Osteoporosis prevention and treatment
the importance of vitamin D

Vitamin D is associated with musculoskeletal health, and deficiency in this vitamin leads to increased risk of falls and osteoporotic fractures.

SIMON CHATFIELD
MB BS

PETER R. EBELING
MD, FRACP

Dr Chatfield is Rheumatology Registrar, and Dr Ebeling is Deputy Director, Department of Diabetes and Endocrinology, and Principal Fellow and Associate Professor, Department of Medicine, The Royal Melbourne Hospital, Parkville, Vic.

Osteoporosis is a growing silent epidemic and fragility fractures related to osteoporosis will affect one in two Australian women and one in three Australian men over 60 years of age. If nothing is done to prevent osteoporosis, the number of hip fractures in women will more than double from 1990 levels by 2025, when the number of hip fractures in men will equate to 1990 levels in women. The consequences of fractures include increased mortality of up to 20% in women at one year following a hip fracture.[1] Mortality is even higher in men. Morbidity is also a major issue. About half of previously independent women remain in long term care or need help with the activities of daily living a year after hip fracture.[2] Up to one-third of individuals who have a hip fracture can become totally dependent.[3]

Osteoporosis-related fractures in Australia are both under-recognised and undertreated.[4] Less than 20% of Australian women known to have an osteoporosis-related fracture had investigations to make the diagnosis, and even fewer were on any treatment to prevent further fractures. Less than 8% of women aged 50 years or more reported having a bone density test, which should be considered in those at risk – particularly those with a family history, a history of glucocorticoid use or a premature menopause. However, the test is meaningless if an action plan is not then instituted to prevent or treat osteoporosis.

This article focuses on the role of vitamin D deficiency in contributing to fragility fractures, and also provides an overview of the available

IN SUMMARY

- **Even in Australia vitamin D deficiency is common, but it is under-recognised.**
- **Evidence is accumulating that vitamin D supplementation reduces falls and fragility fractures, particularly in groups at risk of vitamin D deficiency. The number-needed-to-treat to prevent falls in the elderly is small (n=15).**
- **Assays for 25-hydroxyvitamin D often do not measure vitamin D_2 (ergocalciferol) as well as vitamin D_3 (cholecalciferol). This makes assessing treatment responses to vitamin D_2 supplements difficult.**
- **Vitamin D deficiency should be corrected prior to treatment with intravenous bisphosphonates to avoid hypocalcaemia. Low vitamin D levels should also be corrected in patients on oral bisphosphonates.**
- **Calcium supplements will need to be given with vitamin D supplements if patients' dietary calcium intakes are suboptimal.**
- **More studies regarding the role of vitamin D supplementation in the primary prevention of fragility fractures in the elderly are required.**

treatments for osteoporosis and evidence for their antifracture efficacy.

Vitamin D deficiency

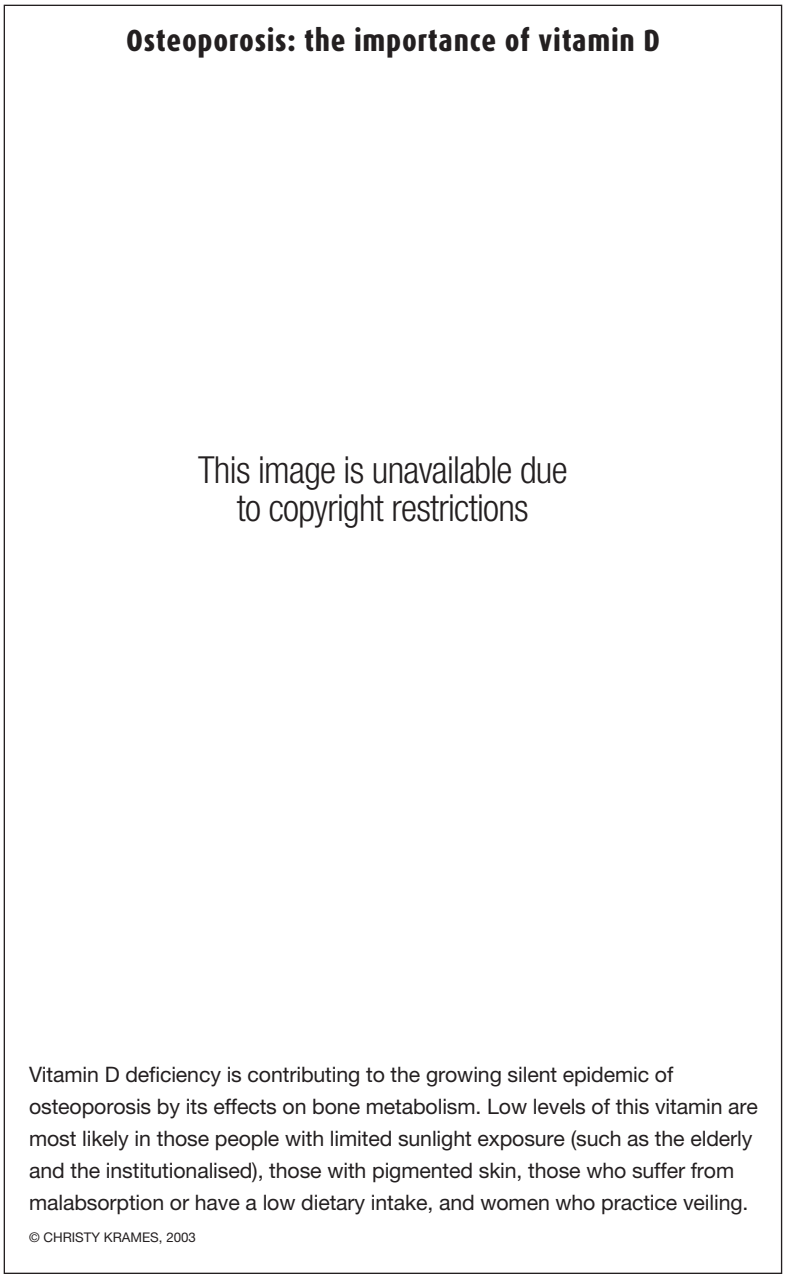
The elderly and institutionalised are particularly at risk of vitamin D deficiency, as are also those with pigmented skin, those who suffer from malabsorption or have a low dietary intake, and women who practice veiling. Although there is a lack of concensus, vitamin D deficiency may be classified as mild (25 to 50 nmol/L), moderate (12.5 to 25 nmol/L) or severe (<12.5 nmol/L). Parathyroid hormone (PTH) levels are elevated in 15% and 30% of patients with mild and severe vitamin D deficiency, respectively, and are intermediate in those with moderate deficiency. A mineralisation defect or osteomalacia is present in severe deficiency, while bone turnover is increased in mild and moderate vitamin D deficiency.

