Osteoporosis IV

Treatment of postmenopausal osteoporosis

Pierre D Delmas

The aim of treatment of postmenopausal osteoporosis is to reduce the frequency of vertebral and non-vertebral fractures (especially at the hip), which are responsible for morbidity associated with the disease. Results of large placebo controlled trials have shown that alendronate, raloxifene, risedronate, the 1-34 fragment of parathyroid hormone, and nasal calcitonin, greatly reduce the risk of vertebral fractures. Furthermore, a large reduction of non-vertebral fractures has been shown for alendronate, risedronate, and the 1-34 fragment of parathyroid hormone. Calcium and vitamin D supplementation is not sufficient to treat individuals with osteoporosis but is useful, especially in elderly women in care homes. Hormone replacement therapy remains a valuable option for the prevention of osteoporosis in early postmenopausal women. Choice of treatment depends on age, the presence or absence of prevalent fractures, especially at the spine, and the degree of bone mineral density measured at the spine and hip. Non-pharmacological interventions include adequate calcium intake and diet, selected exercise programmes, reduction of other risk factors for osteoporotic fractures, and reduction of the risk of falls in elderly individuals.

Osteoporosis is a worldwide health issue, with a high prevalence of disease not only in western countries but also in Asia and Latin America. Of various fragility fractures, which represent the major complication of the disease, vertebral and hip fractures are associated with pronounced morbidity and excess mortality. Thus, the prevention and treatment of osteoporosis should be aimed at reducing substantially this risk of fracture. Although many agents have been suggested for the treatment of osteoporosis, only in the past 10 years have large double blind placebo controlled trials been done in postmenopausal women with the condition, with incident vertebral and non-vertebral fracture as a primary endpoint. Results of these trials have shown that several agents reduce greatly (by 30–50%) the risk of fractures (panel 1). This review will focus on such trials whenever available.

Because a low bone mass is the major risk factor for fractures, the treatment of osteoporosis focuses on agents that prevent bone loss or even increase bone mass. Osteoporosis, however, is a multifactorial disease, and skeletal fragility results from various factors. Thus, achievement of optimum bone health should be the aim throughout life, by age-specific non-pharmacological intervention.

Available treatments

Calcium and vitamin D

Calcium is an important nutrient in the prevention and treatment of osteoporosis. Although calcium supplied in the form of dairy products is as effective as calcium supplements, supplements are necessary in most countries to achieve an adequate calcium intake. Calcium slows the rate of bone loss, especially in elderly women and in those with a low calcium intake. Findings of some studies suggest a reduction in the frequency of fractures in patients who receive calcium supplements.[1–3] Calcium is generally prescribed as an adjunct to other drugs for osteoporosis, and in most trials active and placebo groups receive the mineral (500–1000 mg daily). Thus, calcium supplementation is useful but not sufficient to treat individuals with osteoporosis. Calcium supplementation of about 500–1500 mg per day is safe, though mild gastrointestinal disturbances such as constipation are often reported. The risk of kidney-stone disease related to increased urinary calcium excretion does not seem to be raised in those who take supplements. Bioavailability is greatest during meals and varies with different calcium salts, though these factors are probably of little clinical significance.

Vitamin D is also given as a treatment for osteoporosis. In a French study of 3270 elderly women (mean age 84 years) who lived in care homes and were treated for

Search strategy

This review is based on the available world literature published in English. The analysis of the efficacy of the drugs is almost completely based on double blind placebo-controlled trials with incident fractures as a primary endpoint.

Panel 1: **Antifracture efficacy of the most frequently used treatments of postmenopausal osteoporosis in addition to the effects of calcium or vitamin D supplementation, or both, as derived from placebo controlled randomised trials**

Drug	Vertebral fractures	Non-vertebral fractures (hip)
Alendronate	+++	++
Calcitonin (nasal)	+	0
Etidronate	+	0
Fluoride	±	–
Hormone replacement therapy*	+	0
Parathyroid hormone†	+++	++
Raloxifene	+++	0
Risedronate	+++	++
Vitamin D derivatives	±	0

+++=strong evidence; ++=good evidence; +=some evidence; ±=equivocal; 0=no effects; –=negative effects. *Evidence derived mainly from observational studies. †Effect on hip fractures not documented.

Lancet 2002; **359:** 2018–26

Claude Bernard University of Lyon, France, and INSERM Research Unit 403, Lyon (Prof P D Delmas MD)

Correspondence to: Prof Pierre D Delmas, Hôpital E Herriot, Pavillon F, 69437 Lyon Cedex 03, France (e-mail: delmas@lyon151.inserm.fr)

3 years with calcium (1200 mg daily) and vitamin D (800 IU daily), the probability of hip and all non-vertebral fractures was significantly reduced by 29% and 24%, respectively, compared with placebo.[4,5] The findings of two other smaller studies[6,7] suggest a trend for a reduction in non-vertebral fractures in elderly men and women treated with annual intramuscular injection of vitamin D or a daily supplement of calcium and vitamin D. Conversely, in a Dutch study[8] of 2578 elderly but fairly healthy women with a high calcium intake, daily supplementation with vitamin D 400 IU over 3·5 years had no effect on the risk of hip fracture. Taken together, these data indicate that vitamin D should be used routinely in individuals who live in care homes because of a high prevalence of vitamin D deficiency related to low vitamin D intake, low sunshine exposure, and impaired vitamin D synthesis in the skin. When compliance is low, vitamin D 150 000–300 000 U can be given intramuscularly twice a year. Vitamin D at this dose is safe and does not require monitoring. The efficacy of calcium and vitamin D supplementation in healthy elderly people with adequate dairy product intake and normal bone mineral density (BMD) has not been established.

Hormone replacement therapy (HRT)

Oestrogen stops bone loss in early, late, and elderly postmenopausal women by inhibition of bone resorption, resulting in a 5–10% increase in BMD over 1–3 years.[9–11] There is growing evidence that in elderly women such an increase in BMD can be achieved with smaller doses than those often used in early postmenopausal women, in the range of 0·5–1 mg of oral 17β-oestradiol, 25 μg of transdermal 17β-oestradiol, or 0·3 mg of conjugated equine oestrogens. Calcium supplements could enhance the effect of oestrogen on BMD.[12] When HRT is stopped, bone loss probably resumes at the same rate as after the menopause.[13–15]

