Review

QJM

Calcium and vitamin D in the prevention of osteoporotic fractures

R.M. FRANCIS[1], F.H. ANDERSON[2], S. PATEL[3], O. SAHOTA[4] and T.P. VAN STAA[5]

From the [1]School of Clinical Medical Sciences, University of Newcastle upon Tyne, Newcastle upon Tyne, [2]Geriatric Medicine Group, University of Southampton, Southampton, [3]Department of Rheumatology, St Helier Hospital, Carshalton, [4]Department of Health Care of the Elderly, Queen's Medical Centre, University Hospital, Nottingham, UK and [5]Procter and Gamble Pharmaceuticals and University of Utrecht, Utrecht, Netherlands

Introduction

Osteoporosis has been defined as a skeletal disorder characterized by compromised bone strength, predisposing a person to increased risk of fracture.[1] The three major osteoporotic fractures are those of the forearm, vertebra and hip, but fractures of the humerus, pelvis and ribs are also common. The incidence of these fracture rises steeply with age, such that most occur in people aged >65 years, where they are associated with excess mortality, substantial morbidity, and significant health and social services expenditure.[2] This paper outlines the physiological roles of calcium and vitamin D, and assesses the current criteria for adequate calcium intake and optimal vitamin D status in adults. It highlights the prevalence of vitamin D insufficiency and low calcium intake in the UK, and reviews studies of vitamin D supplementation, with and without calcium, in the prevention of falls and fractures. Relevant clinical trials were identified using the search strategies described in recent meta-analyses.[3,4]

Functions of calcium

Calcium is required for a number of functions in the body, including neuromuscular activity, membrane function, hormone secretion, enzyme activity, coagulation of the blood and skeletal mineralization.[5] Over 99% of the body's calcium is stored in bone, where it provides mechanical strength to the skeleton, and serves as a mineral reservoir that can be drawn upon to maintain a normal plasma calcium. An adequate dietary calcium is therefore required to offset the obligatory losses of calcium in the urine and digestive juices, and prevent unnecessary loss of calcium from the skeletal reservoir.[5]

Dietary calcium requirements

The recommended dietary calcium intake varies widely from country to country.[6] In the US an intake of between 1000 and 1500 mg/day is recommended for adults, depending on age, gender and menstrual status.[7] In contrast, the UK Committee on the Medical Aspects of Food and Nutrition Policy (COMA) recommends a Reference Nutrient Intake (RNI) for calcium of 700 mg/day for adults.[6] This figure is two SD above the Estimated Average Requirement (EAR) of 550 mg/day, which is calculated from the daily losses of calcium in the urine, digestive juices and sweat, and the efficiency of calcium absorption from the diet. The RNI should

---

Address correspondence to Professor R.M. Francis, Musculoskeletal Unit, Freeman Hospital, Newcastle upon Tyne NE7 7DN. email: rmfrancis@compuserve.com
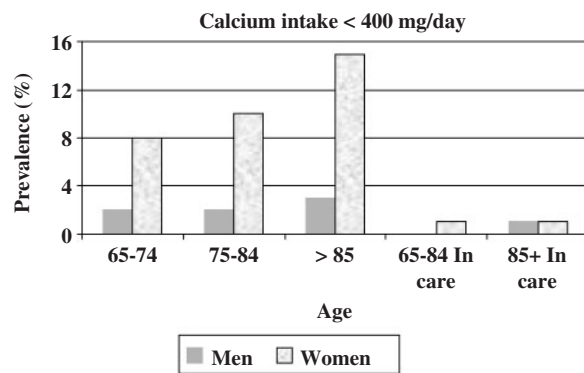
Figure 1. Prevalence of dietary calcium intake below the LRNI (400 mg/day) in older men and women in the UK. Data derived from the National Diet and Nutrition Survey.[8]

therefore provide sufficient calcium for 97.5% of the adult population.[4] COMA also designated a lower reference nutrient intake (LRNI) for calcium of 400 mg/day, two SD lower than the EAR, below which calcium intakes are likely to be inadequate.[6]

