as vitamin D receptor allelic status.

There are substantial difficulties in estimating the amount of calcium required for skeletal health.⁷⁵ Recent recommendations of the National Institutes of Health consensus development panel on optimal calcium intake,⁷⁶ can be summarised as 1200–1500 mg/day for young adults, 1000 mg/day for men and women between 25 and 50 years of age, 1500 mg/day for postmenopausal women not on oestrogen (1000 mg/day if taking oestrogens), and 1500 mg/day for all patients above 65 years of age. How these intakes are achieved and how the daily intake for an individual is assessed in a clinic are the next questions. Ideally dietary sources would seem to be the best option, although some individuals may prefer calcium supplements. There is no easy answer as to how best to assess calcium

intake within an individual, since data from food frequency questionnaires or dietary diaries are unreliable in the average clinic setting. Nonetheless some knowledge of calcium contents of foods may aid in deciding whether supplements should be given, since the other option is to supplement every patient, which has significant cost implications.

More information is also available for vitamin D and osteoporosis.⁷⁷⁻⁷⁸ In the elderly it has been suggested that mild vitamin D deficiency occurs through multiple mechanisms,⁷⁸ resulting in increased levels of serum PTH leading to increase bone turnover and cortical bone loss, without frank osteomalacia. In support of this is the increase in serum PTH seen with aging, and histological evidence of secondary hyperparathyroidism in elderly people.⁷⁷⁻⁷⁸ Vitamin D supplementation (cholecalciferol or ergocalciferol) does correct this subclinical vitamin D deficiency and overall it increases bone mass and decreases fracture incidence.⁷⁷⁻⁷⁸ Small increases in femoral neck bone mineral density (approximately 2-2.5%) with 400 IU vitamin D were shown in a two year placebo controlled study of 348 women aged 70 years and over.⁷⁹ Similar bone mineral density increases in the total proximal femur (2.7%) were found in a larger study of 3270 women, mean age 84 years (range 69-106), treated with 800 IU vitamin D as well as 1.2 g calcium supplementation compared to placebo for 18 months. More importantly, hip fractures were reduced by 43% and total non-vertebral fractures by 32% compared to placebo.⁸⁰

It is possible that this effect is more prominent in patients prone to vitamin D deficiency (usually due to lack of sunlight exposure), for example institutionalised elderly patients and those in northern latitudes. The optimal dose and regimens still have to be clarified and include 800 IU/day of cholecalciferol to yearly bolus injections of ergocalciferol that are stored in body fat.

CALCITRIOL (1,25-DIHYDROXYVITAMIN D)

Calcitriol, which is the active metabolite of parent vitamin D, has recently been licensed for the treatment of osteoporosis (table 5). Although earlier studies were conflicting, a three year study of women with at least one vertebral fracture, aged 50-79 years, showed that the vertebral fracture rate in calcitriol treated patients (0.25 µg twice daily) was 69% lower than in those given 1 g of calcium alone.⁸¹ As would be expected, patients with moderate disease (≤ 5 vertebral fractures at baseline) showed benefit, which was not evident in those with a greater number of fractures. However, a major difficulty with the interpretation of the vertebral fracture data in this study is that the fracture rate remained constant in the calcitriol group; that is, calcitriol did not actually reduce fracture rates during the three years of the study. The statistically significant difference from the calcium group occurred because vertebral fracture rates actually increased in the calcium group over the three year period. Thus it is not strictly true that calcitriol reduces vertebral fracture rates.

Non-vertebral fractures may also be reduced, although the data are limited. Given the potential for hypercalcaemia and hypercalciuria, calcitriol is best, at least for the near future, reserved for specialist use, possibly in patients with renal impairment where parent vitamin D may not be as effective or where there is intolerance to bisphosphonate compounds. Similarly, 1α-hydroxyvitamin D has also been shown to reduce vertebral fractures,⁸²⁻⁸³ and is used in Japan, although currently this form of vitamin D is not licensed in the United Kingdom.

ANABOLIC STEROIDS

Anabolic steroids such as nandrolone deconaoate are synthetic derivatives of testosterone and are licensed in some countries including the United Kingdom for osteoporosis in postmenopausal women. Although small increases in bone mineral density have been noted,⁸⁴⁻⁸⁵ the need for parenteral administration and the high incidence of significant side effects greatly limit the use of this agent. Although initially thought to increase osteoblastic activity, anabolic steroids actually reduce bone turnover, with a greater effect on bone resorption.⁸⁴

IPRIFLAVONE

Flavonoids are ubiquitous natural compounds found in most photosynthesising cells and have a variety of pharmacological properties.⁸⁶ Ipriflavone is a synthetic flavonoid that has been shown to inhibit bone resorption, although the mechanism by which this occurs is debated.⁸⁶⁻⁸⁸ Ipriflavone increases bone density at the radius and lumbar spine in established osteoporosis,⁸⁷⁻⁸⁹⁻⁹⁰ and preserves bone density in early postmenopausal osteoporosis⁹¹ (table 5).

However, these studies have been short term (usually one year) and fracture data are unavailable, although preliminary findings from larger studies of two to three year follow up periods are encouraging.⁹² Moreover since major side effects were absent, ipriflavone does show promise as a useful agent in the treatment of osteoporosis and is already licensed in a number of countries.

INTEGRIN ANTAGONISTS

Attachment of osteoclasts to bone surface before bone resorption is poorly understood but seems to be dependent on cell adhesion molecules (integrins) which bind to matrix proteins containing an RGD (arginine-glycine-aspartate) motif.⁹³ Echistatin and kistrin, snake venom proteins, have been shown to inhibit bone resorption by interfering with osteoclastic attachment in animal models.⁹³⁻⁹⁵ Recently a monoclonal antibody to β₃ integrin has been shown to inhibit osteoclast mediated bone resorption in a rat model.⁹⁶ This suggests that inhibition of osteoclast integrin could be a potential treatment for bone disease, although no data are available in humans.

PROTON PUMP INHIBITORS

Following attachment of osteoclasts to bone surface, an acidified bone resorbing compartment is formed. Lowering of pH in the bone

resorbing compartment is accomplished by a proton ATPase in the osteoclasts membrane,⁹⁷ which can be inhibited by several omperazole-like agents that are currently being assessed.⁹⁸ In vitro animal studies suggest that bone resorption is decreased, but among other difficulties with this approach is that proton ATPases are present in all eukaryotic cells; therefore the potential lack of specificity of these agents is likely to limit clinical use in osteoporosis.

AMYLIN

Amylin is a 37 amino acid peptide first isolated from the amyloid deposits in the pancreas of type II diabetics.⁹⁹ There are limited data available on the physiological function of amylin, although it does seem to have a role in the regulation of bone remodelling. Early in vitro studies suggested a calcitonin-like effect with inhibition of osteoclast adhesion to bone surfaces and decreased osteoclast motility,¹⁰⁰ although more recent reports conclude that amylin stimulates osteoblast proliferation and increases mineralised bone volume.¹⁰¹ Further studies are obviously required to assess the potential role of this peptide in the treatment of osteoporosis. No data are available in humans.

Stimulators of bone formation

Agents that increase bone formation either have a direct mitogenic effect on osteoblasts (for example, fluoride) or seem to act indirectly on bone cells through bone growth factors.

