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Effects of Three-Monthly Oral 150,000 IU Cholecalciferol Supplementation on Falls, Mobility, and Muscle Strength in Older Postmenopausal Women: A Randomized Controlled Trial

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ABSTRACT

Daily vitamin D in addition to calcium supplementation reduces falls and fractures in older women. However, poor adherence to therapy is a common clinical problem. To examine the effects of supervised oral 3-monthly vitamin D therapy on falls, muscle strength, and mobility, we conducted a 9-month randomized, double-blind, placebo-controlled trial in 686 community-dwelling ambulant women aged over 70 years. Participants received either oral cholecalciferol 150,000 IU every 3 months ($n = 353$) or an identical placebo ($n = 333$). All participants were advised to increase dietary calcium intake. Falls data were collected 3-monthly. At baseline, 3, 6, and 9 months, muscle strength was measured by a handheld dynamometer and mobility by the Timed Up and Go (TUG) test. Serum 25 hydroxyvitamin D (25OHD) was measured in a subgroup of 40 subjects. Mean age at baseline was 76.7 ± 4.1 years. The average serum 25OHD value at baseline was 65.8 ± 22.7 nmol/L. By 3, 6, and 9 months after supplementation, 25OHD levels of the vitamin D group were approximately 15 nmol/L higher than the placebo group. Calcium intake did not change significantly between baseline (864 ± 412 mg/day) and 9 months (855 ± 357 mg/day). Faller rates in the two groups did not differ: vitamin D group, 102 of 353 (29%); placebo group, 89 of 333 (27%). At 9 months, compared to placebo or baseline, muscle strength, and TUG were not altered by vitamin D. In conclusion, oral cholecalciferol 150,000 IU therapy administered 3-monthly had neither beneficial nor adverse effects on falls or physical function. These data together with previous findings confirm that intermittent large doses of vitamin D are ineffective or have a deleterious effect on falls. Thus despite adherence issues with daily vitamin D replacement, an intermittent, high-dose vitamin D regimen cannot be supported as a strategy to reduce falls and fractures. © 2012 American Society for Bone and Mineral Research.

KEY WORDS: CHOLECALCIFEROL SUPPLEMENTATION; FALLS; MUSCLE STRENGTH; MOBILITY; OLDER WOMEN

Introduction

Susceptibility to falls increases with aging so that at least one-third of older people living in the community fall each year.[1] Falls are a major cause of injury-related hospitalization and death in persons older than 65 years of age. Falls and fractures represent a major public health problem in Australia, with almost 36,000 women requiring hospitalization or attendance at hospital emergency departments annually.[2] Many studies have demonstrated an association between vitamin D deficiency, falls, and fracture rates in older women and men.[3–5]. A previous 1-year randomized, population-based, controlled trial demonstrated that 1000 IU of daily oral ergocalciferol treatment reduced the risk of falling over a year by about one-third in Western Australian women with a serum 25 hydroxyvitamin D (25OHD) < 60 nmol/L and a history of falls in the previous year.[6]

Received in original form June 16, 2011; revised form September 14, 2011; accepted September 22, 2011. Published online September 28, 2011.
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Journal of Bone and Mineral Research, Vol. 27, No. 1, January 2012, pp 170–176
DOI: 10.1002/jbmr.524

The effect was predominantly notable in winter, the time of the highest rate of falls and lowest 25OHD status. Thus vitamin D insufficiency is a potentially major correctable cause of falls, fractures, morbidity and mortality.

The importance of improved adherence with treatments to prevent falls and fractures has received increasing attention.[7] Because vitamin D is stored in adipose tissue it is biologically plausible that supplements could be administered less frequently than on a daily basis to improve adherence but maintain therapeutic effectiveness. In the present study we used supervised oral administration to ensure high adherence.

A previous population-based randomized trial demonstrated that oral 4-monthly cholecalciferol supplementation with 100,000 IU may prevent fractures in UK community-dwelling individuals over the age of 65 years.[8] A 6-month study of supplementation with 100,000 IU oral cholecalciferol every 3 months demonstrated an increase in mean serum 25OHD from 36.4 ± 12.6 nmol/L at baseline to 124.0 ± 27.9 nmol/L when measured 1 week after third dose administration.[9] Based on these data, we hypothesized that a 3-monthly 150,000 IU oral cholecalciferol regimen would be safe, effective at achieving appropriate target levels of 25OHD, improve treatment adherence, and prevent falls and fall-related costs in unselected female patients over the age of 70 years. In light of the evidence to support the benefits of calcium and physical activity on fracture prevention, advice on increasing calcium intake and physical activity were given to all study participants. Therefore the aim of our 9-month randomized, double-blind, placebo-controlled trial was to evaluate the effects of cholecalciferol treatment and lifestyle advice compared to lifestyle advice alone on falls, serum 25OHD levels, physical function, and adverse events in 686 women aged over 70 years.