The UK National Diet and Nutrition Survey shows a mean calcium intake of 704 mg/day in women aged 65–74 years, 680 mg/day between 75 and 84 years, and 647 mg/day at the age of 85 years and above.[8] The calcium intake of older women living in institutions is higher (900 mg between the ages of 65 and 84 years, 828 mg at age 85 years and above), but may reflect food provided rather than that consumed. The same study showed calcium intakes below the LRNI of 400 mg/day in up to 15% of older women (Figure 1). Over half of older community-dwelling women therefore have a dietary calcium intake below the recommended value, whereas a significant minority in this age group have an inadequate intake (<400 mg/day). The National Osteoporosis Society (NOS) accepts the RNI for calcium of 700 mg/day for the general population, but suggests that higher intakes may be necessary in patients with osteoporosis, who commonly have malabsorption of calcium.[9] It has also been argued that patients on osteoporosis treatments require a higher dietary calcium intake, to optimize the expected improvement in bone density.[10]

Functions of vitamin D

Vitamin D is essential for bone health throughout life. The hormonally active metabolite of vitamin D is 1,25 dihydroxyvitamin D (1,25(OH)$_2$D), which regulates calcium absorption from the bowel, mediates the mineralization of osteoid tissue

within bone, and plays an important role in muscle function.[5] The major source of vitamin D is cutaneous production, following exposure to ultraviolet radiation. It has been suggested that, in temperate latitudes, exposure of the hands, arms and face to sunlight without the use of sun block for 5–10 min, two or three times weekly from April to October, will produce sufficient vitamin D to supply nutritional requirements.[11] The diet provides smaller amounts of vitamin D, but this source is essential when cutaneous production is limited because of lack of exposure to sunlight.

Vitamin D status

As the major source of vitamin D is from cutaneous production after ultraviolet irradiation, there is no recommended dietary intake for vitamin D for adults in the UK up to the age of 65 years, other than for people with reduced exposure to sunlight.[6] The RNI for vitamin D in these people, and in those aged >65 years, is 400 IU (10 μg) daily.[6]

Measurement of circulating 25-hydroxyvitamin D (25OHD) is useful in the assessment of vitamin D status. As serum 25OHD is inversely related to parathyroid hormone (PTH), the 25OHD concentration below which PTH increases may be used to identify the lower limit of adequate vitamin D status. The terms vitamin D insufficiency and vitamin D deficiency are often used synonymously to describe sub-optimal vitamin D status, but some authors reserve the latter for when osteomalacia develops.[12] Vitamin D insufficiency has been classified into mild (serum 25OHD 25–50 nmol/l), moderate (12.5–25 nmol/l) or severe (<12.5 nmol/l), associated with <15%, 15–30% and >30% increases in PTH, respectively.[12] In contrast, investigators from North America have suggested that the optimal serum 25OHD concentration may be as high as 80–100 nmol/l.[11,13,14]

In a study of 1741 subjects aged 19–97 years, there was an inverse relationship between 25OHD and PTH in all age groups, but no plateau in PTH was observed even when 25OHD reached 100 nmol/l.[13] There was also a change in relationship between serum 25OHD and PTH with advancing age, such that higher 25OHD concentrations were required to maintain a low PTH in older people.[13] A recent survey in North American women receiving treatment for osteoporosis showed that 52% have a serum 25OHD <75 nmol/l, a concentration below which PTH increased.[14] In an international survey of six experts, the minimal level of serum 25OHD that was considered optimal for fracture
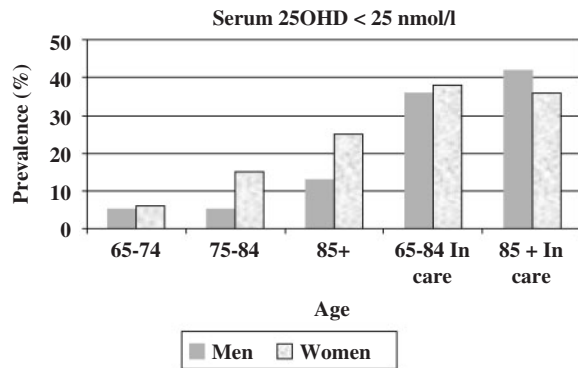
Serum 25OHD < 25 nmol/l

Figure 2. Prevalence of vitamin D insufficiency (serum 25OHD <25 nmol/l) in older men and women in the UK. Data derived from the National Diet and Nutrition Survey.[8]

prevention varied between 50 and 80 nmol/l.[15] These experts also recommended that older men and women needed 800–1000 IU vitamin D daily to achieve a serum 25OHD level of 75 nmol/l.[15] The contrasting criteria for the definition of vitamin D insufficiency may be due in part to systematic differences in the results of high pressure liquid chromatograpy (HPLC), radioimmunoassay (RIA) and competitive protein binding (CPB) assays for 25OHD.[16] Measurements of serum 25OHD may be up to 80% higher with CPB than with HPLC assays, with intermediate values for RIA.[16]

