Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D_3) for prevention of fractures in primary care

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Abstract

Objective To assess whether supplementation with calcium and cholecaliferol (vitamin D_3) reduces the risk of fracture in women with one or more risk factors for fracture of the hip.
Design Pragmatic open randomised controlled trial.
Setting Practice nurse led clinics in primary care.
Participants 3314 women aged 70 and over with one or more risk factors for hip fracture: any previous fracture, low body weight (<58 kg), smoker, family history of hip fracture, or fair or poor self reported health.
Intervention Daily oral supplementation using 1000 mg calcium with 800 IU cholecaliferol and information leaflet on dietary calcium intake and prevention of falls, or leaflet only (control group).
Main outcome measures Primary outcome measure was all clinical fractures and secondary outcome measures were adherence to treatment, falls, and quality of life (measured with the SF-12).
Results 69% of the women who completed the follow-up questionnaire at 24 months were still taking supplements (55% with inclusion of randomised participants known to be alive). After a median follow-up of 25 months (range 18 to 42 months), clinical fracture rates were lower than expected in both groups but did not significantly differ for all clinical fractures (odds ratio for fracture in supplemented group 1.01, 95% confidence interval 0.71 to 1.43). The odds ratio for hip fracture was 0.75 (0.31 to 1.78). The odds of a woman having a fall at six and 12 months was 0.99 and 0.98, respectively. Quality of life did not significantly differ between the groups.
Conclusion We found no evidence that calcium and vitamin D supplementation reduces the risk of clinical fractures in women with one or more risk factors for hip fracture.
Registration ISRCTN26118436, controlled trials registry.

Introduction

Low trauma fractures represent a major burden of illness and cost to society.[1–3] This burden is likely to increase with ageing populations and because the age specific incidence of hip fracture seems to be increasing.[4] Effective strategies are needed in a community setting to prevent the continuing rise in hip and other fractures and to reduce the associated excess morbidity and cost.

One relatively inexpensive method of reducing fracture rates might be supplementation with calcium and vitamin D. A randomised trial among female residents of French nursing homes showed significant reductions in both hip and non-hip fractures among those assigned supplementation with calcium and cholecaliferol (vitamin D_3),[5] and a study among community dwelling American men and women also noted a reduction in non-vertebral fractures in women receiving supplementation.[6] More recently another study among women in French nursing homes noted a large but statistically non-significant reduction in hip, but not non-hip, fractures among those assigned calcium and vitamin D supplementation.[7] The only trial that had fracture as the main end point was the original French nursing home study. It remains unknown whether these results can be generalised to populations outside of institutional care settings in France. Supplementation with calcium and vitamin D might be expected to prevent fractures not only through reductions in bone loss but by reducing falls. A recent systematic review found that vitamin D supplementation can reduce falls and falling by 22%.[8]

We assessed whether giving calcium and vitamin D supplements to community dwelling older women at increased risk of hip fracture would reduce their risk of any fracture.

Participants and methods

We identified women aged 70 and over who had at least one self reported risk factor for hip fracture: low bodyweight (<58 kg), any previous fracture, maternal history of hip fracture, smoker, and poor or fair health. These risk factors were taken from a large population study in the United States[9]: we subsequently confirmed in a British cohort study that, apart from smoking, these risk factors predict the risk of hip and non-hip fractures.[10] We assessed self reported calcium consumption through a brief 10 item questionnaire that was sent to the women along with questions on risk factors for fracture.

Women were excluded from the study if they could not give written consent or were receiving any calcium supplementation of more than 500 mg a day. We also excluded women with a history of kidney or bladder stones, renal failure, or hypercalcaemia.

Details of previous trials are on bmj.com

Recruitment and randomisation

After a pilot study in the York area in September 1999, we began recruitment for the main trial in September 2001. We asked general practices across England to post information about the study, a consent form, and a questionnaire on risk factors for fracture to all women aged 70 and over. Women with cognitive impairment or a life expectancy of less than six months were to be excluded. Eligible women were asked to return the completed questionnaire to the relevant trial coordinating centres (Hertfordshire, Newcastle, or York).

Eligible women were randomised (stratified by practice) by computer at the York Trials Unit by an independent person with no knowledge of the participants' characteristics. We initially randomised in favour of the control group in a 2:1 ratio as this was hypothesised to be the most efficient allocation ratio given the study resources.[11] We included research related costs (for example, extra staff), not the costs of the supplements, in the estimation only. Although a 2:1 ratio in favour of one arm may be considered extreme, the effect is minimal in terms of statistical power—for example, for a fixed sample size the power would be reduced from 80% to 75%. We increased our sample size to compensate for this reduction. A reanalysis of the trial's cost profile once recruitment had started showed that the optimum allocation ratio was 3:2. Towards the end of the study we therefore changed the allocation to 1:1.

