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Original Article

A Comparison of the Effects of Alfacalcidol Treatment and Vitamin D_2 Supplementation on Calcium Absorption in Elderly Women with Vertebral Fractures

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Abstract. Although vitamin D supplementation in the frail elderly improves calcium absorption, suppresses parathyroid hormone, decreases bone loss and reduces the risk of fractures, such treatment may be ineffective in patients with vertebral osteoporosis, because of impaired vitamin D metabolism or resistance to the action of vitamin D metabolites on the bowel. We have therefore performed a randomized, single masked study comparing the effects of alfacalcidol treatment (0.25 μg twice daily) and vitamin D_2 supplementation (500–1000 units daily) on calcium absorption and bone turnover in 46 elderly women (median age 69 years, range 64–79 years) with radiological evidence of vertebral fractures. Serum 25-hydroxyvitamin D increased significantly after 3 and 6 months of treatment with vitamin D_2 ($p<0.001$), but was unchanged in the group receiving alfacalcidol. Serum 1,25-dihydroxyvitamin D did not change significantly in either group over the study period. Fractional ^{45}Ca absorption increased after 3 months of treatment with alfacalcidol ($p<0.05$), but was unchanged with vitamin D_2. There was also a reduction in plasma intact parathyroid hormone and serum alkaline phosphatase after 6 months of treatment with alfacalcidol ($p<0.05$) which was not seen in the group receiving vitamin D_2. Our study shows that vitamin D_2 supplementation is ineffective in stimulating calcium absorption in elderly women with vertebral osteoporosis. By increasing calcium absorption in such patients, alfacalcidol may prove more effective than vitamin D in the management of vertebral osteoporosis.

Keywords: Alfacalcidol; Calcium absorption; Elderly; Osteoporosis; Vertebral fractures; Vitamin D_2

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Introduction

The efficiency of intestinal calcium absorption decreases with age in both sexes, although this becomes particularly apparent above the age of 70 years [1,2]. This decline in calcium absorption may be related in part to the reduction in serum 25-hydroxyvitamin D (25OHD) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) with advancing age [2,3]. If there is no compensatory increase in dietary calcium intake or reduction in urinary calcium, then the decline in calcium absorption might be expected to cause bone loss. Among normal elderly subjects there is a relationship between serum 25OHD and bone density, with an inverse correlation between bone density and circulating parathyroid hormone (PTH) concentrations [4]. Vitamin D treatment in the elderly maintains normal vitamin D metabolite concentrations, improves calcium absorption, suppresses PTH, decreases bone loss and reduces the risk of fractures [5–8].

Patients with vertebral osteoporosis have lower calcium absorption than age-matched control subjects [2,9].The cause of malabsorption of calcium in osteo-

porosis is unclear, but it may be due to impaired metabolism of 25OHD to $1,25(OH)_2D$ [2,10], or be related to resistance to the action of the vitamin D metabolites on the bowel [11]. Previous work suggests that malabsorption of calcium in vertebral osteoporosis is unresponsive to treatment with low-dose vitamin D, although improvement occurs with 10 000–40 000 IU daily [9]. Calcium absorption also increases on treatment with low doses of calcitriol (1,25-dihydroxyvitamin D_3) or alfacalcidol (1α-hydroxyvitamin D_3), which are the hormonally active metabolite of vitamin D and its synthetic analogue respectively [12,13].

We have previously shown that short-term treatment of elderly osteoporotic women with low-dose alfacalcidol increases calcium absorption, decreases PTH and reduces bone resorption [13,14]. We have now performed a prospective, single masked, randomized study comparing the effects of low-dose alfacalcidol treatment with vitamin D_2 supplementation on calcium absorption and bone turnover in elderly women with vertebral osteoporosis over a 6-month period.

Patients and Methods

Patients

We recruited 46 women aged between 65 and 80 years to this study from Newcastle General Hospital, Glasgow Royal Infirmary and Kings College Hospital, London. Each had radiological evidence of vertebral osteoporosis, as demonstrated by one or more of the following: loss of anterior and posterior vertebral height, vertebral wedging with an angulation of at least 30% or biconcavity with at least 30% reduction of mid-vertebral height. The study was approved by the Ethics Committee at each centre, and patients were recruited only after giving written informed consent.