FLUORIDE

Fluoride has probably been the most controversial drug proposed for the treatment of osteoporosis, despite its ability to increase bone mass more substantially than any other agent. Doubts remain because of the formation of "poor quality bone" and a failure to demonstrate a reduction in vertebral fractures.¹⁰²⁻¹⁰³ Clinical studies have given mixed results due to interindividual variability in vertebral bone mineral density response, potential for increased non-vertebral fractures (particularly at the hip because of negative effects on cortical bone), as well as side effects and poor tolerability.¹⁰⁴ These effects may be dose and formulation dependent,¹⁰⁴⁻¹⁰⁷ with variation in fluoride absorption and excretion between patients possibly leading to these differences.

The pendulum is, however, swinging towards fluoride as an acceptable drug for the treatment of osteoporosis. Firstly an extension and retrospective analysis of the study by Riggs *et al*¹⁰² showed a reduction in vertebral fractures in those patients with lower doses.¹⁰⁷ More persuasive is the work by Pak *et al*¹⁰⁸ using cyclical intermittent slow release fluoride in women with postmenopausal osteoporosis (osteopenia with one or more vertebral fractures). This regimen consists of slow release fluoride 25 mg twice daily in four 14 month cycles (12 months of fluoride followed by a two month fluoride-free interval) with continuous calcium citrate 400 mg twice daily. With this approach bone mineral density increased at all skeletal sites (including the

femoral neck) compared to placebo, and was maximal at the lumbar spine, where mean yearly density increased by 4.8%. In addition, 85% of patients taking fluoride were free of new vertebral fractures, compared to 57% of the placebo group ($P < 0.001$). The maximum effect was seen in patients with the highest spinal bone mineral density ($> 65\%$ of the mean for 30 year old women), where new fractures were almost absent. The latter finding emphasises that the best fracture responses are seen in patients with milder forms of osteoporosis where microarchitecture (trabecular connectivity) is still relatively preserved. The effects of fluoride are summarised in table 5.

BONE GROWTH FACTORS

Large amounts of various growth factors are stored within bone in an inactive form bound to specific proteins. It has been suggested that they may be released (in active form) by bone resorption and consequently act as local determinants of site specific bone formation,¹⁰⁹ thereby coupling resorption to formation. The most abundant and well defined bone growth factors are insulin-like growth factors (IGF I and II) and transforming growth factor β (TGF- β).

Originally, IGF were thought to regulate osteoblast function alone, with in vitro studies showing that they are mitogenic and increase osteoblast proliferation and matrix production.¹¹⁰ However, more recent data suggests that bone resorption is also stimulated.¹¹¹⁻¹¹² Whether osteoclasts are directly or indirectly (through osteoblasts) influenced by IGF is unclear, although recent evidence suggests an osteoblast mediated action.¹¹³ The significance of this conflicting data for the potential role of IGF as a treatment for osteoporosis is as yet unclear.

The TGF- β supergene family consists of at least five closely related proteins (TGF- β 1 to β 5) and others such as bone morphogenetic proteins and inhibins.¹¹² All are thought to be involved in the control of development growth and differentiation of human cells. TGF have a prominent role in bone development and remodelling, although there are relative differences between the various factors on their actions on bone. Recent in vivo work suggests that TGF β stimulates bone formation.¹¹⁴

The role of IGF and TGF- β in the pathogenesis of osteoporosis is still unclear, although the decrease in circulating IGF-I (and growth hormone concentration) with age has been implicated in the age related decrease in lean body mass and bone mass.¹¹⁵ However, it should be remembered that serum concentrations of these hormones may not reflect skeletal activity¹¹⁶ and may just be a epiphenomenon, although against this is the fact that recently an age related decrease in IGF-I and TGF- β has been reported in femoral cortical bone.¹¹⁷⁻¹¹⁸ In addition, although a relation between bone density and serum IGF concentration in women with postmenopausal osteoporosis has not been established,¹¹⁹ serum IGF-I concentrations have been shown to be reduced in male patients with idiopathic

osteoporosis¹²⁰ and correlated with osteoblastic surface in young adults with idiopathic osteoporosis.¹²¹ This suggests that relative IGF deficiency (and possibly deficiency of other growth factors) may be important in the pathogenesis of idiopathic osteoporosis in men, whereas in women with postmenopausal osteoporosis oestrogen deficiency is the dominant cause.

Limited data are available for the use of recombinant bone growth factors in the treatment of osteoporosis. Formation and resorption markers of bone turnover increased in normal women administered recombinant human IGF-1 (rhIGF-1) for one week.¹²² Treatment of a patient with idiopathic osteoporosis with rhIGF-1 resulted in a similar increase in bone turnover as well as a variable effect on bone density.¹²³ A more detailed study of a patient with Werner syndrome (an autosomal disorder resulting in premature aging) and osteoporosis found that daily rhIGF-I for six months increased markers of bone turnover and bone density at the lumbar spine by 3%, but had no effect at the femoral neck or radial shaft.¹²⁴ The *in vivo* actions of recombinant human TGF- β and bone morphogenetic proteins have only been assessed at local sites in animal models and humans with resistant non-uniting fractures.^{109 112}

Currently the potential for these growth factors to be considered for the treatment of osteoporosis is limited not only by concerns regarding efficacy but also by the need for parenteral administration and the potential for systemic side effects, since these hormones affect multiple organ systems. Unwanted systemic effects may be overcome by (1) using the lowest effective dose, (2) trying to isolate bone specific growth factors, (3) targeting to bone by either conjugating to bone seeking compounds such as bisphosphonates, or using inactivated forms which are only activated in bone, or finally (4) causing release of endogenous growth factors (which will act locally) by other agents.¹²⁵ The latter approach is likely to be the most attractive, particularly if oral agents can be developed which increase endogenous growth factor secretion.

GROWTH HORMONE

Growth hormone exerts anabolic effects on bone that may be mediated through IGF, as well as through an increase in physical activity due to improvements in muscle mass/strength and exercise capacity.^{126 127} Growth hormone excess in adults (acromegaly) leads to increased bone mineral density,¹²⁷ whereas growth hormone deficiency is associated with decreased bone mineral density in children and adults.^{126 128} Conflicting data exist as to whether growth hormone secretion is reduced in osteoporotic subjects compared to controls.¹²⁶ Data regarding recombinant human growth hormone in the treatment of osteoporotic subjects with normal growth hormone/IGF axis are limited and inconclusive.¹²⁶ Preliminary results suggest that although bone turnover seems to be increased with therapy, increases in

bone mass, when they occur, are minimal (1-2% at the lumbar spine) after one to two years of treatment.^{129 130} Optimal dosage schedules are still far from clear and it is possible that the largest increases in bone mass may be seen in by targeting those with a relative deficiency of growth hormone.

PARATHYROID HORMONE (PTH)

PTH influences calcium and phosphate levels by direct effects on bone and kidneys, and indirect effects on the gut. In the kidneys, PTH regulates tubular reabsorption of these ions and stimulates calcitriol production which indirectly affects gut absorption of calcium. PTH given continuously increases bone turnover, with resorption in excess of formation, leading to net bone loss. Although intermittent administration of PTH also increases bone turnover, formation is in excess of resorption and therefore bone mass is increased.¹³¹ Clinical studies in humans to date suggest that intermittent PTH (and analogues) preserve or increase spinal bone mineral density without an effect on the hip (either beneficial or detrimental).¹³¹ However, the need for parenteral administration is a major limitation to the use of PTH for the treatment of osteoporosis.

PARATHYROID CELL CALCIUM RECEPTOR AGONISTS/ANTAGONISTS

The recent cloning and characterisation of an extracellular calcium sensing receptor (similar to the G protein coupled receptor superfamily) on parathyroid cells¹³² has raised the potential for an agent which could indirectly influence PTH secretion. In theory agonists of this receptor would decrease PTH secretion and may have potential in disease states where there is secondary hyperparathyroidism, such as renal osteodystrophy. Alternatively antagonists would increase PTH secretion, and it is possible that a regimen leading to intermittent blockade of the receptor and therefore intermittent PTH secretion could be anabolic to bone and be used in osteoporosis. An orally active agonist of this receptor is already under development and antagonist compounds with a potential in osteoporosis treatment are awaited.