Findings of several case-controlled and cohort studies[16–18] suggest that HRT decreases the risk of hip fracture by about 30%, and results of two small placebo controlled studies[9,19] done in women with osteoporosis suggest a 50% reduction in the risk of fractures of the spine. The results of a meta-analysis[20] of 13 randomised placebo controlled trials suggest a 33% (95% CI 45–98) reduction in vertebral fracture, and those of a meta-analysis[21] of 22 randomised trials indicate a 27% (0·56–0·94, p=0·02) reduction in non-vertebral fractures in a pooled analysis, with a 40% reduction for hip and wrist fractures alone. There has been no large placebo controlled trial of HRT in women with osteoporosis and with incident fractures as a primary endpoint, so the evidence for efficacy of postmenopausal HRT for prevention of osteoporotic fractures is much weaker than for other compounds. The fact that the reduction in fracture risk seems to be lost within 5 years of HRT withdrawal, irrespective of the duration of treatment, raises the issue of the optimum timing and duration of HRT.[22]

HRT has several non-skeletal effects (panel 2). Women who undergo hysterectomy can be given oestrogen alone. Those with an intact uterus, however, should be given oestrogen and a progestagen in a combined cyclic regimen, in women close to menopause, or in a combined continuous regimen, especially in women who are postmenopausal by more than 5 years, to reduce the risk of endometrial cancer.[23] With the exception of norethisterone acetate, which has an anabolic effect on bone cells, the addition of a progestagen does not affect the effect of oestrogen on bone metabolism.[24] Results of several observational studies[25,26] have shown a small increase in the risk of breast cancer after 10 years of HRT use. Findings of observational studies[27] have suggested a reduction in risk of coronary heart disease in women taking HRT, but this finding has not been confirmed in a randomised secondary prevention trial. HRT increases the risk of deep vein thrombosis and pulmonary embolism.[28] A beneficial effect on cognitive function has been suggested in retrospective analysis of HRT users, but not in randomised controlled studies.[29]

Panel 2: **Benefits and risks of long-term hormone replacement therapy in postmenopausal women**

Degree of evidence	Benefits	Risks
Strong	Relief of menopausal symptoms Prevention of bone loss	Vaginal bleeding Breast tenderness Deep vein thrombosis and pulmonary embolism
Moderate	Prevention of fractures	Increased risk of breast cancer after long-term use
Weak	Primary prevention of chronic heart disease Improvement of cognitive function, and prevention of Alzeihmer's disease	Slight increased risk of endometrial cancer Slight increased risk of ovarian cancer

Selective oestrogen receptor modulators (SERMs) and other oestrogen analogues

SERMs act as oestrogen agonists or antagonists, dependent on the target tissue. Tamoxifen, which has long been used as an adjuvant treatment in breast cancer, is an oestrogen antagonist in breast tissue but a partial agonist in bone, cholesterol metabolism, and the endometrium. Tamoxifen does not wholly prevent bone loss in postmenopausal women[30–32] but it does increase the risk of endometrial cancer,[33] precluding its widespread use in healthy postmenopausal women.

Raloxifene is a benzothiophene that competitively inhibits the action of oestrogen in the breast and the endometrium, and that acts as an oestrogen agonist on bone and lipid metabolism. In early postmenopausal women, raloxifene prevents postmenopausal bone loss at all skeletal sites, reduces markers of bone turnover to premenopausal concentrations, and reduces serum cholesterol concentration and its LDL fraction without stimulating the endometrium.[34,35] Results of the MORE study (Multiple Outcomes of Raloxifene Evaluation),[36] which involved 7705 women with osteoporosis, indicate that a 30% and 50% reduction of incident vertebral fractures in women with and without prevalent vertebral fractures, respectively, happens after treatment with raloxifene. However, no effects on non-vertebral fractures were noted (table).[36–43] In the MORE study, raloxifene also lowered the frequency of breast cancer by 70%.[44,45] The RUTH study will ascertain whether or not the decrease in LDL cholesterol and fibrinogen, seen in individuals taking raloxifene, can result in a reduction in coronary heart disease in the high-risk population of postmenopausal women as shown in the MORE study.[46] Raloxifene does not impair cognitive function in postmenopausal women and might even slow age-related cognitive deterioration; raloxifene-treated women did better than controls in two tests of verbal memory and attention.[47] Although rare, thromboembolic disease (venous thrombosis and pulmonary embolism) is increased in individuals treated with raloxifene, with a relative risk similar to that seen in

	Study	Risk profile of patients at baseline	Mean age (years)	Numbers of patients randomised	Fracture Incidence		
					Placebo	Drug	Relative risk (95% CI)
Vertebral fracture							
Drug		High					
Alendronate 5–10 mg	FIT-1[37]	Vertebral fractures	71	2027	15%	8%	0·53 (0·41–0·68)
Calcitonin 200 IU	PROOF[38]	Vertebral fractures	69	557	16%	11%	0·67 (0·47–0·97)
Raloxifene 60 mg	MORE-2[36]	Vertebral fractures	68	1539	21%	15%	0·70 (0·6–0·9)
Risedronate 5 mg	VERT-US[39]	Vertebral fractures	69	1628	16%	11%	0·51 (0·36–0·73)
Risedronate 5 mg	VERT-MN[40]	Vertebral fractures	71	815	29%	18%	0·59 (0·43–0·82)
rh 1–34 PTH 20 μg	Neer et al[41]	Vertebral fractures	69	892	14%*	5%*	0·35 (0·22–0·55)*
		Low					
Alendronate 5–10 mg	FIT-2[42]	No vertebral fractures	68	4432	3%	2%	0·56 (0·39–0·8)
		Subgroup of women with a T score <–2·5	..	1631	4%†	2%†	0·50 (0·31–0·82)†
Raloxifene 60 mg	MORE-1[36]	No vertebral fractures	65	3012	5%	2%	0·50 (0·4–0·8)
Hip fracture							
Drug							
Risodronate 2·5 and 5 mg	HIP[43]	70–80 years with osteoporosis	74	5445	3·2%	1·9	0·6 (0·4–0·9)
			..	..	5·7%‡	2·3%‡	0·4 (0·2–0·8)‡
		>80 years with or without osteoporosis	83	3886	5·1%	4·2%	0·8 (0·6–1·2)
Alendronate 5–10 mg	FIT-1[37]	Vertebral fractures	71	2027	2·2%	1·1%	0·49 (0·23–0·99)
Calcitonin 200 IU	PROOF[38]	Vertebral fractures	69	557	1·8%	1·2%	0·5 (0·2–1·6)
Risedronate 5 mg	VERT-US[39]	Vertebral fractures	69	1628	1·8%	1·4%	NA
Risedronate 5 mg	VERT-MN[40]	Vertebral fractures	71	815	2·7%	2·2%	NA
rh 1–34 PTH 20 μg	Neer et al[41]	Vertebral fractures	69	892	0·74%*	0·037%*	NA
Raloxifene 60 and 120 mg	MORE[36]	Osteoporosis (T score <–2·5) with or without vertebral fractures	67	7705	0·7%	0·8%	1·1 (0·6–1·9)
Alendronate 5 and 10 mg	FIT-2[42]	T score <–2·5	..	1631	1·6%	0·72%	0·44 (0·18–0·97)
		T score <–1·6	68	4432	0·8%	0·65%	0·79 (0·43–1·44)

3-year incidence extrapolated from 4·2 years in FIT–2, and 5 years in PROOF. NA=not available. *Incidence and relative risk at 21 months. †In subgroup of women with a T score <–2·5. ‡In subgroup of women with prevalent vertebral fractures.