Patients were excluded from this study who had a past history of thyrotoxicosis within the previous year, multiple myeloma, skeletal metastases, gastric surgery, bowel resection, inflammatory bowel disease, significant liver disease, renal stone disease, Paget's disease of bone, hypercalcaemia, ostemalacia, significant renal impairment (serum creatinine >150 μmol/l), alcohol or drug abuse. Patients were also excluded if they were likely to be bedfast, chairfast or housebound for the 6 months of the study. For the purposes of this study, osteomalacia was defined as an intact PTH measurement greater than the upper limit of of the normal range and a 25OHD concentration less than the lower limit of the normal range [15]. The presence of pseudofractures *and* myopathy was also considered an exclusion criterion. Patients were excluded who had received prolonged treatment with oral steroids or anticonvulsants within the past year, or oestrogenic, progestogenic, anabolic steroids or vitamin D (>400 IU/day) within the previous 6 months. Any patient taking calcium supplements or multivitamin preparations containing up to 400 IU vitamin D per day were advised to discontinue these for at least 1 month before entry to the present study. The use of diuretics was allowed provided the dose was kept constant throughout the study.

Methods

An assessment of dietary calcium was made at the beginning of the study using a validated questionnaire [16]. If a patient's dietary calcium intake was below 500 mg/day, advice was given on increasing intake above this figure. The initial investigations were performed after an overnight fast: full blood count, erythrocyte sedimentation rate (ESR), serum biochemical profile, 25OHD, $1,25(OH)_2D$, intact PTH, and fasting urinary calcium, hydroxyproline and creatinine. Fractional calcium absorption was then measured using ^{45}Ca [11]. A 24-h urine sample was also collected for measurement of calcium and creatinine.

Laboratory Techniques

The serum biochemical profile was measured at each centre using a multichannel analyser and included urea, creatinine, calcium, phosphate, alkaline phosphatase, albumin and liver function tests. The serum calcium was corrected for an albumin of 42 g/l. As the serum alkaline phosphatase was determined by different methods in the three centres, all results on treatment are expressed as a ratio of the basal value. Serum for measurement of 25OHD and $1,25(OH)_2D$ and plasma for measurement intact PTH was stored frozen at −20 °C, for later determination at a single laboratory. Vitamin D metabolites were extracted from serum using acetonitrile, and separated and partially purified from interfering lipids using reverse prepacked columns (C18 Bond Elut).The $1,25(OH)_2D$ fraction was separated from 25OHD by high performance liquid chromatography on a straight phase silica column. 25OHD was measured using a competitive protein binding assay with charcoal separation [17]. The reference range for serum 25OHD is 15–100 nmol/l, whilst the intra-assay variation is <5% and the inter-assay variation is <8%. $1,25(OH)_2D$ was measured using a radioreceptor assay with calf thymus receptor and charcoal separation [18]. The reference range for serum $1,25(OH)_2D$ is 20–120 pmol/l, whilst the intra-assay variation is <8% and the inter-assay variation is <11%. Intact PTH was determined by a two-site immunoradiometric assay [19]. The reference range for plasma intact PTH is 1.0–5.5 pmol/l, whilst the intra-assay variation is <6% and the inter-assay variation is <8%.

Urine calcium and creatinine (Cr) was measured using standard autoanalyser techniques, whilst hydroxyproline (OHPr) was determined by colorimetry after acid hydrolysis. The glomerular filtration rate (GFR) was estimated using the Cockroft and Gault formula [20]. Calcium absorption was estimated from measure-

ment of plasma radioactivity before and 60 min after ingestion of 5 μCi ^{45}Ca orally with 0.5 mmol stable calcium as calcium chloride in 250 ml distilled water. Fractional calcium absorption was then calculated using the formula: radiocalcium absorption rate (fraction of dose/h) = $1.17f + 2.54f^2$, where f = % absorbed dose/l plasma at 1 h × body weight (kg) × 0.0015 [11]. The coefficient of variation for measurement of fractional calcium absorption is 11%, which was calculated from repeat estimations in a group of women [21].

Study Treatments

After performing baseline investigations, patients were randomized to receive treatment with alfacalcidol 0.25 μg twice daily (morning and evening) or calcium and vitamin D_2 one or two tablets after breakfast. Each calcium and vitamin D_2 tablet contained 450 mg calcium sodium lactate, 50 mg calcium phosphate (together giving 79 mg elemental calcium) and 12.5 μg ergocalciferol (500 IU vitamin D_2). The patients randomized to receive treatment with calcium and vitamin D_2 took one tablet daily for the first 3 months, followed by two tablets daily for the second period of 3 months, to assess the effect of both doses on calcium absorption. Patients were recruited to the study throughout the year and there was no seasonal clustering in the randomization to the two treatment groups.