VITAMIN D ANALOGUES

Anabolic analogues of vitamin D, which stimulate bone formation without a calcaemic effect, are being examined for the treatment of osteoporosis. One example is ED-71 which has been shown to increase bone formation and mass in rat models.¹³³

ZEOLITE A

Silicon in trace amounts has been shown to enhance bone formation. Zeolite A, a tetrahedral silicon derivative, increases eggshell thickness in hens and *in vitro* studies report increased proliferation and differentiation of human osteoblast-like cells.¹³⁴ Increases in TGF β production in a dose dependent manner have been noted in these cell models and is the

presumed mechanism of action of zeolite A. This compound can be given orally and has been used in a number of animal studies.

STRONTIUM SALTS

Animal studies have shown that low dose strontium salt stimulate bone formation and inhibit bone resorption.¹³⁵ S-12911 is a divalent strontium salt that has been shown to prevent bone loss in rats.^{136 137} Studies in humans are encouraging, with preliminary reports suggesting that S-12911 increases lumbar spine bone mineral density.¹³⁸

Suggested drug treatment approach for postmenopausal osteoporosis

On the current evidence, sustained administration of HRT remains the most appropriate pharmacological intervention for conserving bone mineral density and minimising fracture risk at multiple skeletal sites in postmenopausal women without long term skeletal side effects. When HRT is inappropriate or unacceptable, the agent of choice depends on local availability and licensing, but bisphosphonates should probably be considered next. The newer bisphosphonates are likely to supersede etidronate because of the lesser concern for osteomalacia and possible reduction in non-vertebral fracture, although the issue of the potential adverse effects of long term treatment on bone is unanswered. Optimising vitamin D intake in the elderly patient with osteoporosis would seem to be critical, and in individuals at risk supplementation should be given. Currently it seems appropriate to use calcitriol as a third line agent, probably by specialists, rather than in primary care, given the potential toxic effects described. Other drugs such as calcitonin, tibolone, anabolic steroids, and progestogens could be used as third line agents, if available, but under specialist supervision. The use of combined treatment with two or more of these agents has not yet been adequately explored, but where bone loss continues with one agent, a case could be made for combination therapy, for example, HRT and a bisphosphonate. All postmenopausal patients should have an adequate calcium intake, which in practice may mean that a supplement should be taken. Nonpharmacological strategies are also important and general lifestyle measures, with attempts to reduce the risk of falls, should also be addressed where appropriate.

Glucocorticosteroid osteoporosis

The mechanisms by which glucocorticoids cause osteoporosis are complex. The patients pretreatment bone mineral density has an important bearing on whether glucocorticoids will lead to fractures, thus steroid treatment will compound potential problems in patients already with low bone mineral density. Obvious determinants of the latter include age and menopausal status. In addition the underlying disease may also be detrimental to the skeleton, for example rheumatoid arthritis

causes generalised bone loss independent of glucocorticoids,¹³⁹ as well as influencing mobility and propensity to fall.

The major mechanism by which glucocorticoid induced bone loss occurs is by a reduction in bone formation caused by a direct action on osteoblasts, which show decreased work rate and active life span.^{140 141} Reduced intestinal absorption of calcium and decreased renal tubular reabsorption of calcium caused by hypogonadism (by inhibition of pituitary gonadotrophins and a direct effect on the ovaries and testes) also contribute.¹⁴² The latter changes in calcium homeostasis are compensated for by secondary hyperparathyroidism, which may indirectly lead to increased osteoclastic activity, thereby increasing bone loss.

As in postmenopausal osteoporosis, trabecular areas of the skeleton show the greatest degree of bone loss, which usually occurs in the first year of treatment.¹⁴³⁻¹⁴⁵ The latter observation is probably due to higher doses of glucocorticosteroids used early in treatment and to the effect of active underlying disease. It remains unclear whether there are individuals who are more sensitive than others to glucocorticoid induced bone loss. The fact that bone mineral density in steroid treated patients is normally distributed rather than bimodal has led to suggestions that most patients are similarly affected.¹⁴⁶ However, it should be remembered that patients may have bone mineral density values which are well within the normal range, but have incurred significant bone loss.

Trabecular bone in patients with glucocorticoid associated osteoporosis is characterised by relative preservation of trabecular surface and number compared to patients with postmenopausal osteoporosis, where there is a greater degree of trabecular perforation.¹⁴⁷ Thus, in theory at least, the relation between bone mineral density and fracture risk may be different from that demonstrated in postmenopausal osteoporosis. In addition, these histological findings have led to the suggestion that interventions which increase bone mass will be more effective since there is a preserved trabecular framework on which to add new bone.

Prevention of bone loss (in those starting steroids) and treatment (in those with established steroid osteoporosis) have to be individualised and depend on the patients' age, menopausal status, the underlying disease, and predicted dose and duration of steroid treatment. Pretreatment bone mineral density measurement is vital as a baseline and to see if treatment for osteoporosis should be instituted irrespective of steroid therapy. In addition the finding that a large proportion of glucocorticoid induced bone loss occurs early in treatment has major treatment implications since intervention to prevent bone loss should be instituted as soon as steroid therapy is started (table 6).

The lowest dose of steroid should be used and regular review of the dose and need for treatment made. Progressive bone loss is often

Table 6 Suggested approach for the management of glucocorticosteroid associated osteoporosis (based on the recommendations of a Consensus Group Meeting)¹⁴¹

Prevention

- 1 Measure BMD if course of GCS expected to last for more than 6 months
- 2 Recommend general measures in all patients (regular exercise, prevent falls avoid smoking and excess alcohol)
- 3 If BMD 1 SD below age-matched level or 2.5 SD below young normals or if the mean dose of prednisone is likely to be more than 15mg/day then recommend HRT
- 4 If HRT contraindicated or the patients is premenopausal or loss of BMD greater than 4%/year despite HRT consider prevention of bone loss with other agents such as bisphosphonates, calcitriol or calcitonin. In men supplement with testosterone if necessary. In addition consider deflazacort (if available) in place of prednisolone

Treatment

Similar to postmenopausal osteoporosis

said to be minimal at doses of prednisolone of 7.5 mg/d as this dose level has often been regarded as that required for physiological replacement. However, this dose may be too high since the most recent estimates of endogenous cortisol production are 6 mg/m².¹⁴⁸ This has been calculated to be equal to doses of hydrocortisone of 15 mg/d and 20 mg/d for women and men respectively.¹⁴⁹ Equivalent doses of prednisolone would be 3.75 mg/d and 5 mg/d respectively (assuming a prednisolone:hydrocortisone glucocorticoid potency ratio of 1:4). Apart from concerns about the multiple assumptions needed to derive these doses and the variation due to absorption and metabolism of prednisolone, another factor apart from dose that may influence the effect of glucocorticoids on bone is the underlying disease requiring treatment. Thus if the disease itself leads to bone loss, and glucocorticoid treatment suppresses disease activity and hence bone loss, there may not be a net loss of bone.¹⁴² Therefore in practice one can only try to reduce the dose of steroids to the level which adequately suppresses the disease. There is evidence, predominantly from patients with cured Cushing disease, that restoration of normal plasma cortisol reverses bone loss.^{150 151}

General lifestyle advice should be given regarding smoking, alcohol, exercise, and calcium intake if necessary. Calcium intake should be adequate, although as previously discussed the total intake required may vary. Supplementation of 500-1000 mg may be appropriate in all patients since positive skeletal effects, albeit limited, have been shown.¹⁵² Correction of hypogonadism is important and HRT should be offered to all postmenopausal women. Serum testosterone should be measured in men and supplementation considered, although there are no data confirming efficacy (see below).