Epidemiology

Estimating the incidence of vitamin D deficiency is problematic given the lack of consensus regarding what constitutes deficiency. Coupled with this has been a lack of reproducibility of results between different assays of body stores of the vitamin.[5] Severe deficiency is generally agreed as being vitamin D levels below which patients develop osteomalacia. Current quoted reference ranges usually give the 95% confidence intervals of a 'normal population'; some, however, use optimal target treatment values. Both concepts are not ideal. The vitamin D level at which PTH elevation commences has been proposed as the lower limit for a reference range, because secondary hyperparathyroidism is one of the physiological responses to low serum calcium. Thus low vitamin D levels or a low calcium intake can cause compensatory elevation of PTH levels.

There are a number of studies documenting the relation between vitamin D levels and PTH. Correlation has been found particularly in the lower ranges of 25-hydroxyvitamin D (25-OHD) levels (correlation coefficients between 0.2 and 0.3). The plateau point in one study was 25 nmol/L and in another was 78 nmol/L.[6,7] Most physicians would agree that 25-OHD levels of at least 50 to 70 nmol/L would be optimal. Suboptimal vitamin D levels are common throughout the Western world, even in Australia (Table).[8-11] Some 54.5% of women in southern Victoria have mild–moderate vitamin D deficiency in winter, while 37.2% remain deficient in summer.[8] Most elderly institutionalised individuals in Australia have vitamin D deficiency.

Osteoporosis: the importance of vitamin D



Vitamin D deficiency is contributing to the growing silent epidemic of osteoporosis by its effects on bone metabolism. Low levels of this vitamin are most likely in those people with limited sunlight exposure (such as the elderly and the institutionalised), those with pigmented skin, those who suffer from malabsorption or have a low dietary intake, and women who practice veiling.

Sources of vitamin D

As mentioned in the box on page 21, vitamin D is mainly (80 to 100%) derived from synthesis in

the skin following exposure to ultraviolet rays. Fat solubility allows vitamin D accumulated during the summer months to sustain people through winter. Although generally only a small percentage of a person's vitamin D requirement is derived from the diet, people whose sunlight exposure is limited will derive significant proportions from dietary intake.

There are few dietary sources of vitamin D that contain high enough levels to correct deficiency. Fish with high fat content may account for the relative vitamin D repletion in Scandinavia, but in Australia foods fortified with vitamin D, such as some milk products and margarine, provide the richest source. However, levels obtained are not sufficient to correct deficiency in patients with minimal sun exposure. These patients require supplementation with high doses of vitamin D, the most commonly available form being the plant-derived ergocalciferol or vitamin D_2.

Consequences of vitamin D deficiency

Bone and muscle pains

Severe vitamin D deficiency causes osteomalacia in adults and rickets in children. Unfortunately, rickets is reappearing in Australia, predominantly in children of mothers at risk. In addition to the laying down of demineralised bone or osteoid, a myopathy may occur. Muscle pains may occur in moderate or severe vitamin D deficiency.[12]

Bone mineral density

Epidemiological studies. Epidemiological studies have demonstrated a significant relationship between 25-OHD levels and bone mineral density (BMD) in elderly women.

One study from Amsterdam noted that the relation was significant only for 25-OHD levels below 30 nmol/L.[13] A larger study of 13,432 noninstitutionalised US residents across a wide range of ages, including men and women and people of white, Mexican and black backgrounds, showed a significant relation between 25-OHD levels and BMD for white people of all ages.[14]

Intervention studies. Vitamin D supplementation has been shown to increase BMD in a number of studies, but many studies also included calcium in the treatment groups. Most studies demonstrate an increase in BMD in the treatment groups and ongoing bone loss in the placebo groups.[15,16]

A recent study looking specifically at vitamin D deficient (25-OHD <12 ng/mL [equivalent to <30 nmol/L]) elderly women demonstrated an increase in BMD in the lumbar spine, femoral neck and trochanter in those treated with calcium and vitamin D for 12 months.[17] Another study also showed increased femoral neck BMD.[18] One study comparing calcium alone versus vitamin D alone in relatively vitamin D replete individuals showed that calcium was superior in preventing bone loss.[19]

A meta-analysis investigating effects of vitamin D supplementation on both fractures and BMD found statistically significant but small effects for standard vitamin D with superiority over placebo for lumbar spine only at one year and for femoral neck beyond one year.[20]

Vitamin D and falls

Epidemiological studies. Increasing evidence supports the role of vitamin D deficiency in the pathogenesis of falls. Antifracture efficacy of calcium and vitamin D treatment in institutionalised elderly women occurs in the first six months of treatment, before an appreciable change in BMD would be expected.

