

Effect of four monthly oral vitamin D₃ (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial

Daksha P Trivedi, Richard Doll, Kay Tee Khaw

Abstract

Objective To determine the effect of four monthly vitamin D supplementation on the rate of fractures in men and women aged 65 years and over living in the community.

Design Randomised double blind controlled trial of 100 000 IU oral vitamin D₃ (cholecalciferol) supplementation or matching placebo every four months over five years.

Setting and participants 2686 people (2037 men and 649 women) aged 65-85 years living in the general community, recruited from the British doctors register and a general practice register in Suffolk.

Main outcome measures Fracture incidence and total mortality by cause.

Results After five years 268 men and women had incident fractures, of whom 147 had fractures in common osteoporotic sites (hip, wrist or forearm, or vertebrae). Relative risks in the vitamin D group compared with the placebo group were 0.78 (95% confidence interval 0.61 to 0.99, P=0.04) for any first fracture and 0.67 (0.48 to 0.93, P=0.02) for first hip, wrist or forearm, or vertebral fracture. 471 participants died. The relative risk for total mortality in the vitamin D group compared with the placebo group was 0.88 (0.74 to 1.06, P=0.18). Findings were consistent in men and women and in doctors and the general practice population.

Conclusion Four monthly supplementation with 100 000 IU oral vitamin D may prevent fractures without adverse effects in men and women living in the general community.

Introduction

Osteoporotic fractures are projected to increase exponentially worldwide.¹ Most fracture prevention trials have focused on clinically defined groups such as people with osteoporosis or previous fractures and have mainly been conducted in women.²⁻⁷ Safe, effective, feasible, and cost effective primary prevention measures are needed in older men and women, in whom most osteoporotic fractures occur. We report results from a randomised double blind trial of four

monthly supplementation with oral vitamin D₃ on fractures and mortality in 2686 men and women aged 65-85 years living in the community.

Methods

Study population—This trial was a pilot to assess the feasibility of a community trial (not subsequently conducted owing to lack of funding) in 20 000 men and women. We recruited men and women aged 65-85 from the British doctors study register at the Clinical Trials Studies Unit, Oxford,⁸ and the age-sex register of a general practice in Ipswich, Suffolk. We excluded people who were already taking vitamin D supplements and people with conditions that were contraindications to vitamin D supplementation—for example, a history of renal stones, sarcoidosis, or malignancy. We sent invitations to 11 120 people, and 3504 (31.5%) of them initially agreed to participate. From June 1996 to March 1997 we randomised 2686 (77.5%) people to receive either treatment with vitamin D or a placebo. Participants and investigators were blinded to the treatment until the study ended.

Study design—We conducted the study by post. Participants completed an initial questionnaire. We assessed prevalence of disease with the question “Do you have the following conditions?” followed by a checklist. We used a modified food frequency questionnaire at four years to estimate dietary calcium intake.

Intervention—We sent one capsule containing 100 000 IU vitamin D₃ (cholecalciferol) or matching placebo by post every four months for five years (15 doses in total). We asked participants to take the capsule immediately on receipt, complete a form indicating that they had done so, and return the form by Freepost.

Endpoint ascertainment—On receiving the capsule, participants filled in a checklist of events (fracture or major illness) and returned the form by Freepost. All participants were flagged at the Office for National Statistics for mortality and followed until 31 March 2002. A nosologist blind to the intervention coded death certificates by using ICD-9 (international classification of diseases, 9th revision). We ascertained incidences of fracture, cardiovascular disease, and cancer by using



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Clinical Gerontology Unit, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge CB2 2QQ

Daksha P Trivedi
research fellow

Kay Tee Khaw
professor of clinical gerontology

Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford

Richard Doll
emeritus professor

Correspondence to:
K T Khaw
kk101@medschl.cam.ac.uk

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events identified from questionnaires or death certification by cause.

Serum 25-hydroxyvitamin D, parathyroid hormone, and heel sonometry—After four years we invited 235 participants from general practice who had taken at least 10 capsules to a clinic for measurement of serum vitamin D and parathyroid hormone concentrations.

Statistical analyses—We included all participants randomised to active vitamin D or placebo in the analyses, according to intention to treat. We compared relative risks for incidence of fracture, mortality by cause, and incidence of cardiovascular disease and cancer for active vitamin D versus placebo by using crude rates and then, after adjustment for age, with the Cox regression method.⁹

Results

Characteristics of participants—Baseline descriptive data did not differ between the groups (see [bmj.com](#)). Mean calcium intake at four years was 742 mg/day and did not differ by treatment allocation.

