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A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NoNOF) Study

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Abstract

Background: survivors of hip fracture are at 5- to 10-fold risk of a second hip fracture. There is little consensus about secondary prevention. Many are given calcium and vitamin D, but the evidence supporting this is circumstantial.
Objective: to compare the effects of different calcium and vitamin D supplementation regimens on bone biochemical markers, bone mineral density and rate of falls in elderly women post-hip fracture.
Design: randomised controlled trial.
Setting: orthogeriatric rehabilitation ward.

Methods: 150 previously independent elderly women, recruited following surgery for hip fracture, were assigned to receive a single injection of 300,000 units of vitamin D_2, injected vitamin D_2 plus 1 g/day oral calcium, 800 units/day oral vitamin D_3 plus 1 g/day calcium, or no treatment. Follow-up was one year, with measurement of 25-hydroxyvitamin D, parathyroid hormone, bone mineral density, and falls.
Results: mean 25-hydroxyvitamin D increased and mean parathyroid hormone was suppressed in all the actively treated groups, more so in the group receiving combined oral vitamin D and calcium. Twenty per cent of participants injected with vitamin D were deficient in 25-hydroxyvitamin D a year later. Bone mineral density showed small but statistically significant differences of up to 4.6% between actively treated groups and placebo. Relative risk of falling in the groups supplemented with vitamin D was 0.48 (95% CI 0.26–0.90) compared with controls.
Conclusion: Vitamin D supplementation, either orally or with injected vitamin D, suppresses parathyroid hormone, increases bone mineral density and reduces falls. Effects may be more marked with calcium co-supplementation. The 300,000 units of injected vitamin D may not last a whole year.

Keywords: *hip fracture, vitamin D, osteoporosis, bone mineral density, parathyroid hormone, elderly, randomised controlled trial*

Introduction

Hip fractures are the most serious osteoporotic fractures, with high mortality, and decreased mobility and increased dependency in survivors [1–3]. Moreover, survivors are at 5–10-fold increased risk of fracturing their other hip compared to subjects of similar age [4, 5]. Despite this, there is little consensus over secondary prevention [6, 7]. Oral calcium and vitamin D are often given, on the basis of the high prevalence of hypovitaminosis D in elderly people [8–11], and its efficacy in the primary prevention of hip fractures amongst frail elderly people [12]. However, these oral preparations come as large tablets, and polypharmacy can be a problem for elderly people. An alternative strategy is to give annual injections of 300,000 units of vitamin D, which could, for example, be delivered conveniently at the same time as influenza vaccination. Some evidence, albeit incomplete, supports the bone-protective effects of injected vitamin D [13].

We recently described 'functional hypoparathyroidism' – a failure to mount a secondary hyperparathyroid response to hypovitaminosis D – in about half of elderly women with hypovitaminosis D after hip fracture [8]. In this study we describe the effects of different calcium and vitamin D supplementation strategies on calcium homeostasis, bone mineral density (BMD) and falls, compared with no treatment, in the same population.

Methods

Participants

Participants were recruited over an 18-month period from a 'fast-track' orthogeriatric rehabilitation ward, within 7 days of surgery for a hip fracture. The main criteria for referral to the ward specified previous community residence, and independence in activities of daily living (ADL). Institutionalised patients were excluded from the study, as were patients with diseases or medication known to affect bone metabolism, and those with a 10-point abbreviated mental test score [14] less than seven at the time of recruitment. Two hundred and eight women were invited to participate of whom 150 initially agreed. Fifty-eight declined, mainly through family members considering it inappropriate to include frail elderly people in a research project. Fifteen patients were not eligible for invitation according to the exclusion criteria (six cognitive impairment, nine on medication affecting bone metabolism). All subjects underwent a baseline medical examination, biochemical tests and bone densitometry. The protocol was approved by the university hospital ethics committee and all patients gave written, witnessed, informed consent.

Randomisation

Participants were randomised to four treatment groups, from computer-generated random number lists, using sealed, opaque, envelopes. Groups were assigned to receive a single injection of 300,000 units of vitamin D_2 [ergocalciferol]; injected vitamin D_2 plus oral calcium carbonate (Calcichew, one tablet twice daily, providing 1 g/day elemental calcium); combined oral vitamin D_3 and calcium carbonate tablets (Calceos 1 tablet twice daily, providing vitamin D_3 [cholecalciferol] 800 units/day and 1 g/day elemental calcium); or no treatment. Placebos were not used. Participants' general practitioners were asked to avoid prescribing vitamin D or other osteoporosis drugs during the follow-up period.

