Should vitamin D supplementation be routinely prescribed for the elderly?

Falls are acknowledged as a leading cause of fractures and mortality in the elderly and this begs the question of whether routine supplementation with vitamin D could help prevent fractures in this group. Jyoti Sood appraises the available literature in an attempt to answer this question.

Introduction

The term vitamin D refers to its two major forms — ergocalciferol (vitamin D2) and the more potent form, cholecalciferol (vitamin D3), which is formed in the skin. Vitamin D functions to regulate plasma calcium concentrations through increasing its intestinal absorption, promoting renal re-absorption and increasing calcium mobilisation from bone.

There are a number of different strength vitamin D preparations available. It is available, in one of the two forms, either alone or in combination with calcium. Although vitamin D is known to aid the absorption of calcium, the calcium present in combined supplementation is unnecessary.[1]

Vitamin D deficiency is an established risk factor for osteoporosis, falls and fractures because it results in skeletal muscle myopathy and weakness. A lack of vitamin D is defined either as an 'insufficiency' or a 'deficiency' depending on serum calcitriol levels. A lack of vitamin D cannot be inferred from reference values for the 'normal' population.[2] Instead, vitamin D insufficiency is defined as the lowest threshold value for calcitriol (around 50nmol/L) that prevents secondary hyperparathyroidism, increased bone turn-over, bone mineral loss or seasonal variations in parathyroid hormone. Vitamin D deficiency is defined as values below 25nmol/L.[2]

Based on these definitions, deficiency is very common in institutionalised elderly, those with impaired mobility and those who have already sustained a hip fracture.[2,3] The main causes, particularly among the institutionalised are a lack of cutaneous cholecalciferol production, a poor diet or decreased renal calcitriol production. Vitamin D insufficiency is mainly asymptomatic and found among many elderly community dwellers and almost universally among institutionalised elderly.[2,3] Women are at increased risk including those in manual social classes associated with employment outside the professional, managerial or skilled technical sector, low or normal body mass index (BMI), poor general health and existing longstanding limiting illness.[3]

Falls are the leading cause of mortality in people aged more than 75 years with one third sustaining a fracture.[4] Fractures and in particular fractures of the hip, cost the NHS £1.7 billion annually.[4] Fracture prevention is becoming an important public health issue because of the increasing elderly population. Because vitamin D has a direct action on the skeletal muscle function, supplementation might be expected to reduce the effects of muscle weakness and reduce the incidence of falls through maintaining the biochemical competence of the skeleton.

With this in mind the most important considerations that need to be addressed are:

- Is vitamin D beneficial for primary or secondary fracture prevention?
- Which subgroup, if any, is likely to benefit?
- Should vitamin D be combined with calcium or given as monotherapy?
- What is the optimal dose?

No sole vitamin D supplement for simple vitamin D deficiency is available.[1] However, the vitamin D analogue calcitriol

Table 1. Available preparations for supplementation[1]

	Preparations	Licensed indication
Vitamin D analogues	Alfacalcidol, calcitriol	Primary vitamin D deficiency states associated with intestinal malabsorption, chronic liver disease or severe renal impairment.
Calcium combined with cholecalciferol	Adcal D3, Cacit D3, Calceos, Calcichew D3, Calcihew D3 forte, Calfovit D3	Simple vitamin D deficiency
Calcium combined with ergocalciferol	Calcium and ergocalciferol	Simple vitamin D deficiency

is licensed for the treatment of established postmenopausal osteoporosis. There is also a newly licensed preparation combining alendronate and high dose cholecalciferol as a once-weekly tablet for the treatment of postmenopausal osteoporosis in women at risk of vitamin D deficiency.[1]

Evidence for primary or secondary fracture prevention

Evidence for a benefit of vitamin D primarily relates to its positive effect on gait, balance and calcium homeostasis.[2,5] There is less evidence for benefit in reducing falls. Assessing the disease-oriented outcome of bone mineral density (BMD) may not always highlight patients who are at risk of fractures, because fractures have multifactorial causes. Evidence regarding the patient-oriented outcome of fracture risk reduction is important, although conflicting.[5]