Deflazacort, a oxazoline derivative of prednisolone, has been investigated as a potential "bone sparing glucocorticosteroid". There does seem to be evidence that deflazacort may reduce bone loss compared to prednisolone,^{142 153 154} but the studies have been short (usually up to one year), and this finding is not universal. One major confounding factor is that there are differing potencies between these

steroids which does not allow use within studies on a milligram to milligram basis (the deflazacort:prednisolone dose equivalence is often quoted as 1.2:1, although this is disputed).¹⁴² Therefore there is the possibility that one steroid may be used in slight excess over what is required to control the disease, leading to differences in apparent adverse effects. Thus to date there is no conclusive evidence that deflazacort offers any significant advantages over prednisolone.

Bisphosphonates, calcitonin, and vitamin D have all been assessed in prevention and treatment of glucocorticosteroid osteoporosis. Cyclical etidronate prevented bone loss in a prospective randomised placebo controlled study of 20 patients treated with glucocorticoids for temporal arteritis.⁵⁰ At one year, lumbar spine bone mineral density had increased by 1.4% whereas a decrease of 5.0% was noted in the placebo group. Where significant bone loss with glucocorticoids has already occurred, 150 mg/d of pamidronate over one year was shown to increase vertebral bone mineral density by 19%, whereas a loss of 9% occurred in the placebo group. These findings persisted, with further loss at two years in the placebo group. Other studies of bisphosphonates to date have not always used a control group and further data for the newer bisphosphonates are awaited. Adequate studies of calcitonin in glucocorticoid induced osteoporosis are lacking. Intramuscular calcitonin 100 IU on alternate days compared to 1 g of calcium alone was found, in a randomised study of 62 asthmatics treated with glucocorticoids, to increase lumbar spine bone mineral density by 4%, whereas there was a loss of 2.5% in the control group.¹⁵⁵ However, 11 of the 31 calcitonin patients withdrew because of side effects and a further three because of poor compliance. Most other studies of calcitonin have been of small numbers of patients, with a relatively short period of study. There are conflicting data about the use of parent vitamin D, although more convincing results are available for calcitriol, which was used in the primary prevention of glucocorticoid osteoporosis. This was a two year randomised study of calcium, calcitriol, and calcitriol plus calcitonin in 103 patients with a variety of underlying diseases requiring glucocorticoid treatment.¹⁴⁴ Patients were treated with one of the above regimens for one year and followed without intervention for a further year. Lumbar spine bone mineral density decreased by 4.3% per year in the calcium group, whereas minimal changes were found in the calcitriol group (-0.2 % per year) and the calcitriol plus calcitonin group (-1.3% per year). However, no protective effect was found at the femoral neck or distal radius, and hypercalcaemia requiring calcitriol dose adjustment occurred in 25% of patients. Fluoride has been shown, in an uncontrolled study to increase lumbar spine bone mineral density in patients receiving glucocorticoids following cardiac transplant.¹⁵⁶ However, due to the nature of the study design further work is required, with reduction in fractures as an end point.

Thus to date the optimal drug and regimen for the prevention and treatment of glucocorticoid osteoporosis remains unclear, making it difficult to give clear guidelines for the management of individual patients. However, based on current evidence, table 6 outlines the recommendations of a recent consensus group meeting on the management of glucocorticoid induced osteoporosis.¹⁴¹ The emphasis has to be on prevention of bone loss, since the majority of bone is lost early in the course of steroid treatment, as discussed above.

Male osteoporosis

There are differences in the pathogenesis of bone loss and the interpretation of bone densitometry in men compared to women. In particular the microarchitecture of trabecular bone in men with osteoporosis is characterised by less trabecular perforation than in women, despite similar bone mineral density, resulting in differences in structural integrity.^{157 158} Although there is an inverse relation between bone mineral density and fracture in men, this is not as well defined as in women, and other factors such as bone dimensions also play a role in explaining differences in fracture rates for a given bone mineral density.¹⁵⁷ In addition, osteoporosis in men is often secondary to factors which adversely influence bone mineral density.^{159 160} In most cases secondary causes such as steroid treatment, alcohol excess, and gastrointestinal disorders are obvious. More occult causes include malignancy, especially myeloma, but also idiopathic hypercalciuria, hypogonadism, endogenous glucocorticoid excess, and hyperthyroidism. These factors should be considered in all men with osteoporosis, and appropriate investigations carried out with treatment dependent on whether there is an underlying predisposing factor which can be modified.

Although hypogonadism represents a risk factor for osteoporosis, it is not clear if there is a gradient of risk associated with serum testosterone or a threshold level below which osteoporosis is more likely to occur. The effectiveness of testosterone replacement therapy in osteoporotic men with significant hypogonadism remains unclear, however, as does the value of replacement in men with low normal levels. Modest increases in bone mineral density have been reported in such patients, although the studies are small and of limited duration.¹⁵⁷ It is still unclear what proportion of patients will respond and whether other factors such as the cause and duration of hypogonadism influence outcome. A further concern is that testosterone replacement might exacerbate prostate disease and increase the risk of prostate cancer, although at present this is a theoretical risk. Nonetheless it seems reasonable to give testosterone to men with obvious hypogonadism. Interestingly a recent six month open prospective study of 23 eugonadal men with idiopathic osteoporosis and vertebral fractures has suggested that androgen supplementation may be of benefit. The patients were treated with moderate doses

of testosterone and a significant increase in mean lumbar spine bone mineral density of 5% from baseline was noted.¹⁶¹ No change in bone mineral density was found at the hip and although two men withdrew from the study the reasons for withdrawal did not seem to be related to testosterone treatment. These findings need to be confirmed in a randomised study.

There is a lack of adequate data about the use of non-hormonal pharmacological treatments for osteoporosis in men. Men have been included in studies that have examined mixed sex populations such as patients with steroid induced bone loss.^{144 156} It seems reasonable to give thiazides in patients with hypercalciuria. Otherwise treatment is empirical, using agents which have been assessed in postmenopausal women.

Summary

There has been a major interest in the drug treatment of osteoporosis and an increase in the number of drugs available in most countries. The ideal drug (one which increases or restores bone density and trabecular connectivity) is still not available. However, in patients with relatively preserved trabecular connectivity and moderately reduced bone density, several agents have shown substantial clinical benefit. Oestrogens are still the mainstay of drug treatment, but the risks of breast cancer versus the cardiovascular and skeletal benefits with long term use have to be assessed in the individual. Newer tissue specific oestrogens show some promise in this respect. The bisphosphonates and possibly fluoride are likely to be the major alternatives to oestrogens in the medium term. The newer bisphosphonates, alendronate and in the future risidronate, are likely to supersede etidronate. Calcitriol probably has a limited role, confined to those patients in whom HRT or bisphosphonates are not appropriate. Calcium supplementation, or an increase in dietary intake if deficient, irrespective of which agent is used, is also of benefit. In older patients there is considerable support for using a combination of calcium and vitamin D. Whether combination treatment, for example oestrogens, bisphosphonates, and calcium together, will result in greater efficacy remains to be conclusively shown,⁵² but may be an attractive option in younger patients with higher bone turnover.