Incidence of vertebral and hip fractures over 3 years (% of patients) and relative risk (95% CI) in pivotal trials done with alendronate, nasal calcitonin, raloxifene, risedronate, and the 1–34 fragment of recombinant human parathyroid hormone (rh 1–34 PTH) in the treatment of postmenopausal osteoporosis

those who take HRT.[45] Other SERMs are under development.

Tibolone is a synthetic steroid that acts on oestrogen, progesterone, and androgen receptors either directly or indirectly through its metabolites, with a different pattern according to the target tissue. Tibolone prevents bone loss in early and late postmenopausal women,[48,49] but its effects on fracture risk have not been investigated. The drug reduces menopausal symptoms, does not seem to affect the endometrium,[50] and does not induce breast tenderness, but its overall effect on the uterus and the breast should be studied in large long-term placebo controlled studies. Its effect on cardiovascular disease is also unknown.

Bisphosphonates

Bisphosphonates[51] are stable analogues of pyrophosphate characterised by a phosphorus-carbon-phosphorus (P-C-P) bond. By substituting for hydrogens on the carbon atom, various bisphosphonates have been synthesised, the potency of which depends on the length and structure of the side chain. Bisphosphonates have a strong affinity for bone apatite, which is the basis for their clinical use. They are potent inhibitors of bone resorption, reducing the recruitment and activity of osteoclasts and increasing their apoptosis through a molecular mechanism recently identified. The oral bioavailability of bisphosphonates is low, between 1% and 3% of the dose ingested, and is impaired by food, calcium, iron, coffee, tea, and orange juice. These drugs are quickly cleared from plasma, with about 50% deposited in bone and 50% excreted in urine. The half-life of bisphosphonates in bone is several years. The safety profile of bisphosphonates is favourable; mild-to-moderate gastrointestinal discomfort that rarely results in discontinuation of medication has been reported for all (dyspepsia, abdominal pain, diarrhoea). Rare instances of oesophagitis have also been reported with alendronate.[52] Furthermore, etidronate, but not other bisphosphonates, can induce a mineralisation defect of bone after long-term use, especially in patients with renal insufficiency. The table shows their effects on fractures.

Etidronate was the first bisphosphonate developed. Administered intermittently (400 mg per day for 2 weeks, repeated every 3 months), etidronate increases the BMD of the spine by about 4%, with a reduction of vertebral fracture rate at 2 years[53,54] that was no longer significant after 3 years of treatment in one of two studies.[55] Findings of a meta-analysis[56] of trials of controlled etidronate done over 1–4 years suggest a reduction of vertebral fractures with a relative risk of 0·63 (95% CI 0·44–0·92), but no effect was noted for non-vertebral fractures.

Alendronate prevents postmenopausal bone loss.[57,58] Results of a study[37] in 2025 women with osteoporosis and at least one prevalent vertebral fracture who were treated with alendronate 5 mg daily for 2 years followed by 10 mg daily in a third year showed a 50% reduction of vertebral, wrist, and hip fractures compared with placebo. Women with low BMD but without vertebral fracture at baseline[42] were given alendronate for 4 years with the same placebo controlled design. There was a small though insignificant decrease in frequency of clinical fractures with alendronate (p=0·07), whereas the frequency of new vertebral fractures was significantly reduced by the treatment.[42] When the analysis was restricted to patients with osteoporosis diagnosed according to the WHO criteria—ie, with a BMD less than 2·5 SD below the mean value of healthy premenopausal women (T score ⩽–2·5)—the reduction of all types of clinical fractures was significant.[42] Findings of a pooled analysis[59] of women with osteoporosis who were involved in both FIT studies[37,42] indicate that the reduction of the risk of fracture with alendronate happens early, within

12–18 months. Results of another placebo controlled study[60] in 1908 postmenopausal women with a low BMD (T score ≤–2) show a 47% reduction in the risk of non-vertebral fracture after 1 year of alendronate 10 mg daily.[60] The optimum duration of treatment is unknown. Findings of one study[61] suggest that 7 years of treatment with alendronate is safe, but there might not be additional benefit after 5 years, on the basis of changes of BMD and bone turnover markers. Alendronate 70 mg given once a week has a good safety profile and the same efficacy as 10 mg daily in increasing BMD and reducing bone turnover.[62] Administration once a week rather than daily might improve long-term compliance, a challenge in such a chronic disease.

Risedronate prevents postmenopausal bone loss.[63] 5 mg per day significantly reduced the cumulative incidence of patients with new vertebral fractures by 41% over 3 years and by 65% after the first year in 2400 women with prevalent vertebral fractures.[39] In another study,[40] in 1226 patients with severe osteoporosis (at least two prevalent vertebral fractures), treatment with risedronate resulted in a 49% reduction of vertebral fracture incidence at 3 years. The overall incidence of non-vertebral fracture in two studies was reduced by 30–40%.[39,40] Effects of risedronate on hip fracture have been assessed in 5445 women aged 70–79 years with osteoporosis defined by a low BMD, and in 3896 women older than age 80 years who were mainly recruited on the basis of clinical risk factors for falls, without BMD assessment in most.[43] The overall analysis showed a 30% reduction of hip fracture (p=0·02) with risedronate over 3 years. In the first group, the reduction of hip fractures was large (40%), reaching 60% in those with prevalent vertebral fractures. By contrast, there was no significant reduction in the second group, emphasising the need to target bisphosphonates to women who have osteoporosis as confirmed by BMD measurement.

Clodronate, another bisphosphonate, was developed more than 20 years ago and is still widely used for the treatment of malignant bone diseases. In a study of 677 individuals with osteoporosis, including post-menopausal, secondary, and male osteoporosis, clodronate 800 mg daily decreased significantly the incidence of new vertebral fractures by 46%.[64] Tiludronate is a bisphosphonate used in several countries for the treatment of Paget's disease of bone, though its development as a possible treatment for osteoporosis has been discontinued because of absence of evidence of fracture reduction in large phase III trials. Oral daily pamidronate might be effective in osteoporosis but is associated with a high frequency of upper gastrointestinal adverse events.[65] Intravenous infusion of pamidronate, commonly used in malignant bone disease and in Paget's disease of bone, increases BMD at the spine and hip when infused every 3 months in patients with osteoporosis.[66] No fracture data are available. Ibandronate and zoledronate, two new potent bisphosphonates, are in phase III trials.