Study Timetable

Patients were assessed clinically before and after 3 and 6 months of treatment, when measurement of serum biochemical profile, fasting urine biochemistry, vitamin D metabolites, intact PTH and calcium absorption was performed. Full blood count, ESR and 24-h urine collection were also repeated after 6 months of treatment.

Statistical Analysis

The data from this study were analysed using SAS version 6.07 on an IBM UNIX system. Means and standard errors were calculated for variables at each time point. Comparison of proportions between groups used the chi-squared test or the test of two independent proportions. Comparisons of changes in biochemistry both within and between groups were made using paired and unpaired *t*-tests, corroborated with appropriate non-parametric methods where indicated. The reference ranges for serum alkaline phosphatase varied in the three centres, so the changes on treatment are expressed as a ratio of the basal value for each patient. To normalize the data, the geometric mean of the ratio was calculated for each time point.

The primary efficiency criterion was calcium absorption, and a favourable response was defined before the study commenced as a 25% increase in calcium absorption from the basal measurement to that performed after 6 months treatment. Past experience suggested that 25% of the vitamin D_2 treated group of patients would respond to this manner [9,11]. In order to have therapeutic advantages over vitamin D_2, it was felt that alfacalcidol should increase the percentage of patients who achieve a favourable response by 50%, so that there should be at least a 25% increase in calcium absorption in 75% of patients receiving alfacalcidol. It was therefore calculated that 40 patients (20 in each group) should be available for analysis at the end of the trial, in order to detect a significant difference in response with a power of 80% and a significance level (two-tailed) of 5%.

Results

A summary of the baseline for the two groups of patients is shown in Table 1. The two groups were well matched, but although the urea was significantly higher in the group randomized to receive alfacalcidol, there was no difference in serum creatinine or calculated GFR. There were no significant correlations between the baseline fractional calcium absorption and age, serum creatinine, calculated GFR, serum 25OHD, $1,25(OH)_2D$, plasma PTH, urine OHPr/Cr or dietary calcium intake. There were also no significant correlations between calculated GFR and serum $1,25(OH)_2D$, calcium absorption or plasma PTH.

Serum 25OHD increased in the group receiving treatment with vitamin D_2 ($p<0.001$), but was unchanged in the group receiving alfacalcidol (Table 2). The difference in change in serum 25OHD between the two groups was also significant ($p<0.01$ at 3 months and $p<0.05$ at 6 months). Serum $1,25(OH)_2D$ did not change significantly in either group over the study period (Table 2), but there was a small difference in response between the two groups after 6 months of treatment, with a modest increase in patients and alfacalcidol and a slight decrease with vitamin D_2 ($p<0.05$).

Radiocalcium absorption increased significantly after 3 months of treatment with alfacalcidol, but did not change significantly on treatment with vitamin D_2 (Table 2). Using the predefined efficacy criterion of a 25% increase in fractional calcium absorption, 75% of the patients in the alfacalcidol treated group showed this after 6 months of treatment, compared with only 33.3% in the vitamin D treated group (Table 3). When the two treatment groups were subdivided into those with malabsorption of calcium or normal calcium absorption basally, a greater proportion of patients in both categories achieved a 25% increase in fractional calcium absorption with alfacalcidol than with vitamin D_2, although these differences were no longer statistically significant (Table 3).

The difference in response of calcium absorption is reflected by the 24-h urine calcium/creatinine, which

Table 1. Baseline data for the two groups of patients (mean ± SD)

	Alfacalcidol (n=24)	Vitamin D_2 (n=22)	p value[a]
Age (years)	69.9 ± 4.2	69.3 ± 3.2	NS
Height (cm)	153.25 ± 6.2	155.36 ± 6.2	NS
Weight (kg)	56.82 ± 8.2	55.04 ± 11.3	NS
Armspan (cm)	157.68 ± 7.1	159.49 ± 5.9	NS
Dietary calcium (mg/day)	947.6 ±325.9	873.3 ±430.2	NS
25OHD (nmol/l)	51.00 ± 36.1	35.86 ± 23.0	NS
$1,25(OH)_2D$ (pmol/l)	62.00 ± 28.2	62.57 ± 19.6	NS
Intact PTH (pmol/l)	2.53 ± 1.3	2.57 ± 1.1	NS
Fractional ^{45}Ca absorption	0.52 ± 0.41	0.51 ± 0.2	NS
Urea (mmol/l)	6.35 ± 1.8	5.35 ± 1.4	<0.05
Creatinine (μmol/l)	89.2 ± 21.0	80.27 ± 15.0	NS
Calcium (mmol/l)	2.40 ± 0.10	2.36 ± 0.10	NS
Albumin (g/l)	43.58 ± 3.0	43.73 ± 3.3	NS
Corrected calcium (mmol/l)	2.37 ± 0.10	2.32 ± 0.10	NS
Phosphate (mmol/l)	1.15 ± 0.10	1.17 ± 0.10	NS
Alkaline phosphatase (u/l)	171.38 ±104.6	164.27 ± 88.8	NS
OHPr/Cr (molar units)	0.025± 0.03	0.034± 0.03	NS
Calculated GFR (ml/min)	48.6 ± 11.8	51.5 ± 10.9	NS