Apart from fluoride, bone formation stimulators are unlikely to have a major role until the next century, although it may be possible to use growth factors as part of an ADFR regimen (A = activate remodelling, D = depress resorption, F = free formation, and R = repeat¹⁶²). This is still an important theoretical approach and needs further work with newer agents to see if increased efficacy can be found. In addition sequential treatment may be necessary in view of the limited time periods over which particular agents, such as intermittent fluoride (four years), have been examined, and this will have to be individually tailored.

Other approaches include trying to increase peak bone mineral density, although influencing the young to prevent a disease that may not manifest itself for half a century is daunting.

- 1 Barlow DH. Advisory Group on Osteoporosis. London: Department of Health, 1994.
- 2 Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: a world wide projection. *Osteoporosis Int* 1992;2:285-9.
- 3 Barrett-Connor E. The economic and human costs of osteoporotic fractures. *Am J Med* 1995;98:3-8S.
- 4 Kanis JA, Adami S. Bone loss in the elderly. *Osteoporosis Int* 1994;4(suppl 1):59-65.
- 5 Riggs BL, Melton LJ. The prevention and treatment of osteoporosis. *N Engl J Med* 1992;327:620-7.
- 6 World Health Organisation. *Assessment of fracture risk and its application to screening for postmenopausal osteoporosis*. WHO technical report series. Geneva: WHO, 1994.
- 7 Heaney RP. Interpreting trials of bone-active agents. *Am J Med* 1995;98:329-30.
- 8 Ott SM. Bone mass measurements; reasons to be cautious. *BMJ* 1994;308:931-2.
- 9 Chesnut CH, McClung MR, Ensrud KE, et al. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med* 1995;99:144-52.
- 10 Bonjour JP, Carrie AL, Clavien H, et al. Calcium-fortified aliments selectively increase radial and femoral bone mass in prepubertal girls: a double-blind placebo controlled randomised trial. *J Bone Miner Res* 1995;10:S152.
- 11 Lloyd T, Rollings N, Chinchilli V, et al. The effect of starting calcium supplementation at age 12 or at age 14 on bone acquisition in teenage girls. *J Bone Miner Res* 1995;10:S152.
- 12 Lobo R. Benefits and risks of starting estrogen replacement treatment. *Am J Obstet Gynecol* 1995;173:982-9.
- 13 Stanford JL, Weiss NS, Voight LF, Dahling JR, Habel RA, Rossing MA. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle aged women. *JAMA* 1995;274:137-42.
- 14 Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995;332:1589-93.
- 15 Rymer J, Fogelman I, Chapman MG. The incidence of vaginal bleeding with tibolone treatment. *Br J Obstet Gynaecol* 1994;101:53-6.
- 16 Gennazzani AR, Benedek-Jazman LJ, Hart DM, Andolsek L, Kicovic PM, Tax L. Org OD14 and the endometrium. *Maturitas* 1991;13:243-51.
- 17 Lindsay R, McKHart D, Krasewski A. A prospective double-blind trial of synthetic steroid (Org OD 14) for preventing postmenopausal osteoporosis. *BMJ* 1980;iii:1207-9.
- 18 Rymer J, Chapman MG, Fogelman I. Effect of tibolone on postmenopausal bone loss. *Osteoporosis Int* 1994;4:314-9.
- 19 Rymer J, Chapman M, Fogelman I. Tibolone, a form of HRT without the need for withdrawal bleeding prevents postmenopausal bone loss (4 years follow-up). *Osteoporosis Int* 1996;6(suppl 1):230.
- 20 Guesens P, Dequeker J, Gielen J, Schot LP. Non-linear increase in vertebral density induced by a synthetic steroid (Org OD 14) in women with established osteoporosis. *Maturitas* 1991;13:155-62.
- 21 Pavlov PW, Ginsburg J, Tjon A Hen S, Prelevic G, Coelingh Binnink H, Kicovic PM. A double-blind, placebo-controlled study of the effects of tibolone on bone mineral density in postmenopausal osteoporotic women with and without fractures. *Osteoporosis Int* 1996;6(suppl 1):231.
- 22 Studd J, Arnala I, Zamblera D, Kroger H, Holland N. Tibolone increases bone mass in women with previous fractures in a placebo-controlled bicentre study. *Osteoporosis Int* 1996;6(suppl 1):231.
- 23 Wright CDP, Compston JE. Tamoxifen; oestrogen or anti-oestrogen in bone. *Q J Med* 1995;88:307-10.
- 24 Love RR, Mazess RB, Bardens HS, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. *N Engl J Med* 1995;311:977-80.
- 25 Grey AB, Stapleton JP, Evans MC, Tannell MA, Ames RW, Reid IR. The effect of the antioestrogen tamoxifen on bone mineral density in normal late postmenopausal women. *Am J Med* 1995;99:636-41.
- 26 Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual energy X-ray absorptiometry in healthy premenopausal and postmenopausal women. *J Clin Oncol* 1996;14:78-84.
- 27 McDonald CC, Alexander FE, Whyte BW, Forrest AP, Stewart HJ. Cardiac and vascular morbidity in women receiving tamoxifen for breast cancer in a randomised trial. *BMJ* 1995;311:977-80.
- 28 Ismail SM. Effect of tamoxifen on uterus. *Lancet* 1994;344:622-3.
- 29 Black LJ, Jones CD, Facon JR. Antagonism of estrogen action with a new benzothipene derived antiestrogen. *Life Sci* 1983;32:1031-6.
- 30 Black LJ, Sato M, Rowley ER, et al. Raloxifene (LY 139481 HCL) prevents bone loss and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats. *J Clin Invest* 1994;93:63-9.
- 31 Evans G, Bryant HU, Magee D, Sato M, Turner RT. The effects of raloxifene on tibia histomorphometry in ovariectomized rats. *Endocrinology* 1994;134:2283-8.
- 32 Turner CH, Sato M, Bryant HU. Raloxifene preserves bone strength and bone mass in ovariectomized rats. *Endocrinology* 1994;135:2001-5.
- 33 Sato M, McClintock C, Kim G, et al. Dual-energy X ray absorptiometry of raloxifene effects on the lumbar vertebrae of ovariectomized rats. *J Bone Miner Res* 1994;9:715-24.
- 34 Sato M, Kim J, Short LL, Slemenda CW, Bryant HU. Longitudinal and cross-sectional analysis of raloxifene effects on tibiae from ovariectomized aged rats. *J Pharmacol Exp Ther* 1995;272:1252-9.
- 35 Ke HZ, Simmons HA, Pirie C, Crawford DT, Thompson DD. Droloxifene, a new estrogen antagonist/agonist prevents bone loss in ovariectomized rats. *Endocrinology* 1995;136:2435-41.
- 36 Chen HK, Ke HZ, Jee WSS, et al. Droloxifene prevents ovariectomy-induced bone loss in tibiae and femora of aged female rats: a dual-energy X-ray absorptiometric and histomorphometric study. *J Bone Miner Res* 1995;10:1256-62.
- 37 Horowitz M, Wishart JM, Need AG, Morris HA, Nordin BE. Effects of norethisterone on bone related biochemical variables and forearm bone mineral in post-menopausal osteoporosis. *Clin Endocrinol* 1993;39:649-55.
- 38 Pors Nielsen S, Barenholdt O, Hermansen F, Munk-Jensen N. Magnitude and pattern of skeletal response to long term continuous and cyclic sequential oestrogen/progestin treatment. *Br J Obstet Gynaecol* 1994;101:319-24.
- 39 Lobo R. Effects of hormonal replacement on lipids and lipoproteins in postmenopausal women. *J Clin Endocrinol Metab* 1991;73:925-30.
- 40 Christiansen C, Riis BJ. Five years with continuous combined oestrogen/progestogen therapy. Effects on calcium metabolism, lipoproteins and bleeding pattern. *Br J Obstet Gynaecol* 1990;97:1087-92.
- 41 Gallagher JC, Kable WT, Goldgar D. Effect of progestin therapy on cortical and trabecular bone: comparison with estrogen. *Am J Med* 1991;90:171-8.
- 42 Grey A, Cundy T, Evans M, Reid I. Medroxyprogesterone acetate enhances the spinal bone mineral density response to oestrogen in late post-menopausal women. *Clin Endocrinol* 1996;44:293-6.
- 43 Grey AB, Cundy TF, Reid IR. Continuous combined oestrogen/progestin therapy is well tolerated and increases bone density at the hip and spine in post-menopausal osteoporosis. *Clin Endocrinol* 1994;40:671-7.
- 44 Fleisch H. The use of bisphosphonates in osteoporosis. *Br J Clin Pract* 1994;48:323-6.
- 45 Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990;323:73-9.
- 46 Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990;322:1265-71.
- 47 Bockman RS. Etidronate for postmenopausal osteoporosis. *N Engl J Med* 1990;323:1209-10.
- 48 Harris ST, Watts NB, Jackson RD, et al. Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. *Am J Med* 1993;95:557-67.
- 49 Herd RJM, Blake GM, Ryan PJ, Fogelman I. A 152 patient double blind placebo controlled study of cyclical etidronate therapy for the prevention of early postmenopausal bone loss. *J Bone Miner Res* 1995;10:S153.
- 50 Mulder H, Struys A. Intermittent cyclical etidronate in the prevention of corticosteroid-induced bone loss. *Br J Rheumatol* 1994;33:348-50.
- 51 Miller PD, Erickson AL. Longterm intermittent cyclical etidronate therapy (ICT) for postmenopausal osteoporosis. *Calcif Tiss Int* 1995;56:493.
- 52 Wimalawansa SJ. Combined therapy with estrogen and etidronate has an additive effect on bone mineral density in the hip and vertebrae: four-year randomized study. *Am J Med* 1995;99:36-42.
- 53 Devogelaer JP, Broll H, Correa-Rotter R, et al. Oral alendronate induces progressive increases in bone mass of the spine and hip and total body over 3 years in postmenopausal women with osteoporosis. *Bone* 1996;18:141-50.
- 54 Adami S, Passeri M, Ortolani S, et al. Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. *Bone* 1995;17:383-90.
- 55 Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 1995;333:1437-43.
- 56 Black DM, Cummings SR, Thompson D. The effect of alendronate on rates of vertebral and non-vertebral fractures in women with vertebral fractures: preliminary results of the fracture intervention trial. *Osteoporosis Int* 1996;6(suppl 1):94.
- 57 Eisman JA, Christiansen C, McClung M, et al. Alendronate prevents bone loss at the spine and hip in recently postmenopausal women. *J Bone Miner Res* 1995;10:S176.
- 58 Yates AJ, McClung M, Ravn P, et al. EPIC: a 1609-subject osteoporosis prevention study. *J Bone Miner Res* 1995;10:S254.