Calcitonin

Calcitonin, a peptide produced by thyroid C cells, reduces bone resorption by direct inhibition of osteoclast activity. When given subcutaneously or intramuscularly, tolerance is sometimes poor (nausea, facial flushes, diarrhoea), whereas intranasal administration of salmon calcitonin has no significant side-effects. The minimum intranasal dose needed for a significant effect on BMD is 200 IU daily. Calcitonin is less effective in prevention of cortical bone loss than cancellous bone loss in postmenopausal women.[67,68] Findings of a small controlled study[69] in osteoporotic women suggest a reduction in new fractures in those taking the drug. Furthermore, in the PROOF (Prevent Recurrence Of Osteoporotic Fractures) study,[38] which is a 5-year double blind randomised placebo controlled study of 1255 postmenopausal women with osteoporosis, intranasal salmon calcitonin 200 IU per day seemed to reduce the rate of vertebral, but not peripheral, fractures by about 30% by comparison with placebo. However, 60% of individuals in the study were lost to follow-up, doses of 100 and 400 IU had no effect, and no consistent effect on BMD and bone turnover markers was noted.

Parathyroid hormone (PTH)

Excess secretion and continuous intravenous infusion of PTH result in increased bone resorption and bone loss. By contrast, there is compelling evidence, in a range of species made osteoporotic by gonadectomy, that intermittent PTH injection restores bone strength by stimulation of new bone formation at the periosteal (outer) and endosteal (inner) bone surfaces, thickening the cortices and existing trabeculae of the skeleton, and perhaps increasing trabecular numbers and their connectivity.[70] In a double blind placebo controlled prospective study[41] in 1637 postmenopausal women with previous vertebral fractures, daily treatment with subcutaneous 1–34 fragment recombinant human PTH 20 μg or 40 μg for a median of 19 months reduced greatly the incidence of new vertebral fracture (relative risk 0·35 and 0·31 for the respective doses). The incidence of non-vertebral fragility fractures was reduced by 53% with both doses (table). BMD increased by 9% and 12% at the spine, by 3% and 6% at the femoral neck, and by 2% and 4% overall after administration of PTH 20 μg and 40 μg, respectively, after 21 months of observation. High-dose PTH occasionally caused nausea and headache. There was a dose-dependent rise in serum calcium within 4–6 h after injection that was mild and transient, occuring in 11% of patients who recieved PTH 20 μg. In long-term toxicological studies, high doses of PTH induced osteosarcomas in rats but not in monkeys. In clinical studies in about 1000 patients, treatment with PTH or its fragments for up to 3 years has not increased the frequency of tumours in bone or other tissues. PTH 20 μg per day has been submitted for approval for treatment of osteoporosis in the USA and Europe.

Other treatments

Alfacalcidol and calcitriol are vitamin D analogues and are used in some countries for the treatment of osteoporosis. Both compounds induce a small increase in BMD that seems to be limited to the spine. Data on reduction of fracture risk are scarce and conflicting.[71–74] In a large randomised study that was not placebo controlled,[75] the rate of vertebral fracture was reduced in individuals with osteoporosis who received calcitriol compared with those who received calcium alone. This result might have been biased by an unusual increase of the annual fracture rate in the calcium group with time. No study has compared the effect of vitamin D derivatives versus calcium plus vitamin D on fracture risk. Vitamin D derivatives expose patients to hypercalcaemia and hypercalciuria. Serum and urine calcium concentrations should, therefore, be monitored in patients on these drugs, and the dose adapted when necessary.

When administered, fluoride is incorporated into the hydroxyapatite component of bone, and stimulates osteoblast recruitment and activity, thus increasing the rate of bone formation. In human beings, sodium fluoride

increases spine BMD linearly with time, with little effect at the hip. The findings of two large placebo controlled trials,[76,77] of the effect of different preparations and doses of fluoride salts on incidence of vertebral fractures, indicate that fluoride does not decrease the rate of these fractures. These results do not concur with those of an earlier report.[78] There is also some evidence that fluoride might have an adverse effect on the risk of hip fracture. The use of fluoride in the treatment of postmenopausal osteoporosis cannot be recommended.

Vitamin K has also been suggested as a treatment option for osteoporosis. Serum concentrations of circulating vitamin K, especially of the K2 moieties, fall as a person gets older, and are lower in patients with hip fractures than without such fractures. In the nurses' health study cohort,[79] low intake of vitamin K was associated with an increase risk of hip fracture. The consequences of this deficiency on bone metabolism are still speculative, but probably account for the increase in the under carboxylated fraction of serum osteocalcin, a marker of bone fragility in the elderly.[80] Treatment of patients with osteoporosis with menatetrenone, a vitamin K2 compound, has been associated with improved BMD[81] and is approved in Japan. A positive effect on fragility fractures is suggested by the results of a small controlled study.[82]

Strontium ranelate is under development for the treatment of postmenopausal osteoporosis. There is experimental evidence, both in vitro and in vivo, that this strontium salt reduces bone resorption and might stimulate bone formation.[83] A rise in BMD and a reduction in the frequency of vertebral fractures is suggested by results of a phase II trial.[84] Phase III trials will be completed soon. Growth hormone has been used in the treatment of osteoporosis because of its alleged bone and muscle anabolic properties. However, whether or not it can prevent bone loss in postmenopausal osteoporosis is unclear. Thiazide diuretics reduce tubular reabsorption of calcium and could decrease bone turnover and bone loss, but their role in the management of osteoporosis has not been established. Ipriflavone is a synthetic compound that belongs to the family of isoflavones. Although preliminary results suggested that it could prevent bone loss, the drug does not seem to reduce the incidence of fractures in osteoporotic women.[85] Finally, statins increase bone mass and strength in rats,[86] but results of epidemiological studies with respect to their effectiveness in the prevention of fractures are inconclusive.

Non-pharmacological intervention

Nutrition

Good nutrition and a balanced diet with adequate calories are important for normal growth. Calcium is the most important nutrient for attaining adequate peak bone mass, but there is no universal consensus about the daily calcium requirement by age. The 1994 consensus development conference on optimum calcium intake recommended 1200–1500 mg daily for adolescents, 1000 mg daily for adults up to age 65 years, and 1500 mg daily for postmenopausal women not receiving oestrogen and for elderly people.[87] A recent National Institute of Health panel has reinforced the importance of adequate calcium intake.[88] Although results of most studies indicate a beneficial effect of calcium supplementation, the long-term effect of a high dietary calcium intake on bone health is unclear. Conversely, there seems to be a threshold of calcium intake, around 400 mg per day, below which increasing calcium intake seems beneficial and necessary, both in children and in women older than age 60 years.