[a] The statistical significance of any differences between the groups.

Table 2. Effects of treatment on serum vitamin D metabolites, calcium absorption, plasma intact PTH and fasting urine OHPr/Cr (mean ± SEM)

		Basal	3 Months	6 Months
Serum 25OHD (nmol/)	Alfacalcidol	51.00 ±8.27	47.05 ±5.10	52.16 ±7.02
	Vitamin D_2	35.86 ±5.01	58.82 ±5.41***	60.67 ±4.55***
Serum $1,25(OH)_2D$ (pmol/l)	Alfacalcidol	62.00 ±6.48	60.53 ±5.43	64.44 ±4.26
	Vitamin D_2	62.57 ±4.27	61.24 ±5.72	60.33 ±5.73
^{45}Ca absorption (fraction of dose/hour)	Alfacalcidol	0.52 ±0.08	0.72 ±0.10*	0.68 ±0.09
	Vitamin D_2	0.51 ±0.05	0.56 ±0.08	0.48 ±0.06
Plasma PTH (pmol/l)	Alfacalcidol	2.53 ±0.31	2.28 ±0.23	2.10 ±0.26*
	Vitamin D_2	2.58 ±0.24	2.56 ±0.26	2.39 ±0.25
OHPr/Cr (molar units)	Alfacalcidol	0.025±0.003	0.022±0.002	0.024±0.003
	Vitamin D_2	0.034±0.007	0.033±0.006	0.022±0.002

There were no significant differences between groups, but the significance of changes from basal values is indicated (*p<0.05, ***p<0.001).

Table 3. The number and percentage of patients in each group showing a 25% increase in fractional calcium absorption after 6 months of treatment with alfacalcidol or vitamin D_2

	Alfacalcidol	Vitamin D_2	p value[a]
All patients	15/20 (75%)	5/15 (33.3%)	<0.05
Patients with malabsorption of calcium (basal fractional calcium absorption <0.50)	12/13 (92.3%)	4/8 (50%)	NS
Patients with normal calcium absorption (basal fractional calcium absorption >0.50)	3/7 (42.3%)	1/7 (14.2%)	NS

[a] The statistical significance of any differences between the groups is indicated.

increased from 0.50 ± 0.09 (mean ± SEM) basally to 0.85 ± 0.11 after 6 months of treatment with alfacalcidol, whilst it was 0.51 ± 0.07 basally in the vitamin D_2 group and 0.54 ± 0.07 after 6 months of treatment. The difference in the change in the two groups was significant (p<0.001).

Plasma intact PTH decreased after 6 months of treatment with alfacalcidol, but was unchanged in the group receiving vitamin D_2 (Table 2). There was a significant reduction in serum alkaline phosphatase in the group receiving alfacalcidol compared with the vitamin D_2 treated group, but no significant change in the fasting urine OHPr/Cr (Tables 2, 4). No significant changes were seen in serum calcium, corrected calcium, phosphate, albumin, bilirubin or transaminases. Although the serum urea increases from 6.35 ± 0.36 mmol/l basally to 7.07 ± 0.44 after 3 months of treatment with alfacalcidol (p<0.05), the value at 6 months was 7.71 ± 0.87 mmol/l (NS) and there were no significant changes in serum creatinine or calculated

Table 4. Effects of treatment on serum corrected calcium, phosphate, alkaline phosphatase, creatinine and calculated GFR (mean ± SEM)