Prospective data from an Australian study of residential care patients demonstrated an independent increased risk of falls in patients with low vitamin D.[21] This relation was observed even after controlling for weight, cognitive status, psychotropic drug use, previous Colles' fracture and presence of wandering

Table. Vitamin D deficiency in community dwelling adults in Australia

Study	Mild vitamin D deficiency	Moderate vitamin D deficiency	Severe vitamin D deficiency
Women (20 to 92 years old), Geelong, Vic[8]	30.0% summer; 43.2% winter (<50 nmol/L 25-OHD)	7.2% summer; 11.3% winter (<28 nmol/L 25-OHD)	–
Men and women (17 to 65 years old), SE Qld[9]	23.4% (<50 nmol/L 25-OHD)	8% (<37.5 nmol/L 25-OHD)	–
Women in hostels (WA, NSW, Vic)[10]	–	22% (<25 nmol/L 25-OHD)	–
Women in nursing homes (WA, NSW, Vic)[10]	–	45% (<25 nmol/L 25-OHD)	–
Geriatric inpatients (S Tas – 42°S)[11]	89% (<42 nmol/L 25-OHD)	67% (<28 nmol/L 25-OHD)	15% (<14 nmol/L 25-OHD)

behaviour. A doubling of serum 25-OHD level was associated with roughly a 20% decrease in falls risk. This may reflect an effect of vitamin D to improve muscle function.[22]

Intervention studies. Intervention studies have provided conflicting information regarding the effect of vitamin D supplementation on muscle function. One study in geriatric patients with vitamin D deficiency failed to demonstrate improvement in muscle strength despite biochemically adequate supplementation.[23] Another study showed significant improvement in balance, reaction time and functional performance without affecting muscle strength.[24]

Vitamin D supplementation and falls risk has been reviewed in a recent meta-analysis and a systematic review. The meta-analysis suggested that vitamin D supplementation reduced the risk of falls among ambulatory or institutionalised older individuals by 22%.[25] Fifteen patients would need to be treated with vitamin D to prevent one person from falling. This analysis incorporated the findings of five trials with a total of 1237 patients. The studies were of differing designs, particularly in respect to the vitamin D formulation. Three studies used cholecalciferol (vitamin D_3) at two different doses. Two of these studies also used calcium supplementation. The other two studies used the 'activated' vitamin D forms calcitriol (1,25-dihydroxyvitamin D_3) and alfacalcidol (1α-hydroxyvitamin D; which is converted into calcitriol). The analysis also suggested that supplementation with 800 IU of vitamin D was effective but a dose of 400 IU was not. The data did not enable conclusions to be drawn about effects in men and the role of supplementary calcium.

The earlier systematic review looked at four high quality trials with 1317 patients encompassing trials looking at falls as well as other indicators of strength and physical performance.[26] It concluded that there was insufficient evidence that vitamin D alone improved these parameters in the elderly.

A recent study examined falls and fractures in 601 elderly Australians in residential care with baseline 25-OHD levels of 25 to 90 nmol/L who were treated with ergocalciferol 10,000 IU per week, then 1000 IU per day, or placebo and 600 mg elemental calcium for two years.[27] The risk of ever falling was significantly reduced by 22%, while there was a trend for fracture risk reduction by 28%. The authors conclude this although this effect was additional to calcium, it could be dependent on calcium. Overall the current data are very promising for a beneficial effect of vitamin D supplementation in reducing falls.

Vitamin D and fractures

Intervention studies. The most important outcome in osteoporosis prevention or treatment is fracture risk reduction. A French study in institutionalised, ambulatory elderly women found 800 IU of cholecalciferol and 1.2 g of calcium significantly decreased hip fractures compared with placebo after 18 months.[15] However, antifracture efficacy in other groups is less certain. A Cochrane review from 2001 found that vitamin D supplementation alone was not associated with reduction in either vertebral or nonvertebral fractures.[28] In other populations, this regimen seems to reduce nonvertebral fractures overall, but evidence for hip fracture prevention is not available.

Another meta-analysis reached a similar conclusion. Pooled standard and hydroxylated vitamin D (calcitriol and alfacalcidol) data found a relative risk of vertebral fractures of 0.63 (95% CI, 0.45 and 0.88, respectively).[20] Risk of nonvertebral fractures approached but failed to reach statistical significance (RR 0.77; 95% CI, 0.57 and 1.04, respectively).

A more recent randomised, placebo-controlled trial comprising 2686 elderly community dwelling men and women aged over 65 years, showed cholecalciferol 100,000 IU administered orally four-monthly for five years resulted in a 33% reduction in all major osteoporotic fractures.[29] A subgroup of participants receiving placebo had normal mean 25-OHD levels of 53 nmol/L and, as expected, levels were higher in the treatment group (74 nmol/L). This has led to a level of 70 nmol/L being suggested as a target range by some laboratories.

Problems with the evidence

The combined use of calcium supplementation in many studies has made an individual vitamin D versus calcium effect difficult to detect. Calcium alone

What is vitamin D?

Vitamin D is the essential precursor of 1,25-dihydroxyvitamin D, which plays a central role in calcium and phosphate homoeostasis. There are two forms of vitamin D: vitamin D_3, or cholecalciferol, which is mainly derived from synthesis in the skin following exposure to ultraviolet rays; and vitamin D_2, or ergocalciferol, which is derived from plants and therefore obtained from dietary intake. Dietary intake makes up only a small percentage of a person's vitamin D source, except in people whose sunlight exposure is limited when it may make up a significant proportion.

Vitamin D is hydroxylated in the liver to 25-hydroxyvitamin D (25-OHD), and then in the kidney to 1,25-dihydroxyvitamin D. 1,25-dihydroxyvitamin D is more metabolically active and has a shorter half life than 25-OHD.

The vitamin's fat solubility and long half life allows that accumulated during the summer months to sustain people through winter.

has been shown to have a small positive effect on BMD and a nonsignificant trend towards fracture prevention in a meta-analysis.