Vitamin D is essential for the intestinal absorption of calcium and, as discussed above, serum concentrations of 25-hydroxyvitamin D decline with age. Findings of several studies suggest that the daily intake of vitamin D should be around 400–800 IU if sunlight exposure is low. An adequate protein intake is essential in frail elderly individuals.

Exercise

Physical activity early in life contributes to high peak bone mass.[89] Various activities, including walking, weight training, and high impact exercises, induce a small (1–2%) increase in BMD at some but not all skeletal sites, that is not sustained once the exercise programme is stopped. The results of clinical trials and observational studies suggest that load bearing exercise is more effective for increasing bone mass than other types of exercise.[89] Fitness might indirectly protect individuals from fractures by improving mobility and muscle function, and by reducing the risk of falls.[90] Findings of observational studies suggest that regular exercise and recreational activity reduce hip and leg fracture risk but increase the risk of wrist fracture. After a vertebral fracture, a supervised exercise programme to maintain strength and flexibility of the thoracic and lumbar spine is recommended in elderly individuals. Specific interventions aimed at preventing falls and their consequences in the elderly need to be developed.[91] Results of controlled studies have shown that exercise can increase muscle mass and strength, and reduce the risk of falls by about 25% in frail elderly individuals.[92] However, no controlled study has shown that such exercise programmes can reduce the risk of fracture, irrespective of age.

Orthopaedic management of fractures

Early surgical management of hip fractures is essential to decrease mortality rate and to improve perioperative morbidity, which is pronounced—especially in frail elderly individuals. The surgical treatment of peripheral fragility fractures does not require specific procedures, since the rate at which fracture heals is much the same in patients of a similar age with and without osteoporosis. In patients with major pain related to a crushed vertebra, vertebral plasty, involving injection of polymetalmetacrylate cement into the vertebral body, has been suggested.[93] Although this procedure might have a beneficial effect on acute pain, the long-term effects on the subsequent risk of fractures of adjacent vertebrae have not been assessed in controlled studies.

Other measures

Treatments that predispose to osteoporosis—eg, chronic corticosteroid therapy—should be avoided whenever possible. In addition to an exercise programme, a strategy to decrease the risk of falls in elderly individuals should be implemented. Visual impairment and cataract should, for example, be detected and treated and, whenever possible, the use of drugs that increase the risk of falling—eg, basodiazepine, hypnotics, antidepressants, and medications that induce hypotension—should be reduced. Furthermore, patients should be instructed to avoid slippery floors and install adequate lighting at home. Finally, results of two controlled studies[94,95] done in elderly individuals in care homes have shown that the risk of hip fracture could be reduced as much as 50% by use of energy-absorbing external hip protectors.[94,95] However, long-term adherence with these devices is unknown.

Treatment choice

Decisions with respect to treatment of postmenopausal osteoporosis should be based on an assessment of the

patient's risk of fracture and on the efficacy and side-effects of drugs likely to be prescribed. Fracture risk depends mainly on the magnitude of bone loss. On the basis of results of epidemiological studies, algorithms are being derived to establish the 10-year probability of all low-trauma fractures (including spine, hip, and other sites) according to age, history of fractures, degree of bone mass (assessed by dual energy radiograph absorptiometry or other relevant techniques), and degree of bone resorption (assessed by specific biochemical markers). Such algorithms will provide an absolute risk of fractures, and should help doctors to make a treatment decision. In general, patients with higher absolute risk will derive greater benefit from treatment. However, results of trials with bisphosphonate suggest that the drug will only reduce rate of non-vertebral fractures in individuals with a T score less than –2·5, irrespective of the absolute fracture risk derived from assessment of other risk factors. The decision on when and how to treat, therefore, depends on the clinical presentation.

Individuals with fractures

Vertebral fracture is probably the most common form of osteoporosis in postmenopausal women aged older than 60 years. Other causes of vertebral fractures, such as malignant disease, need to be ruled out by adequate clinical and biological investigation. Although knowledge of degree of BMD is not necessary to make a treatment decision, this index is usually measured. Individuals with a fragility vertebral fracture should always be treated, since their risk of further vertebral fractures is very high, around 20% in the 12 months after a previous break.[96] Alendronate, risedronate, and raloxifene are the best treatment options, based on the scientific evidence.

In patients with other low-trauma fractures, the existence of skeletal fragility underlying the fracture needs to be assessed by BMD measurement. In instances of a low BMD (T score $\leq$–1) treatment should be considered on the basis of the type of fracture (all hip fractures should be treated, whereas fractures of the toes and fingers are usually non-osteoporotic), the age of the patient, additional risk factors, and current BMD (fracture risk doubles for every 1SD decrease in BMD).

Women without a history of low-trauma fractures

If a postmenopausal woman has osteoporosis, according to the WHO definition—ie, T score less than or equal to –2·5—at the spine or hip, or both, the risk of fracture is high enough to justify treatment. If a woman has osteopenia (T score between –1 and –2·5) preventive treatment might be considered if BMD is in the lower range—ie, less than –2—or if there are other clinical risk factors for fractures.

Choice of treatment is affected by age. Thus, HRT is the first choice to prevent bone loss in early postmenopausal women with menopausal symptoms. Raloxifene is an attractive alternative for reducing the risk of vertebral fractures in middle and late postmenopausal women, especially if they are concerned about the risk of breast cancer. Bisphosphonates have no extra skeletal benefits, but reduce the risk of vertebral, hip, and other types of fractures. Thus, although they can be used at any age in postmenopausal women, they seem to be the first choice for women at highest risk of non-vertebral fracture, including elderly women, in whom the risk of hip fracture increases exponentially with age.

Monitoring therapy

As in most chronic diseases, compliance is poor in patients on long-term treatment for osteoporosis. Thus, the aim of monitoring should be to increase adherence to treatment, as well as to ascertain response to treatment. Because fracture events are uncommon, they cannot be used to monitor drug effectiveness. BMD measurement, especially at the spine, is often done once every 2 years, but the fairly low signal-to-noise ratio of this technique, and the antiresorptive nature of most treatments does not allow easy detection of responders to treatment. If a non-response—ie, a pronounced decrease of BMD—is detected, it should be confirmed by a subsequent measurement, to keep regression to the mean to a minimum.[97] Use of biochemical markers of formation and resorption has been proposed as a good way to monitor antiresorptive therapies. Findings of several studies have shown a significant inverse correlation between the short-term (3–6 months) fall in bone turnover markers and the 2–3 year rise in BMD at various skeletal sites with HRT and bisphosphonates.[98–100] Cut-off values for these decreases, for a specific marker and treatment that will identify responders and non-responders with adequate sensitivity and specificity have been proposed by the committee of scientific advisers of the International Osteoporosis Foundation.[101] Studies are being done to correlate short-term changes in bone turnover markers with the probability of future fractures in women with osteoporosis, and such an association has been reported for raloxifene[102] and risedronate.[103] Whether BMD measurement or bone markers, or both, are used to monitor treatment response, there remains no proof that such an approach improves long-term compliance to treatment.