		Basal	3 Months	6 Months
Serum corrected calcium (mmol/l)	Alfacalcidol	2.37±0.02	2.37±0.03	2.38±0.03
	Vitamin D_2	2.32±0.02	2.33±0.02	2.33±0.03
Serum phosphate (mmol/l)	Alfacalcidol	1.15±0.03	1.12±0.03	1.16±0.05
	Vitamin D_2	1.17±0.03	1.18±0.03	1.16±0.03
Serum alkaline phosphatase (ratio to basal value)	Alfacalcidol	1.00	0.93±0.05	0.88±0.05*
	Vitamin D_2	1.00	1.05±0.04	1.01±0.03
Serum creatinine (μmol/l)	Alfacalcidol	89.21±4.29	89.78±4.21	93.36±5.83
	Vitamin D_2	80.27±3.21	81.94±5.76	80.17±3.33
Calculated GFR (ml/min)	Alfacalcidol	48.6 ±2.4	48.2 ±2.3	47.7 ±2.7
	Vitamin D_2	51.5 ±2.3	48.2 ±3.6	52.5 ±1.9

There were no significant differences between groups, but the significance of change from basal values is indicated (*$p<0.05$).

GFR (Table 4). There were also no significant changes in haemoglobin, white cell count, platelets or ESR in either group.

Treatment was generally well tolerated in both groups, but adverse events were experienced by three patients receiving alfacalcidol and by two patients on treatment with vitamin D_2 (Table 5). Seven patients were withdrawn from the study, five of whom were receiving alfacalcidol and two who were taking vitamin D_2 (Table 5).

Table 5. Patient withdrawals and adverse events experienced during the study

Patient	Treatment	Reason for withdrawal
5	Vitamin D_2	Epigrastric discomfort. Patient known to have hiatus hernia. Patient reluctant to continue, although symptoms probably not due to medication
31	Vitamin D_2	Nausea and vomiting. Patient reluctant to continue because of symptoms
42	Alfacalcidol	Patient emigrated to Australia
43	Alfacalcidol	Admitted to hospital during week 20 with pneumonitis, which was attributed to concomitant treatment with methotrexate for rheumatoid arthritis. During this illness became hypercalcaemic, with a corrected serum calcium of 2.90 mmol/l. Hypercalcaemia resolved with high-dose steroids and withdrawal of study medication
52	Alfacalcidol	Admitted to hospital during week 6 with blackouts. No cause found, but corrected serum calcium raised at 2.71 mmol/l. Hypercalcaemia resolved within days of discontinuing treatment with alfacalcidol
61	Alfacalcidol	Patient died of probable myocardial infarction
63	Alfacalcidol	Pain around ribs and down both legs shortly after taking first tablet. Patient reluctant to continue, although symptoms resolved

Discussion

The growing awareness of the importance of reduced production and impaired metabolism of vitamin D in the pathogenesis of bone loss in the elderly has stimulated interest in the therapeutic role of vitamin D and its metabolites in the management of osteoporosis. Our study shows that treatment with low-dose alfacalcidol is superior to vitamin D_2 supplementation in improving calcium absorption in elderly women with vertebral fractures. Alfacalcidol also suppresses PTH and reduces alkaline phosphatase, suggesting that it decreases bone remodelling. Although we could demonstrate no effect on fasting urine OHPr/Cr, other studies using low-dose alfacalcidol or calcitriol have shown an increase in calcium absorption, a decrease in PTH and a reduction in OHPr/Cr [13,21].

The vitamin D_2 treated group in our study showed a significant increase in plasma 25OHD after 3 months of treatment with 500 IU vitamin D_2 daily, with no further increase after treatment with 1000 IU daily for another 3 months. The observed increase in plasma 25OHD of 25 nmol/l was broadly comparable to that seen in other studies examining the effects of vitamin D supplementation in the elderly. A Dutch study showed an increase of 35 nmol/l after 1 year's treatment with 400 IU vitamin D_3 daily [22], whilst a French study showed a larger increase in 25OHD of 60 nmol/l after treatment with 800 IU vitamin D_3 daily for 18 months [7]. The smaller increase in 25OHD in our study may reflect less efficient metabolism of vitamin D_2 compared with vitamin D_3 [23].

We found no significant change in plasma $1,25(OH)_2D$ on treatment with alfacalcidol, although levels were checked 12 h after administration. Furthermore, in a previous study using alfacalcidol 0.25 μg twice daily, we found that the circulating $1,25(OH)_2D$ increased by a maximum of only 10 pmol/l 6 h after administration [13]. It would consequently appear that treatment with low-dose calcitriol or alfacalcidol improves calcium absorption in elderly women with vertebral crush fractures, without any sustained increase in plasma $1,25(OH)_2D$ [12,13]. This may there-

fore avoid the stimulation of bone remodelling which may potentially occur with higher doses of the vitamin D metabolites [21].