Irrespective of the precise criteria used, vitamin D insufficiency is common in older people, particularly in those living in care homes. In the UK National Diet and Nutrition Survey[8] of community-dwelling people, 5% of men and 6% of women aged 65–74 years had a serum 25OHD <25 nmol/l, vs. 13% and 25%, respectively, of those aged >85 years (Figure 2). Over a third of male and female care-home residents aged >65 years had a serum 25OHD <25 nmol/l.[8]

Similar results were reported in the recent Health Survey for England (HSE), which also found a higher prevalence of vitamin D insufficiency (serum 25OHD <25 nmol/l) in women than in men.[17] Vitamin D insufficiency was associated with long-standing illness, manual social classes, poor general health and body mass index <25 kg/m^2.[17]

Vitamin D insufficiency is particularly common in patients with osteoporotic fractures. Among elderly patients admitted to hospital with a hip fracture, 91.6% had a serum 25OHD <50 nmol/l.[18] In a similar study of patients with hip fractures, about 75% had a serum 25OHD <50 nmol/l, and 68% had a 25OHD of <30 nmol/l.[19] In a study of patients with established osteoporosis and vertebral fractures, 39% had a 25OHD <30 nmol/l.[20]

Supplementation with calcium and vitamin D, or vitamin D alone

The high prevalence of vitamin D insufficiency, particularly in older people with osteoporosis, provides a rationale for dietary supplementation. A number of randomized controlled trials have looked at the effect of calcium and vitamin D, or vitamin D alone, in the prevention of fractures. The results from these studies have been inconsistent, possibly reflecting heterogeneity in the populations studied as regards gender mix, residential status, fracture history and baseline vitamin D status (Table 1). There is also considerable variation in the dose, frequency, route of administration and type of vitamin D (ergocalciferol—vitamin D_2 or cholecalciferol—vitamin D_3) used.

Vitamin D alone

This includes studies in which vitamin D has been given by intramuscular (IM) injection or by oral administration. In a study from Finland, IM injections of vitamin D_2 (150 000–300 000 IU) were administered to older men and women living in their own homes or in residential care.[21] This resulted in an overall reduction in fractures of 25%. In contrast, the Wessex Fracture Prevention Trial investigated the effect of an annual IM injection of vitamin D_2 300 000 IU each autumn.[22] There was no reduction in the risk of any first fracture or first forearm fracture with vitamin D, but there was a significantly increased risk of first hip fracture. Treatment was associated with a 20% increase in serum 25OHD and 21% reduction in PTH, suggesting relatively poor bioavailability of IM vitamin D_2, although blood samples were taken in relatively few subjects.

Of the oral vitamin D studies, a Dutch trial showed that 400 IU vitamin D_3 daily increased femoral bone density by 2.2% in elderly subjects, but there was no reduction in hip or other peripheral fractures.[23] A Norwegian study examined the use of 5 ml cod liver oil (~400 IU Vitamin D_3) in male and female nursing-home residents.[24] Although active treatment increased serum 25OHD from 47 to 64 nmol/l, no decrease in PTH was seen. There was also no significant difference in the incidence of hip fracture or non-vertebral fractures, compared with placebo.

A UK study examined the use of oral Vitamin D_3 100 000 IU every 4 months for 5 years in community-dwelling older people, many of whom were retired male doctors.[25] There was a reduction in any fracture with vitamin D, but this only just achieved statistical significance, and there was no

Table 1 Studies of the effect of combined calcium and vitamin D supplementation and of vitamin D alone on non-vertebral fractures