Incidence of fracture—The table shows five year fracture rates. Participants in the vitamin D treatment group had a 22% lower rate for first fracture at any site and a 33% lower rate for a fracture occurring in the hip, wrist or forearm, or vertebrae. The differences were consistent when stratified by sex or by doctor versus general practice population. We observed differences one year into the study (fig 1).

Other health events—The vitamin D group had slightly but not significantly lower mortality from all causes, cardiovascular disease, and cancer than the placebo group (fig 2). The incidence of major health events did not differ significantly between the treatment groups (see [bmj.com](#)).

Physiological variables and compliance—The mean serum concentrations of vitamin D and parathyroid hormone and heel bone ultrasound attenuation in the subgroup are presented on [bmj.com](#). Mean vitamin D concentrations were 40% higher in the active

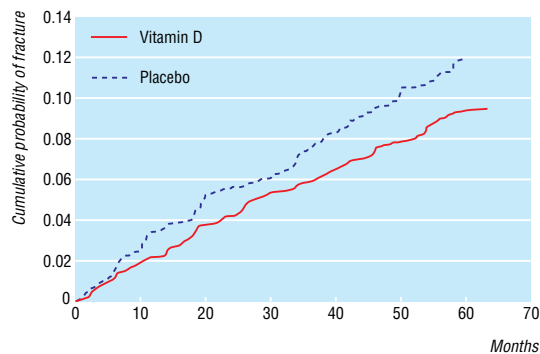


Fig 1 Cumulative probability of any first fracture according to treatment with vitamin D (n=1345) or placebo (n=1341), based on Cox regression; difference between two groups, P=0.04

treatment group than in the placebo group (p < 0.001). Mean parathyroid concentrations were 6% lower, but this difference was not significant. Heel ultrasound measures did not differ by treatment. Compliance did not differ between doctors and the general practice population or between the treatment groups; 76% (2050/2686) of participants had at least 80% compliance (12/15 doses).

Discussion

Limitations

We ascertained the incidence of fracture through self report by questionnaire. This may have led to ascertainment errors, but random errors would underestimate associations. In this randomised double blinded design, biased ascertainment between the treatment groups is unlikely. Most of the participants were doctors, which increases the likelihood of accurate ascertainment of events. Fracture rates did not differ significantly between doctors and the general practice population, indicating that people in the general community report fracture accurately, an assumption supported by several studies.^{10 11}

Comparisons with previous studies

Several studies report that daily supplementation with vitamin D and calcium reduces fractures.^{2 3} In our study the effect size of isolated vitamin D supplementation—about 20% reduction in total fractures and 30% reduc-

Incidence of fractures based on self report or mortality certification 1996-2002 and age adjusted relative risks (Cox regression), according to treatment allocation at randomisation (intention to treat) in 2686 men and women aged 65-85 years. Values are numbers (percentages) unless stated otherwise

Fractures	Vitamin D (n=1345)	Placebo (n=1341)	Age adjusted relative risk (95% CI)	P value*
All				
Any site	119 (8.8)	149 (11.1)	0.78 (0.61 to 0.99)	0.04
Hip, wrist or forearm, or vertebrae	60 (4.5)	87 (6.5)	0.67 (0.48 to 0.93)	0.02
Hip or wrist or forearm	43 (3.2)	62 (4.6)	0.67 (0.46 to 0.99)	0.04
Hip	21 (1.6)	24 (1.8)	0.85 (0.47 to 1.53)	0.59
Vertebrae	18 (1.3)	28 (2.1)	0.63 (0.35 to 1.14)	0.12
Men	(n=1019)	(n=1018)		
Any site	77 (7.6)	91 (8.9)	0.83 (0.61 to 1.13)	0.24
Hip, wrist or forearm, or vertebrae	36 (3.5)	50 (4.9)	0.70 (0.46 to 1.08)	0.11
Hip or wrist or forearm	22 (2.2)	31 (3.0)	0.70 (0.40 to 1.20)	0.19
Hip	11 (1.1)	14 (1.4)	0.76 (0.35 to 1.67)	0.49
Vertebrae	14 (1.4)	22 (2.2)	0.62 (0.32 to 1.22)	0.17
Women	(n=326)	(n=323)		
Any site	42 (12.9)	58 (18.0)	0.68 (0.46 to 1.01)	0.05
Hip, wrist or forearm, or vertebrae	24 (7.4)	37 (11.5)	0.61 (0.37 to 1.02)	0.06
Hip or wrist or forearm	21 (6.4)	31 (9.6)	0.64 (0.37 to 1.11)	0.11
Hip	10 (3.1)	10 (3.1)	0.98 (0.41 to 2.36)	0.97
Vertebrae	4 (1.2)	6 (1.9)	0.65 (0.18 to 2.30)	0.50

*P value (two sided) refers to difference between treatment groups.