Another issue relates to baseline vitamin D level and whether patients had vitamin D deficiency.[30] Most intervention studies assessed the effect of vitamin D replacement rather than vitamin D supplementation. The fracture rate, therefore, might be considerably higher in patients with vitamin D deficiency, and this has implications for an increased absolute fracture risk reduction with vitamin D therapy in this group. However, and as noted above, other data suggest vitamin D therapy may reduce fractures in elderly men and women with normal vitamin D levels. Further studies of vitamin D and its effects on fractures and falls are still needed, particularly using varying doses and in men.

Questions about vitamin D

Who should you test?

All patients who have osteoporosis should have their levels of vitamin D tested, as should those who are at high risk of vitamin D deficiency (see above), are experiencing falls or have osteoporosis risk factors.

Don't test, just treat?

Patient groups such as nursing home or hostel patients are likely to have such a high prevalence of vitamin D deficiency that supplementation without formal testing may be appropriate. As most vitamin D intervention studies have been done on subjects regardless of the baseline vitamin D level, this approach is not unreasonable, particularly because of the expense of vitamin D assays and the relative inexpensiveness of vitamin D supplements.

What to test?

25-hydroxyvitamin D

The serum 25-OHD level is accepted as the best guide to body stores of vitamin D and is the most sensitive test for vitamin D deficiency. The radioimmunoassay for 25-OHD is readily available in Australia, but there are issues regarding test standardisation between laboratories.[31] A more complicated test, high performance liquid chromatography, is the gold standard assay for 25-OHD but is time consuming and expensive. Another concern has been the ability of the assays to detect the two forms of vitamin D – cholecalciferol (naturally occurring vitamin D_3) and ergocalciferol (plant-derived vitamin D_2). Most radioimmunoassays are better at measuring vitamin D_3 than vitamin D_2. The issue is particularly important regarding assessment of the adequacy of replacement.

1,25-dihydroxyvitamin D

Determination of 1,25-dihydroxyvitamin D levels should not be routinely requested since this metabolite is not such a reliable indicator of body stores of vitamin D as 25-OHD and is more difficult and expensive to measure. (As mentioned earlier, low vitamin D levels can cause compensatory elevation of PTH levels. This results in increased levels of 1,25-dihydroxyvitamin D until there is severe deficiency when substrate is depleted and the 1,25-dihydroxyvitamin D levels become low.) Levels of 1,25-dihydroxyvitamin D decrease in moderate to severe renal impairment, and testing for it can be informative in patients with renal disease.

Other biochemistry

Measuring levels of plasma urea and creatinine, calcium, phosphate and alkaline phosphatase may be useful, but they may all be normal in mild vitamin D deficiency. PTH is an independent predictor of not only time to first fall but also mortality (it may be raised in vitamin D deficiency, renal failure and during treatment with loop diuretics), but more data are required before widespread testing for it as a marker of vitamin D deficiency can be advocated.[32-34]

What to treat with?

Dietary vitamin D

Vitamin D deficiency is less common in the USA than it is in Europe, a consequence of the vitamin D fortification of foods in the USA. In Australia, only margarine and some milk products are fortified. Natural sources include fatty fish such as salmon and sardines, and meat, milk and eggs.

The average Australian vitamin D intake is low, with most vitamin D in younger populations being derived from sun exposure. In the older population, particularly those with minimal sun exposure, the recommended levels exceed those practically achievable with dietary changes. Australia currently has no recommended dietary requirement for vitamin D (it is considered that the vitamin D status of the Australian population is determined by exposure to sunlight rather than by diet). However, the US Institute of Medicine's Food and Nutrition Board has published recommended dietary intakes of 200 IU of vitamin D for people aged 50 years or under, 400 IU for those aged 51 to 70 years, and 600 IU for those 71 years or over.[35]

Sunlight

Sunlight is an effective method of increasing vitamin D levels, albeit less so in the older population, as stated previously. Adequate vitamin D levels may be attained by typical day-to-day outdoor activities for most people. In summer, as little as five minutes of exposure of the face, arms and hands or the equivalent surface area to sunlight, either side of the peak UV periods (before 10 am and after 3 pm), on most days of the week is enough.[36] In winter, in southern Australia where UV radiation levels are less intense, levels may be maintained by about two to three hours of sunlight exposure accumulated over a week to the face, arms and hands or equivalent surface area. In northern Australia, the amount of sunlight exposure required to maintain adequate vitamin D levels is significantly less. Nevertheless, the efficacies of these strategies require more study.

Vitamin D supplements

Vitamin D is available as a supplement in Australia in the form of ergocalciferol, which is relatively inexpensive, readily available and relatively well absorbed (Ostelin Vitamin D; containing 1000 IU or 25 μg ergocalciferol). There are no pharmaceutical preparations of cholecalciferol alone but many calcium and/or vitamin supplements contain small amounts of vitamin D (as either ergocalciferol or cholecalciferol). The cod liver oil preparations usually contain vitamin D as cholecalciferol (up to 400 IU) as well as vitamin A, although there is one that contains vitamin D as ergocalciferol 400 IU (Nature's Own Cod Liver Oil). There is also a halibut liver oil preparation that contains cholecalciferol 400 IU and vitamin A (Halibut Liver Oil Vitamins A & D). In other countries, oral preparations containing between 10,000 and 50,000 IU of cholecalciferol are available, allowing weekly or monthly dosing, and a high dose parenteral form has also been used.

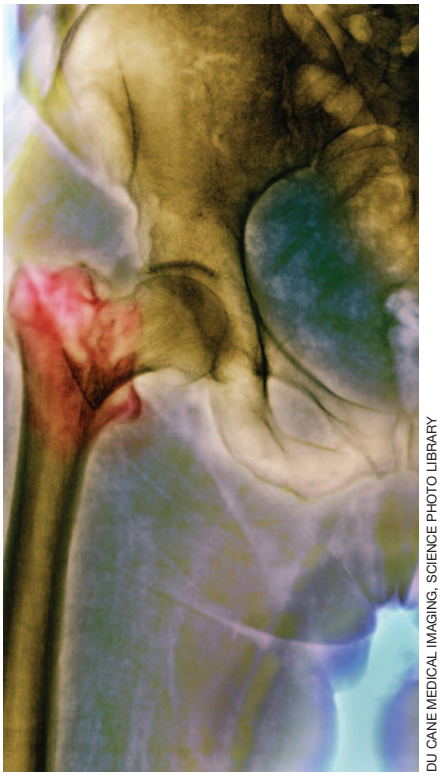
Calcitriol is generally not used for the treatment of vitamin D deficiency unless there is renal impairment or liver disease.