Study	Location	Duration (months)	n	Sex	Residence	Intervention	Prevention (1°/2°)	RR/OR/HR	95%CI	p
Parenteral vitamin D										
Heikinheimo[21]	Finland	24–60	799	F/M	Community or rest home	Vitamin D_2 150 000–300 000 IU annually	1°	0.75 RR	NA	0.03
Smith[22]	UK	36	9443	F/M	Community	Vitamin D_2 300 000 IU annually	1°	1.09 HR	0.93–1.28	0.3
Oral vitamin D										
Lips[23]	Holland	Median 42	2578	F/M	Community	Vitamin D_3 400 IU daily	1°	1.10 RR	0.87–1.39	>0.5
Meyer[24]	Norway	24	1144	F/M	Nursing home	Cod liver oil 5 ml daily (~400 IU D_3)	1°	0.92 RR	0.66–1.27	>0.5
Trivedi[25]	UK	60	2686	M (&F)	Community	Vitamin D_3 100 000 IU 4-monthly	1°	0.78 RR	0.61–0.99	0.04
Daily oral vitamin D and calcium										
Chapuy[27]	France	36	3270	F	Nursing home	Vitamin D_3 800 IU + Calcium 1.2 g daily	1°	0.70 OR	0.51–0.91	<0.01
Dawson-Hughes[28]	US	36	389	F/M	Community	Vitamin D_3 700 IU + Calcium 0.5 g daily	1°	0.5 HR	0.2–0.9	0.02
Larsen[29]	Denmark	36	9605	F/M	Community	Vitamin D_3 400 IU + Calcium 1 g daily	1°	0.84 RR	0.72–0.98	<0.025
Porthouse[30]	UK	18–42, median 25	3314	F	Community	Vitamin D_3 800 IU + Calcium 1 g daily	1° + risk factors	1.01 OR	0.71–1.43	>0.5
Grant[31]	UK	24–62, median 45	5292	F/M	Any except nursing home	Vitamin D_3 800 IU	2°	1.02 HR	0.88–1.19	>0.5
						Calcium 1g daily	2°	0.94 HR	0.81–1.09	>0.5
						Vit D_3 800 IU + Calcium 1 g	2°	1.01 HR	0.75–1.36	>0.5

RR, relative risk; OR, odds ratio; HR, hazard ratio; NA, not available.

significant reduction in fractures at any specific site or in either gender alone.

The results of other UK studies of vitamin D supplementation are still awaited. The BUPA Nursing Home Study is investigating the effect of oral vitamin D 100 000 IU every 3 months in care-home residents, whereas the Welsh Nursing Home Study is examining the effects of oral vitamin D 100 000 IU every 4 months.

Calcium and vitamin D supplementation

Studies of vitamin D used in combination with calcium supplementation have produced more consistent reports of benefits than vitamin D alone. The strongest evidence for the benefits of calcium and vitamin D supplementation in reducing fracture risk is provided by a trial of 1200 mg calcium and 800 IU vitamin D_3 daily in women living in French nursing homes or apartment blocks for the elderly.[26] At 18 months, calcium and vitamin D decreased the risk of hip and other non-vertebral fractures by 43% and 32%, respectively. A significant reduction in fracture incidence with calcium and vitamin D was also observed after 3 years supplementation.[27] Blood samples collected from a small subgroup of subjects showed serum 25OHD increases from 40 nmol/l to 100 nmol/l with calcium and vitamin D, while serum PTH decreased from 54 to 30 pg/ml.[26] There was no change in serum 25OHD in the placebo-treated group, but serum PTH increased to a maximum of 60 pg/ml.

A smaller US study examined the effect of 500 mg calcium and 700 IU vitamin D_3 daily in older men and women (aged >65 years) living in the community.[28] This study was not designed as an anti-fracture study, but had bone density as the main outcome measure. Over the 3-year study period, there was a moderate reduction in bone loss, as measured in the femoral neck, spine, and total body. There was also a reduced incidence of non-vertebral fractures in the group receiving calcium and vitamin D.

A Danish cluster randomized trial investigated the effect of daily 1000 mg calcium and 400 IU vitamin D supplementation and/or an environment and health programme aimed at reducing falls risk in community dwelling older people.[29] This showed a reduction in fracture risk in women of 18% with the environment and health programme, 22% with calcium and vitamin D, and 27% with the combination, but no benefit was observed in men.

More recently, an open-label UK study examined the effect of calcium 1000 mg and 800 IU vitamin D_3 daily in older (aged ⩾70 years) community-dwelling women with clinical risk factor(s) for hip fracture, such as previous fracture, weight <58 kg, smoking, or family history of hip fracture.[30] Eligible subjects were randomized to a nurse-led clinic in primary care, where calcium and vitamin D was started if there was no contraindication, or to no intervention. After a median follow-up of 25 months, there was no significant reduction in all fractures or hip fractures in subjects randomized to receive calcium and vitamin D supplementation.