Follow up

Patients were seen in a dedicated clinic 3, 6 and 12 months after their fracture. Deaths, falls and new fractures were ascertained. Falls diaries were not used, and the researcher was not blinded to treatment allocation. Fracture reports were not verified. Biochemical measurements and BMD were repeated after 12 months.

Biochemical measurements

Blood samples were taken the day following randomisation. Standard, automated, laboratory methods were used, with serum calcium corrected for albumin binding. Intact parathyroid hormone (PTH) was measured by immunochemiluminometric assay [Magic Lite, Ciba Cornig Diagnostics, Gwynned, UK; normal range (NR) 12–72 ng/ml]; 25-hydroxyvitamin D (25OHD) by radioimmunoassay (Incstar Corporation, MN, USA; NR 25–115 nmol/l). Intra and inter-assay variances ranged between 2.5–11% and 4–8% respectively, with all assays measured by the same technician in batch analysis, 7 days post-fracture. Hypovitaminosis D

was defined as a 25OHD ≤ 30 nmol/l, and secondary hyperparathyroidism as a PTH above the upper tertile of the normal range (50 ng/ml), in the presence of hypovitaminosis D [15].

Bone mineral density measurements

BMD of the lumbar spine (L2–L4) and proximal femur contralateral to the fracture was measured by dual energy x-ray absorptiometry (DXA) (Hologic QDR 2000, Madison, WI, USA) within 28 days of the fracture. Positioning of patients during absorptiometry and data analysis were standardised as were machine calibration and technician training. The short-term coefficient of variation within subjects, in this study, calculated from two repeated measurements with re-positioning, was 1.48% at the spine and 0.99% at the total hip.

Statistical analysis

Descriptive baseline characteristics (proportions, means and ranges) were determined, and a comparison made between those with and without full data. Changes in biochemical measurements and BMD were corrected for initial baseline imbalances by general linear modelling regression analysis using SPSS software. *Post hoc* pairwise differences between randomisation groups were explored without correction for multiple comparisons, as in the context type II statistical error was as likely a potential problem as type I error. Proportions were compared with a chi-squared test, and relative risks for deaths, falls and fractures calculated using Epi-info software. Fisher's exact test was used when numbers were too small for the chi-squared test.

Analyses were repeated separately for the sub-group with 'functional hypoparathyroidism' (patients with 25OHD < 30 nmol/l, but without secondary hyperparathyroidism) [8]; those who were vitamin D replete at baseline; and those with PTH levels above the upper tertile of the normal range.

Results

Patient characteristics (Table 1)

Mean age of the subjects was 81.2 years (range 67–92 years). Mean body mass index (BMI) was 24.2 (SD 2.9) kg/m^2. Ten per cent of subjects had a BMI below the lower end of the normal range (19–26 kg/m^2). Eighty-seven per cent of patients were living in a house or bungalow prior to fracture and 13% in warden-assisted accommodation. All subjects were independent in basic ADL prior to their fracture. Sixty-four per cent were independently mobile without the use of any walking aids, 29% used one stick and 7% used two sticks. Abbreviated mental test score was 10 (out of 10) in 83%, 9 in 12% and 7 or 8 in the rest.

Participants in the four randomisation groups were well-matched for age, smoking history, estimated dietary calcium intake, and alcohol consumption. More subjects in the two injected vitamin D groups had intracapsular fracture than in the other two groups. The no treatment group had more subjects with no previous fracture. The groups were well-matched for mean baseline serum calcium, PTH and vitamin D, but the injected vitamin D alone group had a higher proportion of subjects with hypovitaminosis D. Baseline BMD was well-matched across groups (Table 2).

Of the 150 patients recruited into the study, 28 did not want to undergo initial BMD assessment. After a year, 29 patients had died (23%), and 21 withdrew from follow-up (some with partial data), mostly because of difficulty in attending the clinic. There were no cases of hypercalcaemia, and no participants were withdrawn because of adverse effects of study medication. One-hundred and three patients had complete biochemical data, 97 completed BMD data, and 87 both. Participants with complete data had slightly better dietary calcium intake, better pre-fracture mobility, lower mean PTH and marginally higher mean vitamin D levels, but were otherwise similar to those with some missing data (Table 1).