The concern regarding ergocalciferol use arises from pharmacokinetic studies showing that it is less effective at increasing 25-OHD levels than cholecalciferol and most assays provide a better measure of the body store status of vitamin D_3 (cholecalciferol) than of vitamin D_2 (ergocalciferol).[37] Doses of 1000 IU ergocalciferol daily are appropriate for most patients. In the frankly deficient patient, higher doses may be needed initially to increase body stores. Doses of 3000 to 5000 IU daily may be necessary for four to 12 weeks to replenish stores.

Calcium supplements

The evidence for vitamin D treatment has been obscured by the addition of variable quantities of calcium supplements. Adequate calcium intake is necessary for bone formation and PTH suppression and has been an adjunct treatment to all of the osteoporosis intervention trials except those with calcitriol. By itself, calcium supplementation is weakly antiresorptive and increases BMD by about 1%. It is most effective at increasing BMD in the elderly with very low dietary calcium intakes (less than 400 mg/day).

It is important to ensure an adequate calcium intake with supplementation as necessary to attain daily intakes of 1000 to 1500 mg/day as part of treating osteoporosis. Calcium carbonate (Cal-Sup, Caltrate Tablets) depends on acidification for its absorption so is best taken after meals; it is not as well absorbed in the elderly or those with reduced gastric acid secretion. Calcium citrate (Citracal) does not require acidification for absorption. Another preparation (Sandocal) contains calcium carbonate and calcium lactate gluco-nate. There are many preparations available that contain calcium and other minerals and/or vitamins. Low fat dairy products are very effective sources of calcium supplementation and may have the added benefit of reducing total cholesterol levels.



DU CANE MEDICAL IMAGING, SCIENCE PHOTO LIBRARY

Figure. Coloured x-ray of a fractured femur in an elderly woman that had been caused by a fall. Vitamin D deficiency is a risk factor for such fractures.

Problems with treatment?

Side effects

The Cochrane meta-analysis of vitamin D treatment trials showed small significant increases in hypercalcaemia in patients treated with vitamin D (RR 1.71; 95% CI, 1.01, 2.89).[28] This is probably related to the inclusion of active vitamin D metabolites. There was no increase in either renal disease (including stones) or gastrointestinal symptoms. Overall vitamin D treatment was associated with a nonsignificant decrease in overall mortality (RR 0.92; 95% CI, 0.83, 1.03). Vitamin D intoxication is very uncommon and usually large doses of vitamin D are very well tolerated.[38]

Polypharmacy

A barrier to successful vitamin D treatment is the effect of adding to patients' 'polypharmacy', which would reduce compliance. A UK study that administered large doses of vitamin D to patients four times per year showed the replacement to be efficacious in both elevating levels of vitamin D and preventing combined hip, wrist and vertebral fractures.[29] A nonblinded study in Finland used annual injections of vitamin D, akin to an annual flu vaccination. Although a less expensive option, further data are required on its antifracture efficacy.[39,40]

Follow up?

Retesting

In patients who are being treated for deficiency of vitamin D, the efficacy of replacement can be assessed by measurement of the 25-OHD level. The earliest time to check would be after three months of treatment, given the long half life of the vitamin and the long time needed to reach steady state. Patients in whom it is particularly important to retest include those on antiepileptic drugs that increase hepatic metabolism of vitamin D. These patients may require vitamin D doses of 3000 to 5000 IU daily to achieve adequate levels.[41]

Treatment duration

Treatment with vitamin D should be lifelong. One study that monitored bone density after withdrawal of vitamin D therapy found that bone turnover markers increased to their pretreatment level following withdrawal, and gains in BMD at the spine and femoral neck were also lost.[42]

Osteoporosis – who and how to treat?

Primary and secondary fracture prevention are discussed in detail below.

Primary osteoporotic fracture prevention

In patients without fractures, levels of vitamin D should be optimised and adequate calcium intake encouraged to help prevent low BMD and fractures. Although high level vertebral fracture prevention data are available for the bisphosphonates alendronate (Fosamax) and risedronate (Actonel) and the selective oestrogen receptor modulator (SERM) raloxifene (Evista) in patients without a prevalent fracture and osteoporosis, currently there is no PBS reimbursement for this indication. The absolute risk reduction is less in this patient group compared with secondary prevention because of the lower fracture rate. However, those at greatest risk of osteoporotic fracture should still be considered for treatment (that is, older patients with low BMD – over 60 years of age and T-score less than -2.5). Prospective fracture incidence data from epidemiological studies will further refine intervention thresholds in this group.

Secondary osteoporotic fracture prevention

Antiresorptive agents

Bisphosphonates

Systematic reviews have shown that the potent inhibitors of bone resorption alendronate and risedronate reduce the risk of spinal, nonspinal and hip fractures.[43]

A recent study has shown alendronate increases BMD and reduces bone turnover more than risedronate.[44] However, no study has compared the antifracture efficacy of these two bisphosphonates. Both have been reported to reduce the risk of single, multiple and asymptomatic vertebral fractures in women with osteoporosis and one or more baseline vertebral fractures. The risk reduction is rapid (occurring within the first six to 12 months), suggesting a reduction in bone remodelling is critical to their effects. Peripheral fracture rates are also reduced in patients with a prevalent vertebral fracture.