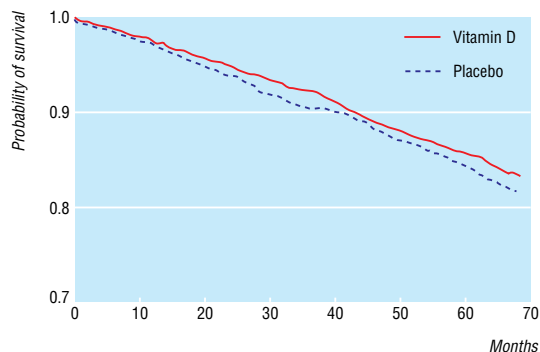


Fig 2 Cumulative survival according to treatment with vitamin D (n=1345) or placebo (n=1341), based on Cox regression; no significant difference between groups

tion in fractures at major osteoporotic sites—is comparable to that reported by Chapuy for combined daily vitamin D and calcium.²

Previous studies of isolated vitamin D supplementation have been inconclusive.^{12–14} The lack of significant reduction in fractures in these studies could be explained by a lack of power due to a lower dose of supplement, shorter duration, or lower number of events as well as ineffectiveness of vitamin D. Lips found no protective effect of vitamin D 400 IU daily in 1578 participants.¹⁵ This dose may have been too low to achieve a clinical effect. In our study the four monthly 100 000 IU dose averages a daily equivalent similar to the 800 IU vitamin D used in the trials by Chapuy and Dawson Hughes.^{2,3} Heikinheimo, using annual injections of 150 000–300 000 IU in 899 participants, reported a reduction in fractures of the upper limb but not the lower limb.¹⁴ This study was not properly randomised or blinded, and a single annual dose may not provide adequate concentrations in the blood over a whole year.

Vitamin D may protect against fractures through concentrations of parathyroid hormone. The 40% higher mean concentrations of vitamin D seen in the active treatment group in our trial, however, were still not high in absolute terms. Parathyroid hormone concentrations were only slightly and not significantly lower. This suggests that 100 000 IU vitamin D four monthly may not have lowered parathyroid hormone concentrations adequately, and a more frequent dose might be considered in future trials.

We found no significant effects of vitamin D on total mortality or incidence of cancer or cardiovascular disease, as suggested by observational studies.^{15,16} However, the fact that the relative risks were in a favourable direction in the active treatment group is reassuring.

Generalisability

To maximise generalisability, this was a pragmatic trial with minimal exclusion criteria. The doctors were similar to the general practice population in terms of compliance, fracture rates, and effects of vitamin D. Blood concentrations of vitamin D in participants taking placebo were comparable to those of population groups of similar ages in northern latitudes in the United States³ and higher than those in older European populations living in northern latitudes.^{13,17}

Public health implications

This trial was a pilot for a larger trial that was not funded and was, consequently, too small for any decisive effect on fractures to be expected. The results, nevertheless, indicate that isolated vitamin D supplementation prevents fractures. The 22% reduction in fractures in our study translates to approximately 250 people treated for one year to prevent any fracture. This is particularly important for primary prevention. Several interventions—such as bisphosphonates, oestrogen, and calcium and vitamin D—reduce fractures in high risk groups.^{2–7} Their application to primary prevention is, however, problematic as the balance of risk-benefit and cost-benefit differs in primary and secondary prevention.