Mortality varied between 14% to 31% across the groups (chi-squared = 8, 3 df, $P = 0.04$). Amongst the groups receiving vitamin D 27% died, compared with 14% in the group receiving no treatment (relative risk 2.0; 95% CI 0.8–4.7, $P = 0.11$). Rate of falling was 18% in the vitamin D groups, compared with 37% in the placebo group (relative risk 0.48; 95% CI 0.3–0.9, $P = 0.02$), and the risk of fracturing was 7% compared with 14% (relative risk 0.50, 95% CI 0.2–1.5, $P = 0.30$), in favour of the vitamin D groups. Numbers were too small to distinguish further between the different vitamin D groups.

After one year of follow up mean 25OHD was much higher and PTH levels lower in the supplemented groups compared with no treatment. Twenty per cent of the injected vitamin D groups were deficient in 25OHD at one year, compared with 63% in the placebo group (which was unchanged from baseline). Participants in the oral combination vitamin D and calcium group had the highest 25OHD and lowest PTH, followed by the injected vitamin D plus oral calcium group, and the injected vitamin D group alone, which in turn was more favourable than the no treatment group. In *post hoc* comparisons, all the supplemented groups were statistically significantly different from placebo, as was the combined oral supplementation group compared with the injected vitamin D alone group (Table 3).

The biochemical changes were paralleled by small differences in BMD (statistically adjusted for differences at baseline) at the hip but not the spine. These were statistically significant for the neck of femur and total hip measurements, in favour of the vitamin D groups over the no treatment group. The size of differences between supplemented and no treatment groups was 1.1–3.3% at the neck of femur, 2.5–4.6% at the trochanter and 2.1–4.6% for the total hip. *Post hoc* comparisons for the total hip measurement showed all vitamin D supplemented groups to be statistically significantly different from no treatment, as was combined oral supplementation from injected vitamin D alone (Table 3).

Results were considered separately for the subgroup of patients with 'functional hypoparathyroidism' (baseline 25OHD < 30 nmol/l and PTH < 50 ng/ml; Table 3) [8]. Due to low numbers, all the vitamin D groups were combined. At baseline, the supplemented group had slightly higher BMD than the no treatment group, but otherwise they were well matched. After 12 months, mean 25OHD

Table 1. Characteristics of participants at baseline

	Treatment allocation group				Missing data analysis		
Variables	Injected vit D	Injected vit D + oral Ca	Oral vit D + Ca	Control	Data complete	Any data missing	Total
n	38	36	39	37	87	63	150
Mean age/years (range)	80 (67–91)	81 (67–92)	83 (67–92)	81 (73–92)	81 (67–92)	82 (69–92)	81 (67–92)
Initial fracture (%)							
Intracapsular	30 (79%)	28 (78%)	21 (54%)	22 (59%)	57 (66%)	44 (70%)	101 (67%)
Extracapsular	8 (21%)	8 (22%)	18 (46%)	15 (41%)	30 (34%)	19 (30%)	49 (33%)
Previous fracture (%)							
None	22 (58%)	18 (51%)	19 (50%)	28 (76%)	52 (60%)	37 (59%)	87 (58%)
Single	12 (32%)	11 (31%)	12 (32%)	6 (16%)	20 (23%)	19 (30%)	40 (27%)
Multiple	4 (11%)	6 (17%)	7 (18%)	3 (8%)	14 (16%)	6 (10%)	19 (13%)
Pre-fracture mobility (%)							
No aid	28 (74%)	19 (53%)	24 (62%)	25 (69%)	63 (72%)	33 (53%)	96 (64%)
1 stick	10 (26%)	15 (42%)	11 (28%)	7 (19%)	20 (23%)	23 (37%)	43 (29%)
2 sticks	0	2 (6%)	4 (10%)	4 (11%)	4 (5%)	6 (10%)	11 (7%)
Bio-chemistry; mean (range) $n = 150$							
Serum calcium (mmol/l)	2.38 (2.0–2.6)	2.37 (2.0–2.6)	2.35 (2.0–2.6)	2.39 (2.0–2.6)	2.38 (2.0–2.6)	2.34 (2.0–2.6)	2.36 (2.0–2.6)
PTH (ng/ml)	47 (16–140)	48 (60–135)	48 (11–125)	49 (12–128)	41 (11–122)	59 (6–140)	48 (6–140)
25 (OH) vit D (nmol/l)	28 (10–67)	30 (12–85)	29 (6–75)	30 (12–64)	31 (6–85)	27 (12–75)	29 (6–85)
Hypo vit D (%)	31 (82%)	26 (72%)	26 (67%)	22 (60%)	57 (66%)	48 (76%)	105 (70%)
Bone mineral density (g/cm^2); mean (range) $n = 122$							
Spine	0.861 (0.62–1.12)	0.861 (0.66–1.16)	0.863 (0.61–1.10)	0.847 (0.62–1.18)	0.856 (0.61–1.16)	0.865 (0.69–1.18)	0.858 (0.61–1.18)
Neck of femur	0.568 (0.44–0.70)	0.570 (0.43–0.78)	0.574 (0.41–0.79)	0.555 (0.48–0.67)	0.568 (0.41–0.79)	0.540 (0.43–0.68)	0.560 (0.41–0.79)
Trochanter	0.514 (0.37–0.71)	0.492 (0.37–0.68)	0.486 (0.31–0.70)	0.496 (0.37–0.66)	0.502 (0.35–0.70)	0.486 (0.31–0.71)	0.498 (0.31–0.71)
Total hip	0.654 (0.48–0.84)	0.658 (0.46–0.82)	0.621 (0.46–0.88)	0.643 (0.51–0.77)	0.649 (0.46–0.88)	0.630 (0.50–0.77)	0.644 (0.46–0.88)