Perspectives

Although there are several treatment options that reduce substantially the risk of fragility fractures, their mechanisms of action remain poorly understood. Most antiresorptive therapies induce a 2–10% increase in spinal BMD, though risk of fracture is reduced still further.[104] Additionally, raloxifene and alendronate increase spinal BMD by 2–3%[34] and 8%,[105] respectively, though the differences in subsequent vertebral fracture rate are modest. The rise in BMD seems to be mainly related to an increase in the amount of mineral per unit of bone, as shown by quantitative microradiography, rather than to an increase in true bone mass.[106] Reduced bone turnover is another determinant of fracture reduction and there are probably other mechanisms that are important, with changes in bone structure and biology that could vary according to the skeletal envelope.[107] Our incomplete understanding of the mechanism by which antiresorptive agents improve skeletal strength at some, but not necessarily all, skeletal sites deserve further investigation.

Because the mechanism of action of PTH is totally different from that of antiresorptive therapy, combination therapy could be an option for individuals with severe osteoporosis. In animals, antiresorptive drugs seem to maintain bone mass, structure, and strength when treatment with PTH is stopped, and drugs such as bisphosphonate, raloxifene, and HRT could have the same effect in people. Concomitant therapy with oestrogen does not seem to blunt the anabolic effects of PTH in postmenopausal women,[108] but there is no evidence that this combination produces a higher bone mass or greater bone strength than PTH alone. A combination of bisphosphonates (alendronate[109,110] or risedronate)[111] with HRT[109,111] or raloxifene[110] induces an increase in BMD slightly above that achieved with either treatment alone, but there is no evidence that it results in a greater reduction of the risk of fracture.

Conclusion

Poor awareness of the consequences means that few individuals who present with fragility fractures are treated for osteoporosis, despite availability of effective treatments. This situation needs to change, since fractures are associated with pronounced morbidity and mortality. Treatment should be offered to postmenopausal women with vertebral fractures, those with non-vertebral fractures associated with low BMD, and those with osteoporosis as defined by WHO. The most rigorously investigated drugs reported to reduce spinal fractures are alendronate, raloxifene, and risedronate, and the most thoroughly investigated drugs reported to reduce non-vertebral fractures are calcium and vitamin D in elderly individuals in care homes, and alendronate and risedronate in the community. PTH, with its ability to reduce the risk of vertebral and non-vertebral fractures, will also be an interesting alternative in patients with severe osteoporosis when approved.

Drugs are also available to prevent osteoporosis, and their prescription should be decided on a case-by-case basis, according to age, degree of BMD, and presence of other risk factors. HRT is the first choice of preventive treatment in early postmenopausal women with menopausal symptoms, whereas women at distance from menopause might prefer raloxifene, or a bisphosphonate in those at high risk of non-vertebral fractures.

Conflict of interest statement

P D Delmas has been a consultant for, a member on the advisory board of, has received honoraria for speaking from, and has received research grants from some or all of: Aventis, Boehringer, Chugaï, Cilag, Cis bio International, Glaxo Wellcome, HMR, Hybritech, Leiras, Lilly, Merck Damstadt, MSD, Novartis, Novo Nordisk, Organon, Osteometer, Pfizer, Procter and Gamble Pharmaceutical, Rhone Poulenc Rorer, Roche, Rotta, Sanofi Recherche, Servier, SmithKline Beecham, and Wyeth-Ayerst.

References

1 Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med* 1990; **323:** 878–83.

2 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:** 331–35.

3 Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Miner Res* 1996; **11:** 1961–66.

4 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.

5 Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *BMJ* 1994; **308:** 1081–82.

6 Heikinheimo RJ, Inkovaara JA, Harju EJ, et al. Annual injection of vitamin D and fractures of aged bones. *Calcif Tissue Int* 1992; **51:** 105–10.

7 Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997; **337:** 670–76.

8 Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. *Ann Intern Med* 1996; **124:** 400–06.

9 Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomised women. *Lancet* 1980; **2:** 1151–54.

10 The Writing Group for the PEPI. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. *JAMA* 1996; **276:** 1389–96.

11 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.

12 Nieves JW, Komar L, Cosman F, Lindsay R. Calcium potentiates the effect of estrogen and calcitonin on bone mass: review and analysis. *Am J Clin Nutr* 1998; **67:** 18–24.

13 Christiansen C, Christensen MS, Transbol I. Bone mass in postmenopausal women after withdrawal of oestrogen/gestagen replacement therapy. *Lancet* 1981; **1:** 459–61.

14 Felson DT, Zhang Y, Hannan MT, Kiel DP, Wilson PW, Anderson JJ. The effect of postmenopausal estrogen therapy on bone density in elderly women. *N Engl J Med* 1993; **329:** 1141–46.

15 Lindsay R, Hart DM, Fogelman I. Bone mass after withdrawal of oestrogen replacement. *Lancet* 1981; **1:** 729.

16 Kiel DP, Felson DT, Anderson JJ, Wilson PW, Moskowitz MA. Hip fracture and the use of estrogens in postmenopausal women. *N Engl J Med* 1987; **317:** 1169–74.

17 Maxim P, Ettinger B, Spitalny GM. Fracture protection provided by long-term estrogen treatment. *Osteoporos Int* 1995; **5:** 23–29.

18 Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur M, Mack TM. Menopausal estrogen therapy and hip fractures. *Ann Intern Med* 1981; **95:** 28–31.

19 Lufkin EG, Wahner HW, O'Fallon WM, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med* 1992; **117:** 1–9.

20 Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials. *BMC Musculoskelet Disord* 2001; **2:** 7.

21 Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001; **285:** 2891–97.

22 Cauley JA, Seeley DG, Ensrud K, Ettinger B, Black D, Cummings SR. Estrogen replacement therapy and fractures in older women. *Ann Intern Med* 1995; **122:** 9–16.

23 Beresford SA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. *Lancet* 1997; **349:** 458–61.

24 Delmas PD. Hormone replacement therapy in the prevention and treatment of osteoporosis. *Osteoporos Int* 1997; 7 (suppl 1)**:** S3–7.

25 Bergkvist L, Persson I. Hormone replacement therapy and breast cancer: a review of current knowledge. *Drug Saf* 1996; **15:** 360–70.