The RECORD study was a pragmatic trial of calcium and vitamin D supplementation in the secondary prevention of osteoporotic fractures in older people.[31] Older men and women with a low trauma fracture were randomized to receive 1000 mg calcium alone daily, vitamin D_3 alone 800 IU daily, calcium and vitamin D in combination, or placebo. Most of the participants in this study were community-dwelling, as the exclusion criteria included being confined to bed or chair, cognitive impairment and limited life expectancy. Overall compliance with study medication was approximately 65% at 2 years, but was 8% lower in subjects taking calcium. Treatment with vitamin D, either alone or in combination with calcium, increased serum 25OHD from 35 to 60 nmol/l in the small sub-set of participants who underwent venepuncture. No reduction in all fractures, low trauma fractures or hip fractures was seen with calcium and vitamin D, either alone or in combination. Pre-planned sub-group analysis stratified by age, gender, body weight, latitude, dietary calcium intake, sunlight exposure and compliance showed no evidence of anti-fracture benefit with any treatment.[31] The negative results of the RECORD study may reflect poor compliance with study medication, although no reduction in fractures was seen in the sub-group analysis stratified by compliance, or in the subsequent per protocol analysis.[32] An alternative possibility is that the serum 25OHD concentrations achieved by supplementation were sub-optimal.

Meta-analyses and systematic reviews

A recent meta-analysis of double-blind randomized controlled trials of oral vitamin D (with or without calcium) compared with calcium alone or placebo, in people aged >60 years, found fracture prevention benefits with higher doses of vitamin D, but not with lower doses.[3] The analysis included five trials where hip fracture was assessed, and seven for all non-vertebral fractures. A vitamin D dose of 700–800 IU daily reduced the relative risk (RR) of hip fracture by 26% (pooled RR 0.74, 95%CI 0.61–0.88) and any non-vertebral fracture by 23% (pooled

RR 0.77, 95%CI 0.68–0.87) compared with calcium or placebo. No significant anti-fracture benefit was observed for trials using 400 IU vitamin D daily (pooled RR for hip fracture 1.15, 95%CI 0.88–1.50; pooled RR for any non-vertebral fracture 1.03, 95%CI 0.86–1.24). This meta-analysis did not include the results of three recent UK studies.[22,30,31]

The Cochrane systematic review of vitamin D has now been updated to include recent studies.[33] This concluded that vitamin D alone was not associated with any reduction in hip or other non-vertebral fracture. Combined calcium and vitamin D supplementation decreased the incidence of hip fractures (RR 0.81, 95% CI 0.68–0.96) and non-vertebral fractures (RR 0.87, 95% CI 0.78–0.97), but this effect appeared to be restricted to those living in institutionalized care.

Effect of calcium and vitamin D on falls risk

There is evidence that a low level of vitamin D is associated with an increased incidence of falling in older people.[34,35] The consensus is that this link is causal, and several mechanisms have been suggested to support it. Vitamin D is known to be important for muscle function, through maintenance of serum calcium, and through a direct effect on skeletal muscle growth and differentiation.[34,36] Body sway increases as serum 25OHD falls below 50 nmol/l, whereas muscle weakness and elevation of serum PTH occur when 25OHD decreases below 30 nmol/l.[37]

The results of studies which examine the effect of vitamin D supplementation on falls risk are conflicting, but two recent meta-analyses suggest that there may be some benefit.[4,38] In a meta-analysis of 13 trials of vitamin D or its metabolites in older people (aged >60 years), no effect on falls or physical performance was found in ten of these studies, although three did find a positive effect for the combined use of vitamin D and calcium.[38] Most of the trials were small and had methodological problems. However, when data from the four highest quality trials were pooled, there was still no evidence that vitamin D reduced the risk of falling, although a single trial of calcium and vitamin D did show a positive effect. The authors concluded that there was insufficient evidence to support the use of vitamin D supplements alone in improving physical performance in older people, while any benefit from the combined use of vitamin D and calcium needed to be confirmed with large well-designed trials. A second meta-analysis

reviewed the results of five randomized controlled trials where 'vitamin D' was compared with calcium or placebo in people aged >60 years.[4] One of these studies used an activated metabolite of vitamin D (calcitriol) rather than parent vitamin D. Although 'vitamin D' was associated with a reduction in the risk of falls (corrected OR 0.78, 95%CI 0.64–0.92), the only individual trial to show a significant reduction was that using calcitriol.

More recently, other studies have added to the controversy about whether vitamin D and calcium in combination can reduce the risk of falls. A 12% risk reduction in severe falls (RR 0.88, 95% CI 0.79–0.98) was noted in the cluster randomized trial in elderly community-dwelling Danish women given 1000 mg calcium and 400 IU vitamin D_3, compared to those offered home safety inspection with dietary and health advice, or no intervention.[29] In contrast, no reduction in falls was seen in three of the recent large UK studies of vitamin D or calcium and vitamin D supplementation.[22,30,31] Although falls were not a primary outcome measure of these studies, and the falls data were collected retrospectively rather than prospectively using a falls diary, these results do not support the widespread use of vitamin D supplementation for the prevention of falls.