Risk of fracture is related to bone health across the whole population distribution, such that most fractures do not occur in the small numbers of people with severe osteoporosis at very high risk but in the large numbers at

What is already known in this topic

Vitamin D and calcium supplements are effective in preventing fractures in elderly women

Whether isolated vitamin D supplementation prevents fractures is not clear

What this paper adds

Four monthly oral supplementation with 100 000 IU vitamin D reduces fractures in men and women aged over 65 living in the general community

Total fracture incidence was reduced by 22% and fractures in major osteoporotic sites by 33%

moderately increased risk. To have a substantial effect on total fractures in the population, intervention would be needed in large numbers of people; consequently, population-wide preventive interventions have been proposed for all elderly people.¹⁸

However, the dilemma for primary prevention is that whereas the population attributable risk is large, the absolute individual risk is still low.¹⁹ The risk-benefit balance for community based prevention differs from that for intervention in clinically defined groups. Safety, feasibility, and cost effectiveness are crucial. Side effects are less acceptable in a healthy group in which the risk of fracture is not high. This is a particular issue in men, in whom evidence on effective fracture prevention is lacking. Many interventions effective in high risk groups are not feasible in the general population owing to poor compliance or side effects or are not cost effective.²⁰ In contrast, the cost of four monthly oral 100 000 IU vitamin D is minimal (<£1 annually).

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Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses

Fujian Song, Douglas G Altman, Anne-Marie Glenny, Jonathan J Deeks

Department of Public Health and Epidemiology, University of Birmingham, Birmingham B15 2TT

Fujian Song
senior research fellow

Centre for Statistics in Medicine, Institute of Health Sciences, Oxford OX3 7LF

Douglas G Altman
professor of statistics in medicine

Jonathan J Deeks
senior medical statistician

Cochrane Oral Health Group, University Dental Hospital of Manchester, Manchester M15 6FH

Anne-Marie Glenny
lecturer in evidence based oral health care

Correspondence to: F Song
f.song@bham.ac.uk

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Details of methods and a worked example, references for 28 systematic reviews, and three tables are on bmj.com

Abstract

Objective To determine the validity of adjusted indirect comparisons by using data from published meta-analyses of randomised trials.

Design Direct comparison of different interventions in randomised trials and adjusted indirect comparison in which two interventions were compared through their relative effect versus a common comparator. The discrepancy between the direct and adjusted indirect comparison was measured by the difference between the two estimates.

Data sources Database of abstracts of reviews of effectiveness (1994-8), the Cochrane database of systematic reviews, Medline, and references of retrieved articles.

Results 44 published meta-analyses (from 28 systematic reviews) provided sufficient data. In most cases, results of adjusted indirect comparisons were not significantly different from those of direct comparisons. A significant discrepancy ($P < 0.05$) was observed in three of the 44 comparisons between the direct and the adjusted indirect estimates. There was a moderate agreement between the statistical conclusions from the direct and adjusted indirect comparisons (κ 0.51). The direction of discrepancy between the two estimates was inconsistent.

Conclusions Adjusted indirect comparisons usually but not always agree with the results of head to head randomised trials. When there is no or insufficient direct evidence from randomised trials, the adjusted indirect comparison may provide useful or supplementary information on the relative efficacy of competing interventions. The validity of the adjusted indirect comparisons depends on the internal validity and similarity of the included trials.

Introduction

Well designed randomised controlled trials generally provide the most valid evidence of relative efficacy of competing interventions in health care and minimise

the possibility of selection bias.¹ However, many competing interventions have not been compared directly (head to head) in randomised trials. Even when different interventions have been compared directly, such evidence is often limited and insufficient. Because of the lack of direct evidence, indirect comparisons have been recommended² and used for evaluating the efficacy of alternative interventions (Glenny AM, et al, international society of technology assessment in health care, The Hague, 2000). There are concerns that indirect comparisons may be subject to greater bias than direct comparisons and may overestimate the efficacy of interventions.³ Empirical evidence is required to assess the validity of indirect comparisons.

We previously examined the validity of indirect comparisons using examples in a systematic review of antimicrobial prophylaxis in colorectal surgery.⁴ We found some discrepancies between the results of direct and indirect comparisons, depending on which indirect method was used. The results of the study, however, were based on only one topic and the findings may not be generalisable. We therefore used a sample of 44 comparisons of different interventions from 28 systematic reviews to provide stronger evidence about the validity of indirect comparisons.

Methods

To identify relevant meta-analyses of randomised controlled trials, we searched the database of abstracts of reviews of effectiveness (1994-8), the Cochrane database of systematic reviews (Issue 3, 2000), Medline, and references of retrieved articles. Our two inclusion criteria were that competing interventions could be compared both directly and indirectly and that the same trial data had not been used in both the direct and indirect comparison.

Comparison methods

The relative efficacy in each meta-analysis was measured by using mean difference for continuous data and log relative risk for binary data. We use two