Intervention and control groups

Before supplementation was started we sought written confirmation from the doctors that the participants had no known contraindications. Participants were also invited to see a nurse at their practice, who discussed the study and also checked for contraindications. Women who after randomisation were identified as having contraindications to calcium and vitamin D supplements were excluded from supplementation but were retained for follow-up and analysis on an intention to treat basis. The nurses gave participants general lifestyle advice on how to reduce their risk of fracture and six months supply of 1000 mg of calcium (calcium carbonate) and 800 IU of cholecalciferol (vitamin D_3) as two tablets daily (Calcichew D_3 Forte; Shire, Hampshire). Participants were recalled to see the practice nurse after six months and given a further supply of supplements if they wanted to continue with the study.

The control group were sent a leaflet with general advice on prevention of falls and on how to consume adequate calcium and vitamin D from dietary sources. The intervention group also received this leaflet.

Outcomes

The main outcome was fracture, excluding those of the digits, rib, face, and skull. Secondary outcomes included hip fracture; quality of life—as measured by the 12 item short form health survey questionnaire (SF-12)[12] and the European quality of life instrument (EuroQol); death; visits to the doctor and hospital admissions; falls and fear of falling. Falls were self reported over the previous six months, and fear of falling was measured on a simple six point Likert scale.

Outcome data were mainly collected from questionnaires posted to participants every six months. Doctors were asked to confirm fractures in those women who reported a fracture in the previous six months. Information on fractures was also collected from the doctors of non-responders to the final questionnaire. For the principal analysis we included only confirmed fractures. Adherence was measured through self report every six months. We chose to report quality of life data at six and 12 months because of the reduction in follow-up rates with time for the quality of life questionnaires.

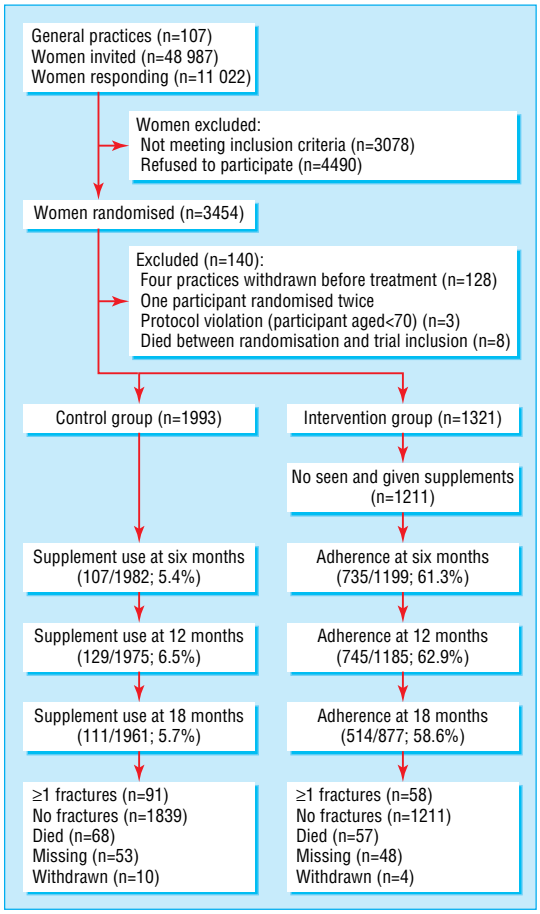

Fig 1 Flow of participants through trial. Adherence was estimated by subtracting those known to have died. Those who failed to return questionnaires were assumed not to be taking treatment

Sample size and statistical analysis

From previous work, and given a median follow-up period of 24 months, we presumed an all fracture rate of 10% among untreated participants.[13] When two studies on calcium and vitamin D were combined in a random effects meta-analysis, the pooled reduction of fracture was 34%.[5 6] We determined that to observe such a reduction in our population with 80% power ($P = 0.05$; two tailed) we would require 2855 participants to be allocated in a 2:1 ratio, allowing for a 20% dropout rate.

All participants were included in the analysis on an intention to treat basis. For our main analysis we used survival analysis to compare time to first fracture between the groups. We also undertook a logistic regression analysis adjusting for practice. We undertook subgroup analyses to compare rates for hip and wrist fracture between the two groups and secondary analyses with all reported fractures whether or not these had been confirmed. If a woman had more than one fracture we included only the first fracture in the analysis. We adjusted for practice because we changed the allocation ratio during the trial. In our unadjusted analysis we present the incidence of fracture by equally or unequally allocated groups as in any meta-analysis these need to be entered as two separate studies.