Primary prevention

NICE guidance states that adequate vitamin D and calcium levels are needed to ensure optimum effects of treatment in osteoporosis. Recommendations are that combined supplementation should be provided with osteoporosis treatment for the secondary prevention of osteoporotic fractures in postmenopausal women unless confident that the patient has an adequate nutritional intake and is vitamin D replete.[6]

Combined supplementation was initially reported to be beneficial compared to vitamin D alone in one of the primary prevention trials documented by Chapuy *et al*.[7] This trial involved 3270 institutionalised women with a mean age of 84 years. The absolute risk reduction (ARR) for hip fractures was found to be 4.2% and for all non-vertebral fractures it was 5.6% (see Table 2). The vitamin D status had only been assessed in 4.3% of the population. All participants were assumed to be deficient in this subgroup because their serum 25-hydroxyvitamin D levels measured at baseline were low (33nmol/L in the placebo group), although they had normalised after three years of supplementation.

Dawson-Hughes *et al*[8] subsequently reported a significant reduction in the cumulative incidence of a first fracture in all 389 (213 women) community dwellers at three years (Table 2). This was a smaller study where the average age was 71 years. The ARR for non-vertebral fractures was 8.5% compared to only 0.5% for hip fractures. The baseline 25-hydroxyvitamin D levels were much higher at 85nmol/L. The study did report benefit from combined supplementation on bone loss but was not powered to assess this benefit on fractures.

A Cochrane review[11] concluded that frail older people may sustain fewer hip and other non-vertebral fractures if given combined supplementation, while the effectiveness of vitamin D alone in fracture prevention is unclear.

The trial reported by Bischoff-Ferrari *et al*[9] (n = 445, 246 women), published after the Cochrane review, showed a significant reduction (overall ARR 11.8%) in the risk of falls especially for ambulatory and less active women with combined supplementation. No beneficial effect was found for

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men irrespective of their level of physical activity (RR 0.98, ARR 1%, 95% CI 0.50 to 1.72). However, a similar randomised trial whose primary outcome was fractures and not falls (which was the secondary outcome) did not find a reduction with combined supplementation (800IU cholecalciferol + 1000mg calcium) among community dwelling women aged 70 years and more with one or more risk factors for hip fracture.[12] Law *et al*[10] published (also after the Cochrane review) another large randomised controlled trial which, found no evidence that ergocalciferol prevented fractures in 3700 institutionalised elderly (2812 women) with an average age of 85 years. The ARR for hip fractures was 0.3%, for non-vertebral fractures was 1% and for falls was 1.1%.[10] The pre-treatment serum

Table 2. Primary prevention trials by dose and effect risk reduction

Citation	Dose	Effect RR (95% CI)	NNT	P value
Chapuy *et al* 1994[7]	800IU cholecalciferol + 1200mg calcium	Hip fractures: 0.73 (0.62–0.78) Non-vertebral fractures: 0.79 (0.69–0.91)	23 18	0.02
Dawson *et al* 1997[8]	700IU cholecalciferol + 500mg calcium	Hip fractures: 0 (only 1 observed fracture in the control group) Non-vertebral fractures: 0.46 (0.24–0.88)	202 12	0.02
Bischoff-Ferrari *et al* 2006[9]	700IU cholecalciferol + 500mg calcium	Falls: 0.79 (0.30–0.97)	8	0.05
Law *et al* 2006[10]	Ergocalciferol 2.5mg every 3 months	Falls: 1.03 (0.95–1.25) Hip fracture: 1.36 (0.80–2.34) Non-vertebral fracture: 1.48 (0.99–2.20)	92* 294* 97*	0.05

*NNT = number needed to be supplemented for three years to prevent one fracture. *NNT over 10 months.*

> Overall, the trials are consistent with a therapeutic benefit of vitamin D on fractures in those who are deficient.

25-hydroxyvitamin D concentrations were high (median 47nmol/L) but measured in only 1% (n = 18) of the population.

Secondary prevention

There has been overall consistency regarding the beneficial effect of vitamin D supplementation for deficient, institutionalised elderly women. It can be assumed that women who have already sustained a primary fracture will be vitamin D deficient and this will significantly increase the risk of experiencing another fracture.