Previous work indicates that both vitamin D_2 and D_3 have a beneficial effect on bone density and fracture incidence in elderly women without apparent vertebral fractures. Supplementation with vitamin D reduces bone loss during winter months in the elderly, suggesting that relative vitamin D deficiency and secondary hyperparathyroidism may contribute to bone loss in this age group [6]. The use of 15000 IU oral vitamin D_2 weekly has also been shown to reduce metacarpal bone loss in normal women aged between 65 and 74 years living in the community [24]. A French study of elderly women living in nursing homes or apartment blocks for the elderly has demonstrated that 800 IU of vitamin D_3 and 1.2 g elemental calcium daily prevents femoral bone loss and decreases the risk of hip and other non-vertebral fractures [7]. In contrast, a recent Dutch study shows that although 400 IU of vitamin D_3 increases femoral bone density slightly, there is no demonstrable effect on the incidence of hip or other peripheral fractures [22]. Nevertheless, Heikinheimo [8] has demonstrated that an annual intramuscular injection of 150000–300000 IU vitamin D_2 decreases fractures in elderly out-patients or municipal home residents [8].

The effect of vitamin D supplementation in elderly people with vertebral osteoporosis is less clear cut. Women with vertebral crush fractures have lower calcium absorption than age-matched control subjects [2,9]. Previous studies show that malabsorption of calcium in elderly women with osteoporosis does not generally respond to vitamin D 1000 IU daily or 25-hydroxyvitamin D_3 [9,11], although it may be corrected by high dose vitamin D [10000–40000 IU daily) or by the use of low dose vitamin D metabolites such as calcitriol or alfacalcidol [9,12,13]. This apparent resistance to the action of vitamin D may be related to polymorphisms in the vitamin D receptor gene, which have recently been shown to account for much of the variation in bone density [25].

The apparent lack of effect of vitamin D_2 supplementation in our study may also reflect the decline in renal function with advancing age, which leads to impaired metabolism of vitamin D to $1,25(OH)_2D$, malabsorption of calcium, secondary hyperparathyroidism and PTH mediated bone resorption [26,27]. The patients in the present study had a mean GFR of about 50 ml/min, the level of renal function at which reduced $1,25(OH)_2D$ and malabsorption of calcium are seen [26]. Whilst the vitamin D_2 preparation used in this study also contained calcium, the amount was small and unlikely to account for the apparent lack of effect of vitamin D_2 supplementation.

Although the malabsorption of calcium seen in elderly women with osteoporosis and vertebral fractures may be overcome by treatment with the vitamin D metabolites [12–14], studies of their effect on bone mass and fractures have yielded contradictory results [28]. Three studies show no reduction in vertebral fractures in women with spinal osteoporosis treated with calcitriol, although these may have been too small to show a significant effect of treatment [28]. The study by Tilyard et al. [29] is the largest to show a beneficial effect of calcitriol (0.25 μg twice daily) on vertebral fractures, involving over 1200 patient-years of observation. This also demonstrated an unexplained increase in vertebral fracture rate in the control subjects receiving calcium supplementation alone, raising doubts about the significance of the apparent reduction in fracture risk with calcitriol [29].

Most of the work examining the effects of alfacalcidol on bone mass and fracture risk in the treatment of women with vertebral crush fractures has been performed in Japan, but shows a reduction in bone loss and a decreased risk of further fracture [30]. Although such studies show a small incidence of hypercalcaemia, this may reflect the low dietary calcium intake of Japanese women. Nevertheless, mild hypercalcaemia developed in two patients receiving alfacalcidol in the present study, suggesting that the therapeutic window may be narrow. Fortunately, in both cases the hypercalcaemia resolved rapidly on discontinuing treatment with alfacalcidol.

We conclude that although vitamin D supplements may decrease bone loss and reduce fracture incidence in the frail elderly, who are likely to have some degree of vitamin D deficiency, they are ineffective in stimulating calcium absorption in elderly women with vertebral osteoporosis. Our study suggests that by increasing calcium absorption in such patients, alfacalcidol may be more effective than vitamin D in the management of vertebral osteoporosis. Further studies are required to compare the effect of vitamin D supplements and low-dose alfacalcidol on bone density and fracture rate in elderly women with vertebral osteoporosis.

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