- 59 Arlot MC, Meunier PJ, Chavassieux P, *et al.* Effects of long-term alendronate treatment for post-menopausal osteoporosis on bone histomorphometry. *J Bone Miner Res* 1995;10:S199.
- 60 Mortensen L, Bekker P, van der Ouweland F, *et al.* Prevention of early postmenopausal bone loss by risedronate: a two year study. *J Bone Miner Res* 1995;10:S140.
- 61 Landahl B, Eriksen EF, Mortensen P, Charles P, Bekker P, Axelrod D. Histomorphometry from a three-year risedronate bone loss prevention study. *J Bone Miner Res* 1995;10:S199.
- 62 Filippini P, Pedetti M, Fedeli L, *et al.* Cyclical clodronate is effective in preventing postmenopausal bone loss: a comparative study with transcutaneous hormone replacement therapy. *J Bone Miner Res* 1995;10:697-703.
- 63 Giannini S, D'Angelo A, Malvasi L, *et al.* Effects of one-year cyclical treatment with clodronate on postmenopausal bone loss. *Bone* 1993;14:137-41.
- 64 Filippini P, Cristallini S, Rizzello E, *et al.* Cyclical intravenous clodronate in postmenopausal osteoporosis: results of a long term clinical trial. *Bone* 1996;18:179-84.
- 65 McCloskey E, Luchetti M, Bernard J, *et al.* Bone loss at the hip in elderly women is prevented by oral clodronate-pilot study. *Osteoporosis Int* 1996;6(suppl 1):271.
- 66 Reid IR, Wattie DJ, Evans MC, Gamble GD, Stapleton JP, Cornish J. Continuous therapy with pamidronate, a potent bisphosphonate, in postmenopausal osteoporosis. *J Clin Endocrinol Metabol* 1994;79:1595-9.
- 67 Overgaard K, Riis B. Nasal calcitonin in osteoporosis. *Calcif Tiss Int* 1994;55:79-81.
- 68 Gennari C, Agnusdei D. Calcitonins and osteoporosis. *Br J Clin Pract* 1994;48:196-200.
- 69 Wimalawansa SJ. Long- and short-term side effects and safety of calcitonin in man. *Calcif Tiss Int* 1993;52:90-3.
- 70 Punni KK, Chan LWL. Analgesic effect of calcitonin in the treatment of osteoporotic vertebral fracture. *Clin Ther* 1989;11:205-9.
- 71 Heaney RP. Bone mass, nutrition, and other lifestyle factors. *Am J Med* 1993;95:29-33S.
- 72 Selby P. Calcium and the skeleton. *Osteoporosis Rev* 1995;3:4-5.
- 73 Carrie Fassler AL, Bonjour JP. Osteoporosis as a pediatric problem. *Pediatr Clin North Am* 1995;42:811-24.
- 74 Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *Am J Med* 1995;98:331-5.
- 75 Selby PL. Calcium requirements—a reappraisal of the methods used in its determination and their application to patients with osteoporosis. *Am J Clin Nutr* 1994;60:944-8.
- 76 NIH Consensus Development Panel on Optimal Calcium Intake. Optimal calcium intake. *JAMA* 1994;272:1942-8.
- 77 Compston JE. The role of vitamin D and calcium supplementation in the prevention of osteoporotic fractures in the elderly. *Clin Endocrinol* 1995;43:393-405.
- 78 Bell NH. Vitamin D metabolism, aging and bone loss. *J Clin Endocrinol Metab* 1995;80:1051.
- 79 Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJ, Bouter LM, Lips P. Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial. *J Clin Endocrinol Metab* 1995;80:1052-8.
- 80 Chapuy MC, Arlot ME, Duboeuf F, *et al.* Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med* 1992;327:1637-42.
- 81 Tilyard MW, Spears GFS, Thompson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N Engl J Med* 1992;326:357-62.
- 82 Orimo H, Shiraki M, Hayashi Y, *et al.* Effects of 1 alpha-hydroxyvitamin D3 on lumbar bone mineral density and vertebral fractures in patients with postmenopausal osteoporosis. *Calcif Tiss Int* 1994;54:370-6.
- 83 Shiraki M, Ito H, Orimo H. The ultra long-term treatment of senile osteoporosis with 1 alpha-hydroxyvitamin D3. *Bone Miner* 1993;20:223-34.
- 84 Riggs BL. Formation-stimulating regimens other than sodium fluoride. *Am J Med* 1993;95:62-8S.
- 85 Johansen JS, Hassager C, Podenphant J. Treatment of postmenopausal osteoporosis: is the anabolic steroid nandrolone deconatoate a candidate? *Bone Miner* 1989;6:77-86.
- 86 Brandi ML. Flavonoids: biochemical effects and therapeutic applications. *Bone Miner* 1992;S3:S3-14.
- 87 Reginster JY. Ipriflavone: pharmacological properties and usefulness in postmenopausal osteoporosis. *Bone Miner* 1993;23:223-32.
- 88 Cheng S, Zhang S, Nelson TL, Warlow PM, Civitelli R. Stimulation of human osteoblast differentiation and function by ipriflavone and its metabolites. *Calcif Tiss Int* 1994;55:556-62.
- 89 Kovacs AB. Efficacy of ipriflavone in the prevention and treatment of postmenopausal osteoporosis. *Agents Actions* 1994;41:86-7.
- 90 Valente M, Bufalino L, Castiglione GN, *et al.* Effects of 1-year treatment with ipriflavone on bone in postmenopausal women with low bone mass. *Calcif Tiss Int* 1994;54:377-80.
- 91 Gambacciani M, Spinetti A, Cappagli B, *et al.* Effects of ipriflavone administration on bone mass and metabolism in ovariectomized women. *J Endocrinol Invest* 1993;16:333-7.
- 92 Agnusdei D. Effect of ipriflavone in established osteoporosis, and long term safety. *Osteoporosis Int* 1996;6(suppl 1):318.
- 93 Hewison M. New trends in bone research. *J R Coll Physicians Lond* 1995;29:383-7.