The randomised evaluation of calcium and cholecalciferol for the secondary prevention of low-trauma fractures in elderly people (RECORD) trial, was designed to test whether calcium alone or combined with vitamin D would lead to a significant decrease in fracture rates, over a median three-year treatment period. This was a large trial of 5292 people aged 70 years or older (4498 women) who were mobile and mostly community dwelling before developing a low-trauma fracture. Of note, 20% were also taking thiazide therapy, which has been associated with an increase in BMD because of the effect in reducing urinary calcium excretion. Daily supplementation was with either 800IU cholecalciferol and 1000mg calcium or placebo. Patients who were immobile before they sustained a fracture were excluded. Follow-up was arranged for between 24 and 62 months. The primary outcome was new low-energy fractures excluding those of the face and skull.[13]

The findings did not support the routine use of oral supplementation with calcium and cholecalciferol, either alone or in combination, for the prevention of further fractures in those previously mobile. Supplementation was not found to prevent one less person per 100 from having one fracture per year over a median of three years.[13]

Although, this appears to be a well conducted study, these findings require further scrutiny because previous trials have found that vitamin D is beneficial in preventing fractures in institutionalised elderly.[2] In the study compliance declined to 63% after two years — and it may have been as low as 45% when including non-responders to questionnaires about compliance.[2,13] Poor compliance may be attributed to the common medicines management problem of polypharmacy. The gastrointestinal side-effects of calcium supplementation were found to be significant but they were not included in the intention to treat analysis. Poor compliance in osteoporosis treatment raises the question of generalising the benefit of treatment amid poor compliance, making it ever more important to target subgroups most likely to benefit.

A further limitation was that the calcitriol levels were unknown for a large proportion of the population. The initial vitamin D status is important in deciding which elderly subgroup will benefit most from supplementation and should be encouraged within routine clinical practice in addition to analysing a patient's diet and other risk factors to determine their status accurately. This study upholds the limitations of many previous studies in that only a small percentage of the sample population had their serum 25-hydroxy-vitamin D levels measured (1.1%, n = 60). It can be assumed that patients were less likely to be deficient because they were ambulatory and living in the community, but the vitamin D status of the trial population at baseline remains largely unknown. The RECORD trial therefore probably indicates that elderly mobile, community-dwellers who are not vitamin D deficient, are least likely to benefit from combined supplementation.

above: *There is some evidence to suggest that institutionalised, inactive post-menopausal women who are vitamin D deplete benefit most from combined supplementation*

What is an adequate vitamin D dose?

Numerous vitamin D doses have been used in trials to determine their efficacy on fracture prevention. Giving 100,000IU of cholecalciferol every four months (equivalent to ~800IU daily) to community dwelling elderly resulted in a significant reduction in all first fractures compared with those given placebo.[14] Over a treatment period of five years, for combined hip and all non-vertebral fractures RR=0.78, ARR=1.7%, 95% CI 0.61 to 0.99, P 0.04 and NNT=60. For hip fractures RR=0.87, ARR=0.2%, 95% CI 0.47 to 1.53 and NNT=438 and for non-vertebral fractures RR=0.69, ARR=1.4%, and NNT=70.[14] The trial involved 2686 persons (649 women) with an average age of 75 years. The clinical significance of these findings is

difficult to establish because no baseline 25-hydroxyvitamin levels were obtained. They were measured four years into the trial in a subgroup (9.4%, n = 253) and found to be 52nmol/L in the placebo group,[14] whereas previous trials have detected normalised vitamin D levels after three years of supplementation.[7]

Community dwellers were also randomised to receive either an annual injection of cholecalciferol 300,000IU (equivalent to ~800IU daily) or placebo, which did not produce any significant benefit against fracture prevention partly due to its reduced bioavailability.[15] Most trials have concentrated upon giving 800IU cholecalciferol daily and found this to be efficacious as concluded by a meta-analysis consisting of only double-blind randomised controlled clinical trials.[16] The dose range of 700–800IU was found to reduce the RR of hip fracture by 26% (pooled RR=0.74, 95% CI 0.61 to 0.88, P<0.001, NNT=45 for a treatment duration of 24 to 60 months) and any non-vertebral fractures by 23% (pooled RR=0.77, 95% CI 0.68 to 0.87, P=0.02 NNT=27 for a treatment duration of 12 to 60 months) in both, institutionalised and ambulatory elderly compared to calcium or placebo.[16] The lower dose of 400IU was found to be insufficient for fracture prevention compared with placebo or calcium.[16]

Summary

The evidence-base for vitamin D supplementation in the elderly — based on the key considerations are summarised below.