26 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.

27 Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; **335:** 453–61.

28 Grodstein F, Stampfer MJ, Goldhaber SZ, et al. Prospective study of exogenous hormones and risk of pulmonary embolism in women. *Lancet* 1996; **348:** 983–87.

29 Tang MX, Jacobs D, Stern Y, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 1996; **348:** 429–32.

30 Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992; **326:** 852–56.

31 Grey AB, Stapleton JP, Evans MC, Tatnell MA, Ames RW, Reid IR. The effect of the antiestrogen tamoxifen on bone mineral density in normal late postmenopausal women. *Am J Med* 1995; **99:** 636–41.

32 Delmas PD, Balena R, Confravreux E, Hardouin C, Hardy P, Bremond A. Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double-blind, placebo-controlled study. *J Clin Oncol* 1997; **15:** 955–62.

33 Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst* 1994; **86:** 527–37.

34 Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med* 1997; **337:** 1641–47.

35 Walsh BW, Kuller LH, Wild RA, et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. *JAMA* 1998; **279:** 1445–51.

36 Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999; **282:** 637–45.

37 Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996; **348:** 1535–41.

38 Chesnut CH 3rd, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. *Am J Med* 2000; **109:** 267–76.

39 Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 1999; **282:** 1344–52.

40 Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 2000; **11:** 83–91.

41 Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; **344:** 1434–41.

42 Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998; **280:** 2077–82.

43 McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001; **344:** 333–40.

44 Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA* 1999; **281:** 2189–97.

45 Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. *Breast Cancer Res Treat* 2001; **65:** 125–34.

46 Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year reults from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomised trial. *JAMA* 2002; **287:** 847–57.

47 Yaffe K, Krueger K, Sarkar S, et al. Cognitive function in postmenopausal women treated with raloxifene. *N Engl J Med* 2001; **344:** 1207–13.

48 Bjarnason NH, Bjarnason K, Haarbo J, Rosenquist C, Christiansen C. Tibolone: prevention of bone loss in late postmenopausal women. *J Clin Endocrinol Metab* 1996; **81:** 2419–22.

49 Berning B, Kuijk CV, Kuiper JW, Bennink HJ, Kicovic PM, Fauser BC. Effects of two doses of tibolone on trabecular and cortical bone loss in early postmenopausal women: a two-year randomized, placebo–controlled study. *Bone* 1996; **19:** 395–99.

50 Johannes EJ. Tibolone: vaginal bleeding and the specific endometrial response in postmenopausal women. *Gynecol Endocrinol* 1997; **11** (suppl 2)**:** 25–30.

51 Fleisch H. Bisphosphonates in bone disease: from the laboratory to the patient, 4th edn. San Diego: Academic Press, 2000.

52 de Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. *N Engl J Med* 1996; **335:** 1016–21.

53 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.

54 Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990; **323:** 73–79.

55 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.

56 Cranney A, Guyatt G, Krolicki N, et al. A meta-analysis of etidronate for the treatment of postmenopausal osteoporosis. *Osteoporos Int* 2001; **12:** 140–51.

57 Hosking D, Chilvers CE, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. *N Engl J Med* 1998; **338:** 485–92.

58 McClung M, Clemmesen B, Daifotis A, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis: a double-blind, randomized, controlled trial. *Ann Intern Med* 1998; **128:** 253–61.

59 Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. *J Clin Endocrinol Metab* 2000; **85:** 4118–24.

60 Pols HA, Felsenberg D, Hanley DA, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. *Osteoporos Int* 1999; **9:** 461–68.

61 Tonino RP, Meunier PJ, Emkey R, et al. Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. *J Clin Endocrinol Metab* 2000; **85:** 3109–15.

62 Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Aging (Milano)* 2000; **12:** 1–12.

63 Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC Jr. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. *J Clin Endocrinol Metab* 1998; **83:** 396–402.

64 McCloskey E, Selby P, de Takats D, et al. Effects of clodronate on vertebral fracture risk in osteoporosis: a 1-year interim analysis. *Bone* 2001; **28:** 310–15.

65 Lufkin EG, Argueta R, Whitaker MD, et al. Pamidronate: an unrecognized problem in gastrointestinal tolerability. *Osteoporos Int* 1994; **4:** 320–22.

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 Metab* 1994; **79:** 1595–99.

67 Reginster JY, Deroisy R, Lecart MP, et al. A double-blind, placebo-controlled, dose-finding trial of intermittent nasal salmon calcitonin for prevention of postmenopausal lumbar spine bone loss. *Am J Med* 1995; **98:** 452–58.

68 Overgaard K, Riis BJ, Christiansen C, Hansen MA. Effect of salcatonin given intranasally on early postmenopausal bone loss. *BMJ* 1989; **299:** 477–79.

69 Overgaard K, Hansen MA, Jensen SB, Christiansen C. Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose-response study. *BMJ* 1992; **305:** 556–61.

70 Seeman E, Delmas PD. Reconstructing the skeleton with intermittent parathyroid hormone. *Trends Endocrinol Metab* 2001; **12:** 281–83.

71 Orimo H, Shiraki M, Hayashi T, Nakamura T. Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1 alpha (OH)-vitamin D3. *Bone Miner* 1987; **3:** 47–52.

72 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 Tissue Int* 1994; **54:** 370–76.

73 Gallagher JC, Goldgar D. Treatment of postmenopausal osteoporosis with high doses of synthetic calcitriol: a randomized controlled study. *Ann Intern Med* 1990; **113:** 649–55.

74 Gallagher JC, Riggs BL, Recker RR, Goldgar D. The effect of calcitriol on patients with postmenopausal osteoporosis with special reference to fracture frequency. *Proc Soc Exp Biol Med* 1989; **191:** 287–92.

75 Tilyard MW, Spears GF, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N Engl J Med* 1992; **326:** 357–62.

76 Meunier PJ, Sebert JL, Reginster JY, et al. Fluoride salts are no better at preventing new vertebral fractures than calcium-vitamin D in postmenopausal osteoporosis: the FAVOS study. *Osteoporos Int* 1998; **8:** 4–12.

77 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:** 802–09.

78 Mamelle N, Meunier PJ, Dusan R, et al. Risk-benefit ratio of sodium fluoride treatment in primary vertebral osteoporosis. *Lancet* 1988; **2:** 361–65.

79 Feskonich D, Weber P, Willett WC, Rockett H, Booth S, Colditz G. Vitamin K intake and hip fractures in women: a prospective study. *Am J Clin Nutr* 1999; **69:** 74–79.

80 Szulc P, Chapuy MC, Meunier PJ, Delmas PD. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture in elderly women. *J Clin Invest* 1993; **91:** 1769–74.