Potential reasons for inconsistent effects of vitamin D on falls and fractures

So why are the results of studies of the effect of vitamin D supplementation inconsistent? Part of the explanation may be that older people at risk of falling and fracture are a very heterogeneous group. For example, although many older people will be at increased risk of falling due to low levels of vitamin D, other risk factors, such as low visual acuity, may be much more important in significant subsets, so that just supplementing the whole study population with vitamin D may not significantly reduce falling. Similarly for osteoporotic fractures, there are multiple skeletal and non-skeletal factors that influence fracture risk, and vitamin D supplementation may not be helpful if non-vitamin D-responsive risk factors are the predominant driver to fracture. The dose of vitamin D used may be another relevant factor: some trials may be examining inadequate doses of vitamin D, and there remains uncertainty as to the role of calcium intake, and whether there is a threshold of calcium intake that is needed to maximize the benefit of vitamin D supplementation. The benefits of vitamin D supplementation may be related not only to vitamin D status, but also to the serum 25OHD achieved by treatment. This may explain the fracture reduction

observed in the study in institutionalized French women.[26] Serum PTH levels may also be important, as a raised PTH (independent of serum 25OHD) was a risk factor for falls and mortality in a study of older Australian men.[39] Interestingly, in this study not all patients with a low vitamin D had a raised PTH, confirming some heterogeneity in the older population that is vitamin-D-deficient. Thus treating people purely on the basis of age is too crude a measure, and may account for the conflicting data seen in studies of falls and fractures.

Adjunctive use of calcium and vitamin D with osteoporosis treatments

In clinical trials of osteoporosis treatments, study participants in both active and control groups generally received calcium and vitamin D supplementation, ranging from 500 to 1000 mg of calcium and 250–1200 IU vitamin D daily. The benefits of treatment can therefore only be assumed if the patient has an adequate dietary calcium intake and is vitamin-D-replete. The National Institute of Health and Clinical Excellence (NICE) recommends that patients receiving bisphosphonate treatment for osteoporosis should also receive calcium and vitamin D supplements, unless the clinician is confident that the patient has an adequate dietary calcium intake and is vitamin-D-replete.[40] Accurate assessment of dietary calcium intake is time-consuming, whereas evaluation of vitamin D status necessitates measurement of serum 25OHD and PTH, which may not be feasible in many clinical settings.

A small study from the Netherlands compared the effect of 12 months' treatment with cyclical etidronate in two groups of patients with low bone density (T score <–2.0): one with vitamin D insufficiency (serum 25OHD <40 nmol/l) and the other without.[41] Significantly greater increases in lumbar spine and femoral neck BMD were observed in the vitamin-D-replete group. In an observation cohort study from Canada, patients who failed to increase BMD on either cyclical etidronate or alendronate, were then given a vitamin D supplement as well as the bisphosphonate.[42] The addition of vitamin D led to a significant increase in lumbar spine BMD. A study from Nottingham showed greater increase in BMD with cyclical etidronate and combined calcium and vitamin D supplementation, than with cyclical etidronate and calcium alone.[43] In contrast, the British Thoracic Society Steroid Osteoporosis Study showed that although cyclical etidronate without calcium increased BMD, there was no additional benefit of adding in calcium.[44]

Use of calcium and vitamin D in the UK

Data from primary-care databases in the UK[45,46] provides an insight into current usage of calcium and vitamin D supplements. Among a set of 11 998 patients on the GPRD (General Practice Research Database) and THIN (The Health Improvement Network) databases who had been prescribed bisphosphonates, around 1 in 3 were also given calcium and vitamin D. Levels of prescribing of calcium and Vitamin D did not vary significantly with age, and those aged >80 years were no more or less likely to be given supplements than those aged <50 years.

Prescribing of combined supplements to those on bisphosphonates has, however, increased dramatically in recent years, rising from 25% of patients in 1996 to 40% in 2003. The data also show that those who were not prescribed calcium and Vitamin D were less likely to still be using the bisphosphonate after a year, than when the supplements were given (61% vs. 68%; RR for discontinuation 0.80, 95%CI 0.74–0.86). This finding is difficult to explain, but it does suggest that compliance is not a problem.