Vitamin D supplementation for primary or secondary fracture prevention?

Secondary fracture prevention with combined supplementation of calcium and 800IU cholecalciferol cannot be entirely ruled out based on the RECORD trial findings alone, because the majority of previous trials are consistent with a therapeutic benefit of this dose on fractures in deficient elderly. Evidence for primary prevention is less clear with NICE recommending supplementation for secondary prevention in those with evidence of depletion. The vitamin D status in the majority of the population studies remains largely unknown making the role of supplementation in primary prevention indecisive particularly as the causes of falls and fractures are multi-factorial.

Which subgroup, if any is likely to benefit?

Trials have found that institutionalised, inactive post-menopausal women who are vitamin D deplete benefit most from combined supplementation. Assessing the baseline vitamin D status is important in deciding the benefits of vitamin D supplementation and targeting those subgroups that would most benefit in terms of those who are classed as deficient or insufficient. A majority of trials fail to do this possibly explaining why the effects of vitamin D supplementation on fractures in the elderly who are vitamin D replete and community dwelling are less clear.

Should vitamin D be combined with calcium or given as monotherapy?

Studies favour combined supplementation because vitamin D is known to aid the absorption of calcium.

What is the optimal dose?

The dose most widely studied is 800IU cholecalciferol combined with calcium (1000–1200mg). 400IU has not been found to be sufficient for fracture prevention.

Conclusion

Overall, the trials are consistent with a therapeutic benefit of vitamin D on fractures in those who are deficient. Current evidence does not support the routine use of calcium and vitamin D in all elderly people. It should be targeted at those with most to gain, either in primary or secondary prevention for combined supplementation — the greatest beneficial evidence being found for institutionalised elderly women. A holistic approach to treatment is required because the causes of osteoporotic fractures are multifactorial. ✣

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References

1. BMA and RPSGB. *British National Formulary* 52, 2007.
2. Lefe M. Vitamin D and the elderly. *Clin Endocrinol* 2005; **62(3):** 265–81.
3. Hirani V *et al*. Vitamin D concentrations among people aged 65 years and over living in private households and institutions in England: population survey *Age Aging* 2005; **34:** 485–91.
4. National Osteoporosis Society www.nos.org.uk [Accessed on 17.03.2007].
5. Anderson F. Vitamin D for older people: how much, for whom and — above all — why? *Age Aging* 2005; **34:** 425–6.
6. National Institute of Clinical Excellence. Osteoporosis – secondary prevention, TA87, Jan 2005, Available at www.nice.org.uk. [Accessed on 11.02.2007].
7. Chapuy MC *et al*. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *BMJ* 1994, **308:** 1081–2.
8. Dawson-Hughes B *et al*. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age and older. *N Engl J Med* 1997; **337:** 670–6.
9. Bischoff-Ferrari HA *et al*. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women. A three year randomized controlled clinical trial. *Arch Intern Med* 2006; **166:** 424–30.
10. Law M *et al*. Vitamin D supplementation and the prevention of fractures and falls: results of a randomized trial in elderly in residential accommodation. *Age Aging* 2006; **35:** 482–6.
11. Avenell A *et al*. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis, *The Cochrane Reviews* 2005.
12. Porthouse J *et al*. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ* 2005; **330:** 1003–8.
13. Grant A *et al*. Oral Vitamin D3 and calcium for the secondary prevention of low-trauma fractures in elderly people. (Randomised evaluation of calcium and vitamin D – RECORD): a randomized placebo-controlled trial. *Lancet* 2005; **365:** 1621–8.
14. Trivedi DP *et al*. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomized double blind controlled trial. *BMJ* 2003; **326:** 469–75.
15. Anderson FH *et al*. Effect of annual intramuscular vitamin D supplementation on fracture risk in 9440 community living older people: the Wessex Fracture Prevention Trial. *J Bone Miner Res* 2004; **19(suppl 1):** 1220 (abstr).
16. Bischoff-Ferrari HA *et al*. Fracture Prevention with Vitamin D Supplementation. *JAMA* 2005; **293(18):** 2257–64.