Table 2. Outcomes compared between the different supplementation groups

	Injected vit D	Injected vit D + oral Ca	Oral vit D + Ca	Control	F (3 df)	P
Biochemical outcomes						
n	25	20	26	32	–	–
Mean serum calcium	2.46	2.45	2.42	2.40	3.5	0.02
Mean serum PTH	45	41	40	56	4.8	0.003
Mean 25(OH) D	40	44	50	27	19.2	<0.0005
Hypovitaminosis D (%)	5 (20%)	4 (20%)	2 (8%)	20 (63%)	$\chi^2 = 24$	0.00002
Bone mineral density outcomes						
n	28	21	26	22	–	–
Mean spine BMD	0.852	0.860	0.862	0.850	1.3	0.3
Mean neck of femur BMD	0.556	0.560	0.568	0.550	3.4	0.02
Mean trochanter BMD	0.495	0.505	0.495	0.483	3.2	0.3
Mean total hip BMD	0.640	0.647	0.656	0.627	11.7	<0.0005
Vital status						
Died/*n* with status known (%)	7/32 (22%)	11/25 (31%)	6/31 (19%)	5/36 (14%)	$\chi^2 = 8$	0.04
Falls						
No	28 (93%)	19 (83%)	22 (84%)	22 (65%)	$\chi^2 = 8$	0.04
Yes, no fracture	2 (7%)	3 (8%)	4 (8%)	8 (22%)		
Yes, new fracture	0	3 (8%)	3 (8%)	5 (14%)		
Mobility at 3 months						
No aid	4 (11%)	4 (12%)	7 (19%)	8 (24%)	$\chi^2 = 12$	0.006
1 stick	19 (54%)	6 (18%)	9 (25%)	14 (41%)		
2 sticks	7 (20%)	14 (41%)	11 (31%)	6 (18%)		
Crutches	0	2 (6%)	0	0		
Frame	5 (14%)	8 (24%)	9 (25%)	6 (18%)		

Units as Table 1.

had doubled in the supplemented group, but was unchanged in the no treatment group. Twenty-six per cent in the supplemented groups had hypovitaminosis D (25OHD ≤ 30 nmol/l) compared with 67% in the no treatment group. Mean PTH increased slightly in both groups, and at the end of the study there was no difference between them. BMD changes were similar to those for the study population as a whole. Neck of femur BMD was 2.7% greater in the treated groups, trochanter BMD 3.2% greater, and total hip 3.5% greater. The latter two reached statistical significance, and the former nearly so. Relative risk of falling in the supplemented groups was 0.31 (95% CI 0.08–1.14, $P = 0.11$) compared with the no treatment group. There were 3 fractures, 2 (5%) in the supplemented group, and one (11%) in the no treatment group.