Pilot study

Between December 2000 and August 2001 we undertook a pilot trial at the York Centre to estimate recruitment rates. The 117

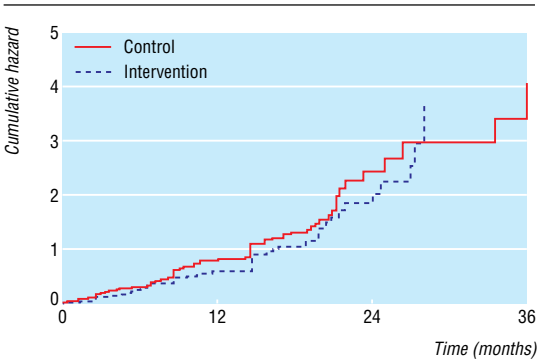

Fig 2 Time to first fracture in women allocated calcium and vitamin D supplementation or only advice on diet and prevention of falls

participants recruited in this pilot are included in the main trial report.

Results

Between September 2001 and November 2002 we recruited 3197 women in addition to the 117 participants recruited during the pilot trial (3314 in total). The recruitment rate of 7% instead of the presumed 5% allowed us to exceed our planned sample size by 16%.

Overall, 48 987 women registered with 107 general practices were invited to take part in our trial (fig 1). Of the 11 022 women who returned the questionnaire, 3078 were ineligible and 4490 did not want to take part, leaving 3454 women (7.0% of those originally invited). Table 1 shows the baseline characteristics of the participants. The intervention and contol groups were well balanced across all important predictors of fracture.

Over a median follow-up of 25 months, 149 confirmed fractures were reported, lower than anticipated. Time to fracture did not differ between the groups (fig 2) and we found no evidence of a benefit of supplementation in the prevention of fractures (table 2). When we took into account all reported fractures (including those not confirmed by a doctor) the results were not changed (adjusted odds ratio 1.60, 95% confidence interval 0.75 to 3.40).

We also examined the risk of falls, falling, and quality of life. We found no evidence of an effect on falls. After adjusting for practice, the odds ratio of a woman having a fall at six months was 0.99 (0.81 to 1.20). At 12 months we found no evidence that supplementation reduced falling (0.98, 0.79 to 1.20). We also found no differences in quality of life (table 3).

Adherence

Rates for adherence at 12 months were about 63% when we included all women randomised but excluded those who had died. We compared women taking supplements with those in the control group to determine whether women who adhered to treatment might have had a reduced fracture rate. We found no evidence of any benefit (1.03, 0.68 to 1.56).

Discussion

We found no evidence that supplementation with calcium and cholecalciferol (vitamin D_3) affects fracture rates over two years in

Table 1 Baseline characteristics of women receiving calcium and cholecalciferol (vitamin D_3) supplementation (intervention group) or only advice on diet or prevention of falls to prevent fractures. Values are percentages (numbers) unless stated otherwise

Variable	Intervention group (n=1321)	Control group (n=1993)
Mean (SD) age	77.0 (5.10)	76.7 (5.02)
Mean (SD) weight (kg)	64.9 (12.07)	64.9 (11.93)
Bodyweight <58 kg	32.7 (417/1277)	32.8 (629/1918)
Previous fracture (any)	58.7 (776/1321)	58.3 (1161/1990)
No fracture 10 years before randomisation	80.6 (1064/1321)	80.2 (1599/1993)
Smoker	8.6 (101/1171)	7.4 (127/1717)
Self reported poor or fair health	38.9 (510/1311)	37.1 (737/1986)
Maternal hip fracture	16.8 (222/1320)	16.1 (320/1991)
Fall in previous 12 months	33.7 (445/1320)	34.2 (681/1993)
Mean (SD) SF-12 scores*:		
Mental health component	51.42 (9.75)	51.16 (9.66)
Physical component	40.14 (11.96)	40.29 (12.18)
EuroQol	0.700 (0.251)	0.694 (0.254)
Mean estimated dietary calcium intake (mg/d)†	1075 (338)	1084 (346)

*High scores denote good mental and physical health.
†Self reported.