After completion of the present study, a randomized, double-blind, placebo-controlled trial of 500,000 IU oral cholecalciferol annually in community dwelling women aged over 70 years at higher risk of fracture reported an increased risk of falls and fractures with vitamin D supplementation.[10] Our data are therefore relevant to the latter findings as it is important to determine if less frequent, higher-dose vitamin D replacement is as equally efficacious on falls and fracture rates as lower dose, daily oral replacement therapy.

Subjects and Methods

Participants

Women aged over 70 years living independently in the metropolitan area of Perth, Western Australia, were recruited to the study between February and July 2009 (mid-summer to mid-winter) by invitation letter. Name lists of potential study recruits were obtained from four General Practitioner (GP) clinics and a random selection of women from the electoral roll also received letters of invitation ($n = 10{,}500$). A total of 2110 women (657 from GP clinic name list; 1453 from electoral roll) responded to the invitation letter, 831 attended clinic screening, and 686 women who fulfilled the inclusion criteria entered the study. Inclusion criteria for the study included age over 70 years, registration with a general practitioner, and likelihood, in the investigators' opinion, of attending four study visits over 9 months. Exclusion criteria included consumption of vitamin D supplementation either in isolation or as part of a combination treatment; eg, Actonel combi +D or Fosamax plus, cognitive impairment (Mini Mental State Score [MMSE] < 24), and individuals who in the investigators' opinion would not be suitable for the study. All procedures followed were in accordance with institutional guidelines and were conducted at the Sir Charles Gairdner Hospital in Perth. The trial ended in April 2010 when the last subject was seen at the 9-month clinic visit. The study was approved by the Sir Charles Gairdner Hospital Human Research Ethics Committee, and all participants provided written informed consent. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices Guidelines, and registered with the Australian New Zealand Clinical Trials Registry (Registration number: ACTRN12609000748213).

Study design

A 9-month randomized, double-blind, placebo-controlled, prospective, parallel study was conducted. Eligible participants were randomized to one of two treatment groups (cholecalciferol or matching oral placebo). The study used a computer-generated randomization sequence with a block size of 10 to assign participants to either cholecalciferol therapy or placebo in a ratio of 1:1. The randomization sequence was generated by a pharmacist at Captain Stirling Pharmacy, Perth, Western Australia, where participants were assigned to intervention and test capsules were appropriately labeled. Because an individual prescription was required for each subject, the allocation to study and placebo groups and the labeling of test capsules were completed by the pharmacist before each subject's baseline visit. However, more subjects allocated to the placebo group could not fulfill the selection criteria at the baseline visit. Consequently, there were slightly higher subject numbers in the vitamin D group ($n = 353$) compared to the placebo group ($n = 333$). Research assistants at Sir Charles Gairdner Hospital dispensed the test capsules to participants at clinic visits and supervised the consumption of the test capsules. The study participants and researchers at the Sir Charles Gairdner Hospital responsible for recruitment and assessment of outcomes measures remained blinded to group assignment. Any capsules that were not consumed by participants at clinic visits were recorded.

Intervention

Subjects in the cholecalciferol group (active group) received three capsules containing 150,000 IU of vitamin D and subjects in the placebo group (standard practice group) received three placebo capsules identical in appearance to the cholecalciferol capsules at their clinic visits at baseline, 3 months, and 6 months. The cholecalciferol content of the capsule has been quantified and verified by the Professional Compounding Chemists of Australia (PCCA) quality control laboratory. Both groups received written lifestyle advice on maintaining physical activity (optimally 30 minutes per day outside) and consuming 1300 mg calcium

per day using diet and/or supplements. Assessments of outcome variables were undertaken at baseline, 3, 6, and 9 months.