Results were also similar for sub-groups which were vitamin D replete, or who had PTH above the upper tertile of the normal range.

Table 3. Estimated mean differences (and 95% confidence intervals) between randomisation groups, adjusted for baseline values. Positive values indicate that the comparator, *in italics*, is smaller. 95% confidence intervals are not adjusted for multiple comparisons.

	Injected vit D	Injected vit D + oral Ca	Oral vit D + Ca
Compared with control			
Mean serum PTH	−11 (−1; −20)	−15 (−5; −24)	−16 (−7; −25)
Mean 25(OH) D	13 (7; 20)	18 (11; 25)	23 (17; 30)
Mean neck of femur BMD	0.006 (−0.006; 0.018)	0.010 (−0.003; 0.023)	0.019 (0.007; 0.031)
Mean trochanter BMD	0.012 (−0.015; 0.025)	0.022 (0.007; 0.036)	0.012 (−0.013; 0.026)
Mean total hip BMD	0.013 (0.003; 0.023)	0.020 (0.010; 0.031)	0.029 (0.019; 0.039)
Compared with injected vitamin D alone			
Mean serum PTH	–	−4 (−14; 7)	−5 (−15; 5)
Mean 25(OH) D	–	4 (−3; 12)	10 (3; 17)
Mean neck of femur BMD	–	0.004 (−0.008; 0.016)	0.012 (0.001; 0.024)
Mean trochanter BMD	–	0.010 (−0.003; 0.024)	0 (−0.012; 0.013)
Mean total hip BMD	–	0.007 (−0.003; 0.017)	0.016 (0.007; 0.026)
Compared with injected vitamin D plus oral calcium			
Mean serum PTH	–	–	−1 (−11; 9)
Mean 25(OH) D	–	–	6 (−2; 12)
Mean neck of femur BMD	–	–	0.009 (−0.004; 0.021)
Mean trochanter BMD	–	–	−0.010 (−0.023; 0.004)
Mean total hip BMD	–	–	0.009 (−0.001; 0.019)

Units as Table 1.

Table 4. Outcomes in the 'functional hypoparathyroid' sub-group

	Vitamin D (all groups)	Control	*F* (1 df)	*P*
Baseline				
n	31	9	–	–
Mean age (range)	83 (71–92)	81 (79–83)	–	–
Mean serum calcium	2.34	2.37	–	–
Mean serum PTH (range)	34 (11–50)	33 (18–46)	–	–
Mean serum 25 (OH)D (range)	21 (6–29)	23 (14–28)	–	–
Mean spine BMD	0.884	0.808	–	–
Mean neck of femur BMD	0.576	0.555	–	–
Mean trochanter BMD	0.519	0.507	–	–
Mean total hip BMD	0.665	0.636	–	–
Outcomes				
Mean serum calcium*	2.42	2.37	2.8	0.11
Mean serum PTH*	41	41	0.1	0.94
Mean serum 25(OH)D*	37	26	9.5	0.004
Hypovitaminosis D (%)	8 (26%)	6 (67%)	Fisher exact	0.04
Spine BMD*	0.870	0.874	0.1	0.73
Mean neck of femur BMD*	0.565	0.550	3.6	0.07
Mean trochanter BMD*	0.512	0.496	5.9	0.02
Mean total hip BMD*	0.655	0.633	8.8	0.005
Falls	4 (10%)	3 (33%)	Fisher exact	0.11
Fractures	2 (5%)	1 (11%)	Fisher exact	0.47

*Corrected for initial differences.
Units as Table 1.

Discussion

Our initial intention was to investigate the effect of different calcium and vitamin D supplementation regimens on the 'intermediate outcomes' of markers of calcium homeostasis, BMD and falls. We succeeded in demonstrating that calcium and vitamin D has a measurable and beneficial effect on bone after one year of treatment following a hip fracture. More surprisingly, and more perhaps importantly, we demonstrated that the rate of falling is halved by vitamin D supplementation, confirming other recent evidence [16–20]. The most important outcome, fracture risk, is a function of the risk of falling, and the force applied to the bone during the fall, as well as bone density and architecture. Our numbers were insufficient to be certain, but we also observed a halving of fracture risk.