Table 2 Odds of fracture in women receiving calcium and cholecalciferol (vitamin D_3) supplementation (intervention group) and those receiving only advice on diet and prevention of falls. Values are percentages (numbers) unless stated otherwise

Confirmed fractures	Intervention group (n=1321)	Control group (n=1993)	Adjusted odds ratio (95% CI)*	P value
All fractures:				
Unequally allocated group†	4.8 (34/714)	5.0 (69/1391)	1.01 (0.71 to 1.43)	0.97
Equally allocated group	4.0 (24/607)	3.7 (22/602)		
Hip fractures:				
Unequally allocated group	0.4 (3/714)	1.1 (15/1391)	0.75 (0.31 to 1.78)	0.51
Equally allocated group	0.8 (5/607)	0.3 (2/602)		
Hip and wrist fractures:				
Unequally allocated group	2.4 (17/714)	3.2 (44/1391)	0.89 (0.56 to 1.44)	0.64
Equally allocated group	2.0 (12/607)	1.5 (9/602)		

*Adjusted for practice.
†Two women randomised to control group for every one allocated to treatment group.

women aged 70 or over with one or more risk factors for fracture of the hip.

Combined calcium and cholecaliferol

Five trials have been published on combined calcium and vitamin D (see bmj.com). Two were in French nursing homes.[5 7] Our population was recruited from the community. A community study in Denmark showed a modest (16%), statistically significant, reduction in fractures.[14] This study was a 2×2 factorial trial, however, which did not take clustering into account in the analysis despite the participants being randomised by cluster. With only one cluster in each cell, this resulted in two clusters receiving calcium and vitamin D and cluster replication may have been insufficient to control for confounding at the level of the cluster.[15] Another community based trial in the United States studied bone density and although it showed a significant benefit on fractures, this study was relatively small.[6] The latest calcium and vitamin D study to be published is the Medical Research Council RECORD trial,[16] which is a secondary prevention study in hospital based fracture clinics in the United Kingdom. This study essentially showed the same findings as our trial, that there was no evidence of a benefit from calcium or vitamin D supplementation either alone or in combination in preventing fractures.

Our study differs from the two French studies,[5 7] which showed a large benefit from supplementation on hip fractures, in that our population was generally more healthy and living independently in the community. People living in sheltered accommodation or nursing homes may be at more risk of a low calcium and vitamin D intake and at higher risk of fracture. Also because our study was undertaken among women living independently in the community who could give consent, our results do not apply to men, those in residential care, or those with dementia. Patients in residential care or with dementia are of particular interest clinically because they have a higher risk of fracture.

Vitamin D alone

Four large randomised studies looked at vitamin D supplementation (see bmj.com). Lips et al observed a non-significant increase in the hazard of hip fractures in 2578 older Dutch men and women in primary care receiving a daily dose of 400 IU vitamin D.[17] A more recent primary care trial of an annual injection of 300 000 IU of vitamin D among 9440 men and women from southern England reported a small non-significant increase in all fractures with a large, borderline statistically significant increase in hip fractures.[18] In contrast, a trial of high dose oral vitamin D (100 000 units) every four months among 2686 mainly retired male doctors showed a borderline statistically significant 22% reduction in all osteoporotic fractures.[19] The RECORD trial also studied vitamin D alone and found no evidence of benefit in preventing fractures (see bmj.com). Our study differed from these four in that we included only women and selected them on the basis of risk factors for fracture, whereas these studies included men and may have sampled a population at lower risk. Nevertheless, putting our study into the context of these four large trials, with only one showing a significant benefit, suggests that overall vitamin D supplementation among a general primary care population may not be an effective intervention for reducing fractures. A recent Norwegian study, using a quasirandom method of allocation (alternation) of vitamin D supplements in cod liver oil among 1144 nursing home residents, found a slight, non-significant increase in hip fractures and a slight, non-significant decrease in all fractures (relative risk 1.09, 95% confidence interval 0.73 to 1.63 and 0.92, 0.66 to 1.27, respectively).[20]

Falls

We found no evidence that vitamin D supplementation reduced the incidence of falls, as previously hypothesised.[8]

Strengths and weaknesses of the study

Our study was large and targeted women at high risk of fracture. We chose to use a pragmatic design, which allows our results to be generalised to a usual care setting. We did not, however, use a placebo preparation in the control group and this could have biased the results in several ways. Firstly, dilution effects could have occurred if significant numbers of control participants had started calcium and vitamin D. This was not a problem, however, as by 18 months this applied to fewer than 6% of the participants, with about 3% being prescribed supplementation by their doctor. Secondly, differential reporting of fracture

Table 3 Secondary outcomes in women receiving calcium and cholecalciferol (vitamin D_3) supplementation (intervention group) and those receiving only advice on diet and prevention of falls. Values are percentages (numbers) unless stated otherwise