- 94 Oursler MJ, Spelsberg TC. Echinatin: a potential new drug for osteoporosis. *Endocrinology* 1993;132:939-40.
- 95 Crippes BA, Engelman WV, Settle SL, *et al.* Antibody to β_3 integrin inhibits osteoclast-mediated bone resorption in the thyroparathyroidectomized rat. *Endocrinology* 1996;137:918-23.
- 96 King K, D'Anza JJ, Bodary SC, *et al.* The effects of kistrin on bone resorption in vitro and in vivo. *J Bone Miner Res* 1994;9:381-7.
- 97 Vaananen HK, Karhukorpi EK, Sundquist K, *et al.* Evidence for the presence of a proton pump of the vacuolar H⁺ ATPase type in the ruffled border of osteoclasts. *J Cell Biol* 1990;111:1305-11.
- 98 David P, Baron R. The vacuolar H⁺ATPase: a potential target for drug development in bone diseases. *Expert Opin Invest Drugs* 1995;4:725-40.
- 99 Pittner RA, Albrandt K, Beaumont K, *et al.* Molecular physiology of amylin. *J Cell Biochem* 1994;55:S19-28.
- 100 Cooper GJC. Amylin compared with calcitonin gene-related peptide: structure, biology and relevance to metabolic diseases. *Endocrine Rev* 1994;15:163.
- 101 Cornish J, Callon KE, Cooper GJ, Reid IR. *Biochem Biophys Res Commun* 1995;207:133-9.
- 102 Riggs BL, Hodgson SF, O'Fallon WM, *et al.* Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med* 1990;322:802-9.
- 103 Kleerekoper M, Peterson EL, Nelson DA, Phillips E, Schork MA, Tilley BC. A randomized trial of sodium fluoride as a treatment for postmenopausal osteoporosis. *Osteoporosis Int* 1991;1:155-61.
- 104 Ringe JD, Meunier PJ. What is the future for fluoride in the treatment of osteoporosis? *Osteoporosis Int* 1995;5:71-4.
- 105 Kanis JA. Effect of fluoride on postmenopausal osteoporosis. *N Engl J Med* 1990;323:416.
- 106 Lindsay R. Fluoride and bone-quantity versus quality. *N Engl J Med* 1990;322:845-6.
- 107 Riggs BL, O'Fallon WM, Lane A, *et al.* Clinical trial of fluoride therapy in postmenopausal osteoporotic women: extended observations and additional analysis. *J Bone Miner Res* 1994;9:265-75.
- 108 Pak CY, Sakhaee K, Adams-Huet B, *et al.* Treatment of postmenopausal osteoporosis with slow-release sodium fluoride. Final report of a randomized controlled trial. *Ann Intern Med* 1995;123:401-8.
- 109 Mohan S, Baylink DJ. Bone formation factors. *Clin Orthop Rel Res* 1991;263:30-48.
- 110 Schmid C. IGFs: function and clinical importance. 2. The regulation of osteoblast function by hormones and cytokines with special reference to insulin-growth factors and their binding proteins. *J Intern Med* 1993;234:535-42.
- 111 Mochizuki H, Hakeda Y, Wakatsuki N, *et al.* Insulin-like growth factor I supports formation and activation of osteoclasts. *Endocrinology* 1992;131:1075-80.
- 112 Centrella M, Horowitz MC, Wozney JM, McCarthy TL. Transforming growth factor- β gene family members and bone. *Endocrine Rev* 1994;15:27-39.
- 113 Hill PA, Reynolds JJ, Meikle ME. Osteoblasts mediate insulin-like growth factor-I and -II: stimulation of osteoclast formation and function. *Endocrinology* 1995;136:124-31.
- 114 Mackie EJ, Trechsel U. Stimulation of bone formation in vivo by transforming growth factor β : remodelling of woven bone and lack of inhibition by indomethacin. *Bone* 1990;11:295-300.
- 115 Wemeau JL. Calcitropic hormones and ageing. *Hormone Res* 1995;43:76-9.
- 116 Rosen CJ. Growth hormone, insulin-like growth factors, and the senescent skeleton: Ponce de Leon's Fountain revisited? *J Cell Biochem* 1994;56:348-56.
- 117 Nicolas V, Prewett A, Bettica P, *et al.* Age-related decreases in insulin-like growth factor-I and transforming growth factor-beta in femoral cortical bone from both men and women: implications for bone loss with aging. *J Clin Endocrinol Metab* 1994;78:1011-6.
- 118 Nicolas V, Mohan S, Honda Y, *et al.* An age-related decrease in concentration of insulin-like growth factor binding protein-5 in human cortical bone. *Calcif Tiss Int* 1995;57:206-12.
- 119 Bennett AE, Wahner HW, Riggs BL, Hintz RL. Insulin-like growth factors I and II: aging and bone density in women. *J Clin Endocrinol Metab* 1998;59:701-4.
- 120 Ljunghall S, Johansson AG, Burman P, Kampe O, Lindh E, Karlsson FA. Low plasma levels of insulin-like growth factor 1 (IGF-1) in male patients with idiopathic osteoporosis. *J Intern Med* 1992;232:59-64.
- 121 Reed BY, Zerwekh JE, Sakhaee K, Brelau NA, Gottshalk F, Pak CY. Serum IGF is low and correlated with osteoblastic surface in idiopathic osteoporosis. *J Bone Miner Res* 1995;10:1218-24.
- 122 Ebeling PR, Jones JD, O'Fallon WM, Janes CH, Riggs BL. Short-term effects of recombinant human insulin-like growth factor I on bone turnover in normal women. *J Clin Endocrinol Metab* 1993;77:1384-7.
- 123 Johansson AG, Lindh E, Ljunghall S. Insulin-like growth factor I stimulates bone turnover in osteoporosis. *Lancet* 1992;339:1619.
- 124 Rubin CD, Reed B, Sakhaee K, Pak CY. Treating a patient with the Werner syndrome and osteoporosis using recombinant human insulin-like growth factor. *Ann Intern Med* 1994;121:665-8.
- 125 Turner CH. Toward a cure for osteoporosis: reversal of excessive bone fragility. *Osteoporosis Int* 1991;2:12-19.