81 Orimo H, Shiraki M. Clinical evaluation of menatetrenone in the treatment of involutional osteoporosis. IVth International Symposium on Osteoporosis 1993, Hong Kong: 148–49.

82 Shiraki M, Shiraki Y, Aoki C, Miura M. Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. *J Bone Miner Res* 2000; **15:** 515–21.

83 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.

84 Meunier PJ, Slosman DO, Delmas PD, et al. Strontium ranelate: dose-dependent effectsin established post menopausal vertabral osteoporosis—a 2-year randomised placebo controlled trial. *J Clin Endocrinol Metab* 2002; **87:** 2060–66.

85 Alexandersen P, Toussaint A, Christiansen C, et al. Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 2001; **285:** 1482–88.

86 Mundy G, Garrett R, Harris S, et al. Stimulation of bone formation in vitro and in rodents by statins. *Science* 1999; **286:** 1946–49.

87 Anon. NIH consensus development panel on optimal calcium intake. *JAMA* 1994; **272:** 1942–48.

88 Anon. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001; **285:** 785–95.

89 Marcus R. The mechanism of exercise effects on bone. In: Bilezikian JP, Raisz LG, Rodan GA, eds. Principles of bone biology. San Diego: Academic Press, 1996: 1435–45.

90 Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA,

Evans WJ. High-intensity strength training in nonagenarians: effects on skeletal muscle. *JAMA* 1990; **263:** 3029–34.
91 Tinetti ME, Baker DI, McAvay G, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med* 1994; **33:** 821–27.
92 Taaffe DR, Duret C, Wheeler S, Marcus R. Once-weekly resistance exercise improves muscle strength and neuromuscular performance in older adults. *J Am Geriatr Soc* 1999; **47:** 1208–14.
93 Lane JM, Girardi F, Parvataneni H, et al. Preliminary outcomes of the first 226 consecutive kyphoplasties for the fixation of painful osteoporotic vertebral compression fractures. *Osteoporos Int* 2000; **11**(suppl 2)**:** S206.
94 Lauritzen JB, Petersen MM, Lund B. Effect of external hip protectors on hip fractures. *Lancet* 1993; **341:** 11–13.
95 Kannus P, Parkkari J, Niemi S, et al. Prevention of hip fracture in elderly people with use of a hip protector. *N Engl J Med* 2000; **343:** 1506–13.
96 Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001; **285:** 320–23.
97 Cummings SR, Palermo L, Browner W, et al. Monitoring osteoporosis therapy with bone densitometry: misleading changes and regression to the mean. *JAMA* 2000; **283:** 1318–21.
98 Garnero P, Shih WJ, Gineyts E, Karpf DB, Delmas PD. Comparison of new biochemical markers of bone turnover in late postmenopausal osteoporotic women in response to alendronate treatment. *J Clin Endocrinol Metab* 1994; **79:** 1693–700.
99 Ravn P, Christensen JO, Baumann M, Clemmesen B. Changes in biochemical markers and bone mass after withdrawal of ibandronate treatment: prediction of bone mass changes during treatment. *Bone* 1998; **22:** 559–64.
100 Delmas PD, Hardy P, Garnero P, Dain M. Monitoring individual response to hormone replacement therapy with bone markers. *Bone* 2000; **26:** 553–60.
101 Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J. The use of biochemical markers of bone turnover in osteoporosis. *Osteoporos Int* 2000; **11**(suppl 6)**:** S2–17.
102 Bjarnason NH, Sarkar S, Duong T, Mitlak B, Delmas PD, Christiansen C. Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal osteoporosis. *Osteoporos Int* 2001; **12:** 922–30.
103 Eastell R, Barton I, Hannon R, et al. Antifracture efficacy of risedronate: prediction by change in bone resorption markers. *J Bone Miner Res* 2000; **16:** S163.
104 Riggs BL, Melton LJ 3rd, O'Fallon WM. Drug therapy for vertebral fractures in osteoporosis: evidence that decreases in bone turnover and increases in bone mass both determine antifracture efficacy. *Bone* 1996; **18** (suppl 3)**:** 197S–201S.
105 Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med* 1995; **333:** 1437–43.
106 Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. *Bone* 2000; **27:** 687–94.
107 Delmas PD. How does antiresorptive therapy decrease the risk of fracture in women with osteoporosis? *Bone* 2000; **27:** 1–3.
108 Lindsay R, Nieves J, Formica C, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet* 1997; **350:** 550–55.
109 Bone HG, Greenspan SL, McKeever C, et al. Alendronate and estrogen effects in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2000; **85:** 720–26.
110 Johnell O, Scheek WH, Lu Y, Reginster J-Y, Need AG, Seeman E. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002; **87:** 985–92.
111 Harris S, Eriksen EF, Davidson M, et al. Effects of combined risedronate and hormone replacement therapies on bone mineral density in postmenopausal women. *J Clin Endocrinol Metab* 2002; **86:** 1890–97.

Uses of error

A developing country perspective

Buddha Basnyat

One of the joys of working in Nepal is the gratitude the patient expresses when you try to help. Yet the doctor-patient ratio is low; the potential for error is high, and we may actually be negligent and unhelpful while the patient perceives us to be useful and dedicated. The story of one patient I mismanaged several years ago illustrates this point.

As a medical consultant that night I did not have a house officer with me. It was late and I felt I had had my fill of patients for that day. Then they wheeled in a fifty-year-old gentleman with abdominal pain and a history of peptic ulcer. He was tachycardic and anxious but his blood pressure was normal, and his abdomen soft with mild epigastric tenderness. He also complained of arthralgia and some mild weakness in his legs. I read the referral note which said that the patient had some black stool and therefore needed hospital admission. I found no blood on rectal examination, and no coffee grounds on nasogastric aspiration. I concluded that the main problem was his peptic ulcer. I admitted him to the general medical ward, scheduled a gastroscopy for the following day, and started omeprazole. I did not address his arthralgia nor his mild weakness beyond checking to see that he could grossly move his legs. I thought that many Nepalese patients had vague, disjointed complaints and that he was no exception. The next morning a colleague discovered that he had a left foot drop and no tibialis posterior or dorsalis pedis pulse. Overnight, unbeknown to me, he had developed a more tender abdomen and a radiograph showed air under the diaphragm. His creatinine was raised and he had proteinuria. At laparotomy he was found to have a perforated ileum with extensive necrosis and polyarteritis nodosa was subsequently diagnosed.

The patient and his relatives had thanked me profusely before I went off to sleep that night, little knowing that my preconceptions about patients with vague symptoms not amounting to much and my failure to carry out a proper physical and neurological examination were not going to help them in the least.

Institute of Medicine, Tribhuvan University, Lal Durbar, GPO Box 3596, Kathmandu, Nepal (B Basnyat MD)