Data for antihip fracture efficacy are available for both alendronate and risedronate. Alendronate studies have shown a consistent hip fracture risk reduction, but hip fracture was not a primary endpoint. In a large risedronate trial, in which hip fractures were the primary endpoint, there was a 40% reduction in hip fracture risk among women aged 70 to 79 years with osteoporosis confirmed on dual energy x-ray absorptiometry scan (DXA; baseline T-score less than -3).[45] However, women aged 80 years and over, included because they had at least one falls risk factor, did not achieve the same benefit. This highlights the need to address also falls-related factors, such as vitamin D deficiency, in the elderly.

Bisphosphonate use has been associated with dyspepsia, abdominal pain and oesophageal ulceration. However, the overall risk of upper gastrointestinal complications is very low and it has been reduced further by weekly administration rather than the more frequent administration used previously.

Etidronate (Didronel, Didrocal [the latter also contains calcium]) is a weak bisphosphonate that is used cyclically, for two weeks every three months, because its continuous use may result in mineralisation defects. Etidronate treatment tends to reduce vertebral fractures by 50%. Its use may be considered in patients intolerant of the more potent bisphosphonates because of the upper gastrointestinal side effects of these drugs. Etidronate use, however, has been associated with lower gastrointestinal side effects.

Bisphosphonates are polar drugs and their oral bioavailability is low (less than 1%). Calcium should not be taken at the same time of day as a bisphosphonate, because the calcium will prevent absorption of the bisphosphonate. Also, bisphosphonates should be taken at least 30 minutes before meals. In patients who are intolerant of oral bisphosphonates, intravenous bisphosphonates such as pamidronate (Aredia, Pamisol) and zoledronic acid (Zometa) may be used. Studies assessing the antifracture efficacy of zoledronic acid are in progress. This is the most potent bisphosphonate and vitamin

D deficiency should be corrected prior to its use to avoid the potential complication of hypocalcaemia. Although extremely rare with oral bisphosphonates, profound hypocalcaemia has been reported in patients treated with zoledronic acid infusions for osteoporosis who had coexistent vitamin D deficiency.

The increase in BMD that occurs with prolonged use (for five years) of alendronate is maintained at the spine for up to five years after cessation, but may gradually decline over that time at other sites. Bone resorption increases slightly but does not return to pretreatment levels. Although the optimal duration of bisphosphonate therapy remains uncertain, five years seems appropriate. Following cessation, BMD should be monitored.

SERMs

Raloxifene decreases bone resorption but does not increase the risk of breast or uterine cancer. Lipid profiles are improved and breast cancer incidence appears to be reduced. Increases in BMD are modest, and somewhat less than those seen with bisphosphonates or oestrogen. In postmenopausal women with or without prevalent vertebral fractures, the risk of vertebral fractures is reduced. Risk reduction is greater for the latter group (55% *v.* 36% over four years). Nonvertebral fractures were not reduced. Hip fracture reduction was not an endpoint in the MORE study of raloxifene.[46]

An increased risk of deep venous thrombosis has been reported with raloxifene and is similar to that seen with hormone therapy. Treatment should be stopped if patients are immobilised for any prolonged period. Raloxifene may also worsen menopausal symptoms. Raloxifene has been shown to be effective for prevention of postmenopausal bone loss and should be considered as an alternative to oestrogen for this indication.

Hormone therapy – oestrogen and progestin

Long term postmenopausal hormone therapy (HT) use in the prevention and management of osteoporosis is controversial following the results of the Women's Health Initiative (WHI) study of combined oestrogen and progestin therapy (cHT) and oestrogen-alone therapy (ET). WHI initiated HT in women aged 50 to 79 years, many of whom were not screened for osteoporosis risk. Despite this, significant reductions in subsequent osteoporotic fractures occurred in both arms of the trial. There were trends for other risks, however. There was a doubling of thromboembolism risk, and an increased risk of stroke neared statistical significance. An increased risk in cardiovascular disease was seen only in the cHT arm.[47]

Also in the cHT arm, an almost statistically significant increase in breast cancer was seen by five years (of eight cases per 10,000 per year).[47] This was matched by a similar reduction in colon cancer risk. There were no changes in overall cancer and mortality rates.

The ET arm of the WHI study ceased after 6.8 years, showing an almost statistically significant reduction in breast cancer of seven cases per 10,000 per year.[48] This suggests a different risk profile for women using an oestrogen-only regimen. Again, the absolute risk for vascular disease, particularly cerebrovascular disease, increased with age in the oestrogen-only study.

HT is an option for the prevention of osteoporotic fractures, particularly in the at-risk symptomatic woman around early menopause. It can be used as an initial therapy in a long term osteoporosis management program in which the HT is reviewed annually and may be changed to another effective therapy at any time.

Ideally, oestrogen therapy should be continuous. Adjuvant progestogens are necessary in women who still have a uterus, to protect against endometrial cancer. They may be given cyclically for 10 to 14 days each month in perimenopausal women, or as continuous therapy combined with oestrogen in postmenopausal women.

Women should be fully informed of the risks and benefits of their particular HT regimen, and their therapy should be individualised and reviewed annually.

Hormone therapy – tibolone

Tibolone (Livial) – a synthetic steroid that has oestrogenic, progestogenic and androgenic effects – is an alternative to oestrogen therapy and its effect on BMD appears to be similar. There are currently no antifracture data available, but an ongoing randomised controlled trial (LIFT) has vertebral fractures as a primary outcome.[49] There are no prospective, controlled studies examining the effects of tibolone on breast cancer risk, but the relative risk of breast cancer was increased in one large nonrandomised case–control study.[50]

Anabolic agents

Parathyroid hormone

Teriparatide (Forteo), a synthetic version of PTH produced by a recombinant

Reviewer's comment

This is a timely article that addresses the role of vitamin D in osteoporosis, a much neglected aspect of bone metabolism that has been greatly overshadowed in recent years by the development of the antiresorptive bisphosphonates. The high level of vitamin D deficiency in the geriatric institutionalised population associated with deficient dietary intake and lack of sun exposure has been largely ignored yet is probably a relatively cheap and accessible option for preventing or delaying the consequences of age-related osteopenia and reduced muscular co-ordination.