- 126 Johansson AG, Lindh E, Ljunghall S. Growth hormone, insulin-like growth factor I, and bone: a clinical review. *J Intern Med* 1993;234:553-60.
- 127 Inzucchi SE, Robbins RJ. Clinical review 61: effects of growth hormone on human bone biology. *J Clin Endocrinol Metab* 1994;79:691-4.
- 128 Rosen T, Johannsson G, Johannsson JO, Bengtsson BA. Consequences of growth hormone deficiency in adults and the benefits and risks of recombinant human growth hormone treatment. A review paper. *Hormone Res* 1995;43:93-9.
- 129 Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF. Effects of human growth hormone in men over 60 years old. *N Engl J Med* 1990;232:1-6.
- 130 Holloway L, Kohlmeier L, Marcus R. Effects of cyclic recombinant human growth hormone and salmon calcitonin on bone mineral density and bone turnover in postmenopausal women. *J Bone Miner Res* 1995;10:S253.
- 131 Dempster DW, Cosman F, Parisien M, Shen V, Lindsay R. Anabolic actions of parathyroid hormone on bone. *Endocrine Rev* 1993;14:690-709.
- 132 Brown EM, Gamba G, Riccardi D, Lombardi M. Cloning and characterisation of an extracellular Ca^{2+} -sensing receptor from bovine parathyroid. *Nature* 1993;366:575-80.
- 133 Tsurukami H, Nakamura T, Suzuki K, Sato K, Higuchi Y, Nishii Y. A novel synthetic vitamin D analogue, 2 beta-(3-hydroxypropoxy)1 alpha, 25-dihydroxyvitamin D3 (ED-71), increases bone mass by stimulating the bone formation in normal and ovariectomized rats. *Calcif Tiss Int* 1994;54:142-9.
- 134 Keeting PE, Oursler MJ, Wiegand KE, Bonde SK, Spelsberg TC, Riggs BL. Zeolite A increases proliferation differentiation and transforming growth factor β in normal adult human osteoblast-like cells in vitro. *J Bone Miner Res* 1992;7:1281-9.
- 135 Brandi ML. New treatment strategies: ipriflavone, strontium, vitamin D metabolites and analogs. *Am J Med* 1993;95:69-74S.
- 136 Marie PJ, Hott M, Modrowski D, et al. An uncoupling agent containing strontium prevents bone loss by depressing bone resorption and maintaining bone formation in estrogen-deficient rats. *J Bone Miner Res* 1993;8:607-15.
- 137 Marie PJ, Hott M, Modrowski D, et al. S-12911, a new agent containing strontium, inhibits bone loss due to immobilisation in rats. *J Bone Miner Res* 1995;10:S165.
- 138 Delmas PD, Sebert JL, Albanese CV, et al. The strontium salt S-12911: a new candidate for the treatment of osteoporosis. *Osteoporosis Int* 1996;6(suppl 1):241.
- 139 Gough AK, Lilley J, Eyre S, Holder RL, Emery P. Generalised bone loss in patients with early rheumatoid arthritis. *Lancet* 1994;344:23-7.
- 140 Dempster DW. Bone histomorphometry in glucocorticoid-induced osteoporosis. *J Bone Miner Res* 1989;4:137-41.
- 141 Eastell R. Management of corticosteroid-induced osteoporosis. *J Intern Med* 1995;237:439-47.
- 142 Olbricht T, Benker G. Glucocorticoid-induced osteoporosis: pathogenesis, prevention and treatment, with special regard to the rheumatic diseases. *J Intern Med* 1993;234:237-44.
- 143 Grotz WH, Mundinger FA, Gugel B, Exner VM, Kirste G, Schollmeyer PJ. Bone mineral density after kidney transplantation. A cross-sectional study in 190 graft recipients up to 20 years after transplantation. *Transplantation* 1995;59:982-6.
- 144 Sambrook P, Birmingham J, Kelly P, et al. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. *N Engl J Med* 1993;328:1747-52.
- 145 Sambrook PN, Kelly PJ, Keogh AM, et al. Bone loss after heart transplantation: a prospective study. *J Heart Lung Transplant* 1994;13:116-20.
- 146 Reid IR, Heap SW. Determinants of vertebral mineral density in patients receiving long-term glucocorticoid therapy. *Arch Intern Med* 1990;150:2545-8.
- 147 Aaron JE, Francis RM, Peacock M, Makins NB. Contrasting microanatomy of idiopathic and corticosteroid-induced osteoporosis. *Clin Orthop Rel Res* 1987;243:294-305.
- 148 Esteban NV, Loughlin T, Yergely AL. Daily cortisol production rate in man determined by stable isotope dilution / mass spectrometry. *J Clin Endocrinol Metab* 1991;71:39-45.
- 149 Kleerekoper M. Skeletal recovery after treatment of Cushing's: still room for improvement. *J Clin Endocrinol Metab* 1995;80:2856-7.
- 150 Pocock NA, Eisman JA, Dunstan C, Evans R, Thomas D, Laila Huq N. Recovery from steroid-induced osteoporosis. *Ann Intern Med* 1987;107:319-23.
- 151 Hermus AR, Smals AG, Swinkels LM, et al. Bone mineral density and bone turnover before and after surgical cure of Cushing's syndrome. *J Clin Endocrinol Metab* 1995;80:2859-65.
- 152 Reid IR, Ibbertson HK. Calcium supplements in the prevention of steroid-induced osteoporosis. *Am J Clin Nutr* 1986;44:287-90.
- 153 Olgaard K, Storm T, van Wouern N, et al. Glucocorticoid-induced osteoporosis in the lumbar spine, forearm, and mandible of nephrotic patients: a double-blind study on the high-dose, long-term effects of prednisone versus deflazacort. *Calcif Tiss Int* 1992;50:490-7.
- 154 Reid IR, Grey AB. Corticosteroid osteoporosis. *Baillieres Clin Rheumatol* 1993;7:573-87.
- 155 Luengo M, Picado C, Del Rio L, Guanabens N, Montserrat JM, Setoain J. Treatment of steroid-induced osteopenia with calcitonin in corticosteroid-dependent asthma. *Am Rev Respir Dis* 1990;142:104-7.
- 156 Meys E, Terreaux-Duvert F, Beaume-Six T, Dureau G, Meunier PJ. Bone loss after cardiac transplantation: effects of calcium, calcitriol and monofluorophosphate. *Osteoporosis Int* 1993;3:322-9.
- 157 Orwoll ES, Klein RF. Osteoporosis in men. *Endocrine Rev* 1995;16:87-116.
- 158 Seeman E. The dilemma of osteoporosis in men. *Am J Med* 1995;98:76-88S.
- 159 Baillie SP, Davison CE, Johnson FJ, Francis RM. Pathogenesis of vertebral crush fractures in men. *Age Ageing* 1992;21:139-41.
- 160 Peris P, Guanabens N, Monegal A, et al. Aetiology and presenting symptoms in male osteoporosis. *Br J Rheumatol* 1995;34:936-41.
- 161 Anderson FH, Francis RM, Faulkner K. Androgen supplementation in eugonadal men with osteoporosis—effects of 6 months treatment on bone mineral density and cardiovascular risk factors. *Bone* 1996;18:171-7.
- 162 Frost HM. Treatment of osteoporosis by manipulation of coherent bone cell populations. *Clin Orthop Rel Res* 1979;143:227-44.