We may have under-ascertained falls and fractures as we did not use diaries or scrutinize case notes. This should not have biased the study as the same methods were used for all treatment groups, but may have reduced the statistical power to show real differences. The study was not blinded, and no placebos were used, for practical reasons – we were not funded to do so. This might have introduced bias. However, most of our outcomes were objective biochemical or BMD measurements, and a reduction in falls with vitamin D treatment was not anticipated at the study outset, both of which make bias less likely.

An unresolved question is whether maximal bone effects can be achieved with vitamin D alone, or if calcium supplementation is also required. We found that oral calcium and vitamin D was more effective than injected vitamin D alone. The effect of injected vitamin D plus oral calcium was intermediate between these two, and not statistically significant from either (even using liberal statistical assumptions). About a quarter of patients given injected vitamin D were overtly deficient a year later, suggesting that the injected supplement had not lasted until the time of re-testing, which complicates interpretation of this finding. Moreover, some evidence suggests that cholecalciferol (vitamin D_3) is metabolised to 25-OHD more efficiently than ergocalciferol (vitamin D_2), which would also favour the combined oral preparation [21]. Our data are consistent with both a requirement for additional calcium, and the sufficiency of vitamin D alone. A larger trial is required.

Our observations on the baseline data from this population showed that some elderly people fail to mount a secondary hyperparathyroid response to hypovitaminosis D – a group we termed to have 'functional hypoparathyroidism' [8]. This suggested a secondary hypothesis – that patients with functional hypoparathyroidism would not benefit from supplementation with unhydroxylated vitamin D, and might instead require more activated forms of vitamin D, such as calcitriol. The reasoning was, firstly, that there is no secondary hyperparathyroidism to suppress, and therefore no increase in bone demineralisation to inhibit. Secondly, 1-hydroxylation of 25-OHD to active 1,25 $(OH)_2$ D would be impaired, as this process is PTH-dependent. In the event, the results for the functional hypoparathyroid group were remarkably similar to those for the study population as a whole. Mean PTH remained similar between vitamin D supplemented and placebo groups, suggesting that the entity of functional hypoparathyroidism does exist. Mean PTH increased in both supplemented and no treatment groups, presumably due to regression to the mean. BMD increased to approximately the same extent in each group, and falls risk was about halved (although, with small numbers this was statistically uncertain). Unfortunately we were unable to measure 1,25 $(OH)_2$ D, or other bone turnover markers, as intermediate outcomes, for funding reasons, and so could not directly confirm the concern about lack of activation of 25-OHD in functional hypoparathyroidism. Participants who were vitamin D replete (on conventional criteria [15]) at baseline also benefited from supplementation, with their PTH levels being suppressed further, and their BMD increasing.

We were surprised at the difficulty we had in both recruiting and retaining trial participants, in particular the vehemence with which some families objected to the inclusion of an elderly relative (who had capacity to give their own consent, and who had freely done so). The group we studied are at high medical risk, and stand to gain much from effective intervention. This issue deserves further study, and requires imaginative solutions to be found.

The high prevalence of hypovitaminosis D in hip fracture patients justifies routine supplementation, having first excluded co-incidental hypercalcaemia from another aetiology. If biochemical confirmation is required, vitamin D should be measured rather than relying on detecting

secondary hyperparathyroidism alone. The differences in BMD between supplemented and control groups were relatively small (albeit over only 1 year of follow-up). Additional bone protection, such as with bisphosphonates, may also be justified. Moreover, since increased mineralisation with bisphosphonates is uncertain in the presence of vitamin D insufficiency, vitamin D supplementation would be wise in any case [22, 23]. Our results suggest that the mechanism of action of vitamin D may be independent of PTH (since changes were also seen in patients without raised PTH levels). A mechanism of action for vitamin D, with or without additional calcium, to reduce falls may be important. This might be effective over a shorter time frame than bone mineral changes.

Key points

- Seventy per cent of elderly women after hip fracture have hypovitaminosis D.
- Vitamin D supplementation by annual injection or oral tablets increases 25-hydroxyvitamin D levels, suppresses parathyroid hormone, increases bone mineral density and reduces falls over the following year.
- It remains uncertain whether adding calcium produces benefits over vitamin D supplementation alone.
- Recruitment and retention of this frail group into a trial was difficult.

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