Secondary outcome measures	Intervention group (n=1321)	Control group (n=1993)	Adjusted odds ratio* (95% CI)	Adjusted mean difference* (95% CI)	P value
Deaths:					
Unequally allocated group†	3.8 (27/714)	3.7 (51/1391)	1.26 (0.87 to 1.83)	—	0.22
Equally allocated group	4.9 (30/607)	2.8 (17/602)			
≥1 hospital admissions in first 12 months:					
Unequally allocated group	41.7 (220/528)	42.8 (481/1124)	0.86 (0.72 to 1.03)	—	0.10
Equally allocated group	38.2 (126/330)	46.7 (189/405)			
≥1 visits to doctor in first 12 months:					
Unequally allocated group	80.4 (430/535)	80.5 (917/1139)	0.84 (0.67 to 1.04)	—	0.11
Equally allocated group	76.5 (251/328)	82.8 (346/418)			
SF-12 (SD) scores at 12 months					
Physical component:					
Unequally allocated group	41.66 (11.74)	41.20 (11.92)	—	–0.152 (–0.10 to 0.7)	—
Equally allocated group	41.33 (11.38)	39.68 (12.05)			
Mental health component:					
Unequally allocated group	52.02 (9.17)	51.87 (9.23)	—	0.03 (–0.04 to 0.97)	—
Equally allocated group	51.73 (9.23)	50.77 (10.00)			

*Adjusted for practice and age.
†Two women randomised to control group for every one allocated to treatment group.

What is already known on this topic

Calcium and vitamin D supplements have been shown to reduce hip fractures among older women living in French nursing homes

No randomised trials have been carried out of supplements among high risk women living in the community in the United Kingdom

What this study adds

No evidence was found that calcium and vitamin D supplementation reduces the risk of fractures among community dwelling older women

outcomes could have occurred. We therefore confirmed all fractures with the participants' doctors and we ascertained fracture status from the doctors of non-responders to the questionnaires. Self reports of fracture have been shown to be reliable.[21] Therefore, lack of a placebo control was not, in our view, a problem.

Fewer fractures occurred than we anticipated in our population, thus reducing the power of our study to observe modest differences between groups. This was, however, offset to some degree by us exceeding our planned sample size. Furthermore, a trial published subsequent to the start of our study noted little effect of supplementation on all fractures[7] (our main end point). Including this result in a meta-analysis would have reduced the difference in fracture rates we might have expected to find. Therefore, our study was underpowered so that we could not reliably exclude a reduction in all fractures of less than 30%. Furthermore, adherence rates were only a little more than 60% at 12 months. This may have attenuated any effect of treatment. As this was a pragmatic trial this will be the level of adherence seen routinely in general practice.

Although we found no evidence of a benefit on fractures in older community dwelling women given calcium and vitamin D supplementation, we cannot exclude a clinically significant benefit of supplementation owing to the relatively wide confidence intervals around our estimate of effect.

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Contributors: YB was the original trial coordinator for the pilot study and helped write guidance for the practice nurses. SC was a trial coordinator and was responsible for data entry and cleaning, combining the datasets, and undertaking part of the analysis. JD assisted with data management and analysis and undertook the quality of life data analysis. CI undertook the randomisation and advised on collection of economic data. SP was assistant trial coordinator and helped enter and clean data. JP took over as trial coordinator and was responsible for recruitment to the main trial at the York centre and liaising with collaborating centres, she also undertook and supervised data entry and data management and helped draft practice nurse guidance. DJT, principal investigator, drafted the trial protocol, helped obtain funding for the main study, undertook some of the analysis, and wrote the first draft of the report. He is guarantor for the paper. IW helped draft the trial protocol, advised on primary care and clinical issues, and contributed to successive drafts of the main manuscript. TA helped draft the protocol and advised on clinical issues. RMF helped draft the protocol and advised on clinical issues. CK recruited, and managed data from, the doctors and participants for the main trial. AS helped draft the protocol and write practice nurse guidance. ES recruited doctors and participants for the main trial, managed data from participants, and helped write practice nurse guidance. MB helped recruit doctors, supervised the Hertfordshire centre, and provided primary care expertise. LS recruited doctors and participants and managed the resulting data. YB, SC, CI, SP, TA, RMF, AS, and MB commented on drafts of the paper.

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Competing interests: RMF has served as an adviser to, and spoken at meetings organised by, Shire and Nycomed. JP and SP have been sponsored by Shire to attend conferences. AS has spoken at meetings organised by Shire and served as nurse adviser. DJT has received funding from Shire and other pharmaceutical companies for research and sponsorship to attend conferences and meetings.

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