The THIN data also showed that only 22% of women with osteoporosis not on bisphosphonates were given a calcium and vitamin D supplementation, compared to 36% of bisphosphonate users and 1% of the general population of women aged >50 years. This compares unfavourably with data from the US, where of 2932 subjects (mean age 74 years), 67% of women and 25% of men were taking a calcium supplement.[47] Women with a history of fracture, and those with osteoporosis, were more likely to be taking calcium supplements than other females. Among women on treatments for osteoporosis, 92% were taking calcium supplements. Co-prescribing of calcium and vitamin D with a bisphosphonate therefore appears to be low in the UK, although the extent of over-the-counter (OTC) supplementation of calcium and vitamin D is unknown.

Conclusions

Although the adult population should be encouraged to have a dietary calcium intake greater than the RNI of 700 mg/day, individuals with probable osteoporosis and those at risk of osteoporosis should consider increasing their dietary calcium intake to 1000–1500 mg/day. The adult population should also be encouraged to maintain regular exposure to sunlight (5–10 min two or three times weekly without sunblock) during summer months.

In healthy older people with a calcium intake >700 mg/day and regular sunlight exposure, there is no need for calcium and vitamin D supplementation. In contrast, older people likely to have vitamin D insufficiency, such as those with limited or no exposure to sunlight, should receive calcium and vitamin D supplementation. Although calcium and vitamin D should be considered in care-home residents, this may be ineffective in those who are chair- or bed-bound, as their risk factor profile for falls and fractures may be very different from that of more ambulant residents.

Combined calcium and vitamin D supplementation alone is ineffective in the secondary prevention of osteoporotic fractures in community-dwelling older people, where other treatment options should be considered. Nevertheless, patients receiving osteoporosis treatment should also be offered calcium and vitamin D supplementation daily, unless the clinician is confident that the patient has an adequate dietary calcium intake and is vitamin-D-replete.

Acknowledgements

References

1. NIH Conference Development Panel. Osteoporosis prevention, diagnosis and therapy. *JAMA* 2001; **285**:785–95.

2. Tuck SP, Francis RM. Best practice: osteoporosis. *Postgrad Med J* 2002; **78**:526–32.

3. Bischoff-Ferrari HAD, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA* 2005; **293**:2257–64.

4. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB. Effect of vitamin D on falls: a meta-analysis. *JAMA* 2004; **291**:1999–2006.

5. Francis RM. Prevention and treatment of osteoporosis: Calcium and vitamin D. In: Compston JE, ed. *Osteoporosis. New perspectives on causes, prevention and treatment*. London, Royal College of Physicians of London, 1996:123–34.

6. Department of Health. *Nutrition and Bone Health*. London, The Stationary Office, 1998.

7. National Institutes of Health Consensus Development Panel. Optimal calcium intake. *JAMA* 1994; **272**:1942–8.

8. Finch S, Doyle W, Lowe C, Bates CJ, Prentice A, Smithers G, Clarke PC. *National Diet and Nutrition Survey: people aged 65 years and over. Volume 1: Report of the diet and nutrition survey*. London, The Stationary Office, 1998.

9. Francis RM, Peacock M, Taylor GA, Storer JH, Nordin BEC. Calcium malabsorption in elderly women with vertebral fractures: evidence for resistance to the action of vitamin D metabolites on the bowel. *Clin Sci* 1984; **66**:103–7.

10. Heaney RP. The importance of calcium intake for lifelong skeletal health. *Calcif Tissue Int* 2002; **70**:70–3.

11. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* 2004; **80(Suppl.)**:1678–88S.

12. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: Consequences for bone loss and fractures and therapeutic implications. *Endocrine Reviews* 2001; **22**:477–501.

13. Vieth R, Ladak Y, Walfish PG. Age-related changes in the 25-Hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. *J Clin Endocrinol Metab* 2003; **88**:185–91.

14. Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, Petruschko RA, Chen E, de Papp AE. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* 2005; **90**:3215–24.

15. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporos Int* 2005; **16**:713–16.

16. Lips P, Chapuy MC, Dawson-Hughes B, Pols HAP, Holick MF. An international comparison of serum 25-hydroxyvitamin D measurements. *Osteoporos Int* 1999; **9**:394–7.

17. Hirani V, Primatesta P. Vitamin D concentrations among people aged 65 years and over living in private households and institutions in England: population survey. *Age Ageing* 2005; **34**:485–91.

18. Gallacher SJ, McQuillian, Harkness M, Finlay F, Gallagher AP, Dixon T. Prevalence of Vitamin D inadequacy in Scottish adults with non-vertebral fragility fractures. *Cur Med Res Opin* 2005; **21**:1355–61.