The significant benefits of vitamin D supplementation in terms of both fracture rate and fall precipitation are not addressed by treating patients with bisphosphonates alone. Vitamin D not only increases bone strength when combined with calcium supplementation but also reduces the risk of falls resulting in fractures.

Osteoporosis, like diabetes and cardiovascular disease, must be managed with a multifactorial prevention plan to achieve the best long term benefits for our patients and ultimately diminish the cost to the community of hip and vertebral fractures that add greatly to the morbidity of the ageing population.

Dr John Dearin
Consultant Medical Editor, *Medicine Today,* and
General Practitioner, Lithgow, NSW

DNA technique, has a net anabolic action stimulating osteoblasts more than osteoclasts when presented to bone intermittently (such as in daily subcutaneous injections). It increases cancellous bone mass by about 15 to 20% over three years and reduces the relative risk of vertebral fractures by 65% in women with osteoporosis and one or more baseline fractures.[51] It also reduces peripheral fractures, but its effect on hip fracture reduction has not been studied.

Teriparatide is registered in Australia as an 18-month course of injections, but is not reimbursed under the PBS. Oncogenicity studies in rats showed an increased risk of osteogenic sarcoma, but this has not been seen in any human studies and only very rarely in patients with hyperparathyroidism. In view of its appreciable cost, it is anticipated that teriparatide will become a treatment option for individuals with severe osteoporosis with ongoing fractures who have failed other therapies or those with very low BMDs. It should not be used in addition to bisphosphonates and patients should have a bisphosphonate-free period before commencing PTH treatment, although the optimal duration of this break is unclear. No gap is required if changing from raloxifene to PTH.

As it is complex, PTH treatment is probably best initiated by a specialist. After PTH is stopped, antiresorptive therapy should be recommenced and further increases in BMD can occur.

Strontium ranelate

Strontium ranelate stimulates osteoblast proliferation *in vitro* and in animal models and also reduces bone resorption, but its exact mechanism of action remains unclear. In a large clinical trial (SOTI), strontium ranelate reduced vertebral fractures by 41% over three years.[52] There was a significant 14.4% increase in lumbar spine BMD and an 8.3% increase in the femoral neck BMD. The former increase remained significant after correction for bone strontium content. In another large controlled prospective trial (TROPOS), strontium ranelate reduced all vertebral fractures by 16% and fragility fractures, including hip fractures, by 19% over three years.[53] Strontium ranelate is not currently available in Australia.

Conclusion

Most currently available and effective treatments for osteoporosis reduce bone resorption. It is important that calcium intake is optimal and vitamin D deficiency has been corrected for them to be most effective.

The increased understanding of the role of vitamin D in musculoskeletal health over recent years, including the association between low vitamin D levels and falls and low BMD, has led to more attention being paid to this vitamin. Vitamin D replacement is relatively easy and safe, but needs to be cheaper. At the minimum, treatment with calcium and vitamin D reduces falls in elderly patients, and fractures in elderly institutionalised women. While vitamin D may also have a role in preventing fractures in ambulant elderly men and women, more studies, particularly using varying doses of cholecalciferol and including men, are required before widespread vitamin D supplementation can be recommended as a primary prevention of osteoporotic fractures. MT

A list of references is available on request to the editorial office.

DECLARATION OF INTEREST: None.

Medicine Today 2005; 6(4): 16-32

Osteoporosis prevention and treatment the importance of vitamin D

SIMON CHATFIELD MB BS PETER R. EBELING MD, FRACP

References

1. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 1999; 353: 878-882.
2. Cummings SR, Kelsey JL, Nevitt M, O'Dowd K. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev 1985; 7: 178-208.
3. Jensen JS, Bagger J. Long-term social prognosis after hip fractures. Acta Orthop Scand 1982; 53: 97-101.
4. Eisman J, Clapham S, Kehoe L. Osteoporosis prevalence and levels of treatment in primary care: the Australian BoneCare study. J Bone Miner Res 2004; 19: 1969-1975.
5. Lips P, Chapuy MC, Dawson-Hughes B, Pols HAP, Holick MF. An international comparison of serum 25-hydroxyvitamin D measurements. Osteoporos Int 1999; 9: 394-397.
6. Ooms ME. Osteoporosis in elderly women; vitamin D deficiency and other risk factors. PhD thesis. Amsterdam: Vrije Universiteit, 1994 .
7. Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 1997; 7: 439-443.
8. Pascoe J, Henry, M, Nicholson G, et al. Vitamin D status of women in the Geelong Osteoporosis Study: association with diet and casual exposure to sunlight. Med J Aust 2001; 175: 401-405.
9. MacGrath J, Kimlin M, Saha S, et al. Vitamin D insufficiency in south-east Queensland. Med J Aust 2001; 174: 150-151.
10. Flicker L, Mead K, MacInnis RJ, et al. Serum vitamin D and falls in older women in residential care in Australia. J Am Geriatr Soc 2003; 51: 1533-1538.
11. Inderjeeth CA, Nicklason F, Al-Lahham Y, et al. Vitamin D deficiency and secondary hyperparathyroidism: clinical and biochemical associations in older non-institutionalised Southern Tasmanians. Aust N Z J Med 2000; 30: 209-214.
12. Frame B, Parfitt AM. Osteomalacia: current concepts. Ann Intern Med 1978; 89: 966-982.
13. Ooms ME, Lips P, Roos JC, et al. Vitamin D status and sex hormone binding globulin: determinants of bone turnover and bone mineral density in elderly women. J Bone Miner Res 1995; 10: 1177-1184.
14. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. Am J Med 2004; 116: 634-639.
15. 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: 1637-1642.
16. 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: 670-676.
17. Grados F, Brazier M, Kamel S, et al. Effects on bone mineral density of calcium and vitamin D supplementation in elderly women with vitamin D deficiency. Joint, Bone, Spine: Rev Rheum 2003; 70: 203-208.
18. Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJF, 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: 1052-1058.
19. Peacock M, Liu G, Carey M, et al. Effect of calcium or 25(OH) vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. J Clin Endocrinol Metab 2000; 85: 3011-3019.
20. Papadimitropoulos E, Wells G, Shea B, et al; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev 2002; 23: 560-569.
21. Flicker L, Mead K, MacInnis RJ, et al. Serum vitamin D and falls in older women in residential care in Australia. J Am Geriatr Soc 2003; 51: 1533-1538.
22. Simpson RU, Thomas GA, Arnold AJ. Identification of 1,25-dihydroxyvitamin D3 receptors and activities in muscle. J Biol Chem 1985; 260: 8882-8891.
23. Corless D, Dawson E, Fraser F, et al. Do vitamin D supplements improve the physical capabilities of elderly hospital patients? Age Ageing 1985; 14: 76-84.
24. Dhesi JK, Jackson SH, Bearne LM, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing 2004; 33: 589-595.
25. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls: a meta-analysis. JAMA 2004; 291: 1999-2006.
26. Latham NK, Anderson CS, Reid IR. Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: a systematic review. J Am Geriatr Soc 2003; 51: 1219-1226.
27. Flicker L, MacInnis RJ, Stein MS, et al. Should all older people in residential care receive vitamin D to prevent falls? Results of a randomised trial. J Bone Miner Res 2004; 19 (S1): S99.
28. Gillespsie WJ, Avenell A, Henry DA, O'Connell DL, Robertson J. Vitamin D and vitamin D analogues for preventing fractures associated with