19. Sahota O, Gaynor K, Harwood RH, Hosking DJ. Hypovitaminosis D and 'functional hypoparathyroidism'—the NoNoF (Nottingham Neck of Femur) study. *Age Ageing* 2001; **30**:467–72.

20. Sahota O, Mundey MK, San P, Godber IM, Lawson N, Hosking DJ. The relationship between vitamin D and parathyroid hormone: calcium homeostasis, bone turnover, and bone mineral density in postmenopausal women with established osteoporosis. *Bone* 2004; **35**:312–19.

21. Heikinheimo RJ, Inkovaara JA, Harju EJ, Haavisto MV, Kaarela RH, Kataja JM, Kokko AM, Kohlo LA, Rajala SA. Annual injection of vitamin D and fractures of aged bones. *Calcif Tissue Int* 1992; **51**:105–10.

22. Smith H, Anderson F, Raphael H, Crozier S, Cooper C. Effect of annual intramuscular vitamin D supplementation on fracture risk: population-based, randomised, double-blind, placebo-controlled trial. *Osteoporos Int* 2004; **15(Suppl. 1)**:S8.

23. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomised, placebo-controlled clinical trial. *Ann Intern Med* 1996; **124**:400–6.

24. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduced the risk of fracture in the elderly? A randomised controlled trial. *J Bone Miner Res* 2002; **17**:709–15.

25. 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: randomised double blind controlled trial. *Br Med J* 2003; **326**:469–72.

26. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ. Vitamin D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992; **327**:1637–42.

27. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *Br Med J* 1994; **308**:1081–2.

28. 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**:670–6.

29. Larsen ER, Mosekilde L, Foldsprang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *J Bone Miner Res* 2004; **19**:370–8.

30. Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, Baverstock M, Birks Y, Dumville J, Francis RM, Iglesias C, Puffer S, Sutcliffe A, Watt I, Torgerson DJ. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *Br Med J* 2005; **330**:1003–6.

31. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, Anderson FH, Cooper C, Francis RM, Donaldson C, Gillespie WJ, Robinson CM, Torgerson DJ, Wallace WA; RECORD Trial Group. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* 2005; **365**:1621–8.

32. Grant AM. RECORD Trial Group. Prevention of low-trauma fractures in older people. *Lancet* 2005; **366**:543–4.

33. Avenell A, Gillespie W, Gillespie L, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev* 2005; **3**:CD000227.

34. Mosekilde L. Vitamin D and the elderly. *Clin Endocrinol* 2005; **62**:265–81.

35. Venning G. Recent developments in vitamin D deficiency and muscle weakness among elderly people. *Br Med J* 2005; **330**:524–6.

36. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. *Am J Physiol Renal Physiol* 2005; **289**:F8–28.

37. Pfeifer M, Begerow B, Minne HW. Vitamin D and muscle function. *Osteoporosis Int* 2002; **13**:187–94.

38. 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**:1219–26.

39. Sambrook PN, Chen JS, March LM, Cameron ID, Cumming RG, Lord SR, Zochling J, Sitoh YY, Lau TC, Schwartz J, Seibel MJ. Serum parathyroid hormone predicts time to fall independent of vitamin D status in a frail elderly population. *J Clin Endocrinol Metab* 2004; **89**:1572–6.

40. NICE. *Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.* NICE Technology Appraisal 87, January 2005.

41. Koster JC, Hackeng WHL, Mulder H. Diminished effect of etidronate in vitamin D deficient osteopenic postmenopausal women. *Eur J Clin Pharmacol* 1996; **51**:145–7.

42. Heckman GA, Papaioannou A, Sebaldt RJ, Ioannidis G, Petrie A, Goldsmith C, Adachi JD. Effect of vitamin D on bone mineral density of elderly patients with osteoporosis responding poorly to bisphosphonates. *BMC Musculoskeletal Disorders* 2002; **3**:6.

43. Sahota O. *Hypovitaminosis D in postmenopausal women with established vertebral osteoporosis.* Doctorate of Medicine Thesis, University of Nottingham, 2002.

44. Campbell IA, Douglas JG, Francis RM, Prescott RJ, Reid DM, on behalf of the Research Committee of the British Thoracic Society. Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids. *Thorax* 2004; **59**:761–8.

45. van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. *Q J Med* 2000; **93**:105–11.

46. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Inform Prim Care* 2004; **12**:171–7.

47. Dawson-Hughes B, Harris SS, Dallal GE, Lancaster DR, Zhou Q. Calcium supplement and bone medication use in a US medicare health maintenance organisation. *Osteoporos Int* 2002; **13**:657–62.