involutional and post-menopausal osteoporosis (Cochrane review). In: The Cochrane Library, Issue 2, 2003.
29. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: a randomised double blind controlled trial. BMJ 2003; 326: 469-475.
30. Shea B, Wells G, Cranney A, et al; Osteoporosis Methodology Group; Osteoporosis Research Advisory Group. Calcium supplementation on bone loss in postmenopausal women. Cochrane Database Syst Rev 2004; 1: CD004526.
31. Lips P, Chapuy MC, Dawson-Hughes B, Pols HAP, Holick MF. An international comparison of serum 25-hydroxyvitamin D measurements. Osteoporos Int 1999; 9: 394-397.
32. Stein MS, Scherer SC, Walton SL, et al. Risk factors for secondary hyperparathyroidism in a nursing home population. Clin Endocrinol (Oxf) 1996; 44: 375-383.
33. Sambrook PN, Chen JS, March LM, et al. Serum parathyroid hormone predicts time to fall independent of vitamin D status in a frail elderly population. J Clin Endocrinol Metab 2004; 89: 1572-1576.
34. Sambrook PN, Chen JS, March LM, et al. serum parathyroid hormone is associated with increased mortality independent of 25-hydroxy vitamin D status, bone mass, and renal function in the frail and very old: a cohort study. J Clin Endocrinol Metab 2004; 89: 5477-5481.
35. Food and Nutrition Board (Institute of Medicine Staff, Vedral J). Dietary reference intakes for: calcium, phosphorus, magnesium, vitamin D, and fluoride (Dietary reference series). Washington DC: National Academic Press, 1997.
36. Diamond TH, Eisman JAE, Mason RS, et al. Vitamin D and adult bone health in Australia and New Zealand. Med J Aust 2005. In press (accepted 10 January 2005).
37. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab 2004; 89: 5387-5391.
38. Adams JS, Lee G. Gains in bone mineral density with resolution of vitamin D intoxication. Ann Intern Med 1997; 127: 203-206.
39. Heikinheimo RJ, Inkovaara JA, Harju EJ, et al. Annual injection of vitamin D and fractures of aged bones. Calcif Tissue Int 1992; 51: 105-110.
40. Torgerson DJ, Kanis JA. Cost-effectiveness of preventing hip fractures in the elderly population using vitamin D and calcium. QJM 1995; 88: 135-139.
41. Drezner MK. Treatment of anticonvulsant drug-induced bone disease. Epilepsy Behav 2004; 5 (Suppl 2): S41-S47.
42. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of withdrawal of calcium and vitamin D supplements on bone mass in elderly men and women. Am J Clin Nutr 2000; 72: 745-750.
43. O'Neil S, MacClennan A, Bass S, et al. Guidelines for the management of postmenopausal osteoporosis for general practitioners. Aust Family Physician 2004; 33: 910-917.
44. Rosen CJ, Hochberg MC, Bonnick SL, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res 2005; 20: 141-151.
45. McClung MR, Geusens P, Miller PD, et al. Effects of risedronate on the risk of hip fracture in elderly women. N Engl J Med 2001; 344: 333-340.
46. Kanis JA, Johnell O, Black DM, et al. Effect of raloxifene on the risk of new vertebral fracture in postmenopausal women with osteopenia or osteoporosis: a reanalysis of the Multiple Outcomes of Raloxifene Evaluation trial. Bone 2003; 33: 293-300.
47. Roussouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288: 321-333.
48. Anderson GL, Limacher M, Assaf AR, et al; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291: 1701-1712.
49. Gallagher JC, Baylink DJ, Freeman R, McClung M. Prevention of bone loss with tibolone in postmenopausal women: results of two randomised, double blind, placebo controlled, dose finding studies. J Clin Endocrinol Metab 2001; 86: 4717-4726.
50. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003; 362: 419-427.
51. 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: 1431-1441.
52. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis, N Engl J Med 2004; 350: 459-468.
53. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: TROPOS study. J Clin Endocrinol Metab 2005; 22 February, epub.