Fall assessment

Falls defined as "unintentionally coming to rest on the ground, floor, or other lower level" were the primary outcome of the study. Falls ascertainment used a diary method, previously employed to demonstrate treatment effectiveness of daily oral ergocalciferol over 1 year in a study of women of a similar age to those recruited in the present study.[6] The definition of a fall was explained to subjects at the baseline visit. Participants were instructed to record the nature, timing, and any associated features of each fall shortly after this happened in the falls diary. Study staff reviewed the falls diaries at 3-monthly intervals during study visits, sought clarification from the participant if further information was required, and determined if a fall, as defined in the study protocol, had eventuated.

Physical function assessment

At baseline, 3, 6, and 9 months, the secondary outcome of the study—physical function—was assessed. Hand grip strength was measured by a handheld dynamometer and mobility functioning was measured by the Timed Up and Go test (TUG), which required the subjects to be timed while getting up, walking 3 m, turning, returning to chair, and sitting down again.[11] The interobserver coefficient of variation (CV) error was 6.7% and 5.7% for hand grip strength and TUG test in our laboratory, respectively.

Biochemistry

Venous blood samples were collected before cholecalciferol dosing following a 12-hour overnight fast at baseline, 3-, 6-, and 9-month clinic visits for the assessment of serum 25OHD. One hundred-sixty samples from 40 randomly selected subjects (20 from each group) were assayed in three analytical runs, performed on the same day, after study completion, using sera stored at $-80\,^{\circ}C$ and measured using the automated Liaison method (DiaSorin Inc, Stillwater, MN, USA). The minimal detectable concentration using this method was 10 nmol/L and the interassay coefficient of variation was 10.7% at 19 nmol/L, 8.9% at 42 nmol/L, and 5.5% at 150 nmol/L. This method is used for routine reporting of patient samples and our laboratory, accordingly, is accredited with the National Association of Testing Authorities, Australia, and our 25OHD method is enrolled and performs well in both national and international quality-assurance programs.

Calcium intake

We assessed calcium intake at baseline and 9 months by a food frequency questionnaire developed in a previous study[12] to evaluate the effectiveness of the request to consume 1300 mg calcium per day given to both groups.

Other clinical assessments

Demographic information for participants including health history, education, past occupation, and smoking history were collected using a questionnaire. This questionnaire includes 39 food items and utilizes the Australian Tables of Food Composition 1990 (NUTTAB 90) database, a nutritional database that uses chemical analysis of Australian foods. Weight and height were measured retaining light clothing but not shoes. The Mini–Mental State Examination (MMSE) test was administered at baseline with the aim of excluding those participants who demonstrate significant cognitive impairment.

Adverse events

Participants were asked to complete an adverse event diary. Diary records were collated using a previously validated method[13] that records adverse events and every clinical physician visit. At preplanned clinic visits every 3 months, the adverse event diary was reviewed at the study center. Adverse events were coded using the International Classification of Primary Care (ICPC2 Plus) system database of disease coding, a validated method of event recording developed for use in general practice.[14]

Sample size calculation

We anticipated the falls rate in the placebo group would be 30% considering historical data. To detect a relative risk reduction of 0.33 with cholecalciferol therapy, using an alpha of 0.05 plus power of 0.8, a sample size of 300 participants per treatment group was needed. To allow for an attrition rate of 10%, the number of subjects required to be recruited per group was at least 330.

Statistical analysis

Descriptive statistics were reported as mean $\pm$ SD and differences as mean $\pm$ SEM for all variables unless otherwise stated. The normality of continuous variables was checked by histogram construction. Comparison of baseline characteristics was made by Student's *t* test or chi-square test. Intention-to-treat analytical approaches were employed to quantify the effectiveness of cholecalciferol therapy on outcome measures. The effects on the primary outcome measure—falls—were evaluated using logistic regression, adjusting for baseline age, falls in the previous 12 months, and length of follow-up. The effects on secondary outcome measures including serum 25OHD, muscle strength, and TUG were tested by repeated-measures analysis of variance (ANOVA). These analyses were preplanned on the basis of clinical considerations and previous findings. Values of $p < 0.05$ (two-tailed) were regarded as statistically significant. All data were analyzed by PASW (version 18; SPSS Inc, Chicago, IL, USA).

Results

Participant characteristics

Subject disposition is presented in Figure 1. At study entry, the mean age of participants was 76.7 $\pm$ 4.1 years and the estimated mean calcium intake was 864 $\pm$ 412 mg/day. There were no significant differences between the cholecalciferol and placebo groups according to baseline age, anthropometry, MMSE, calcium intake, and physical performance (Table 1; all

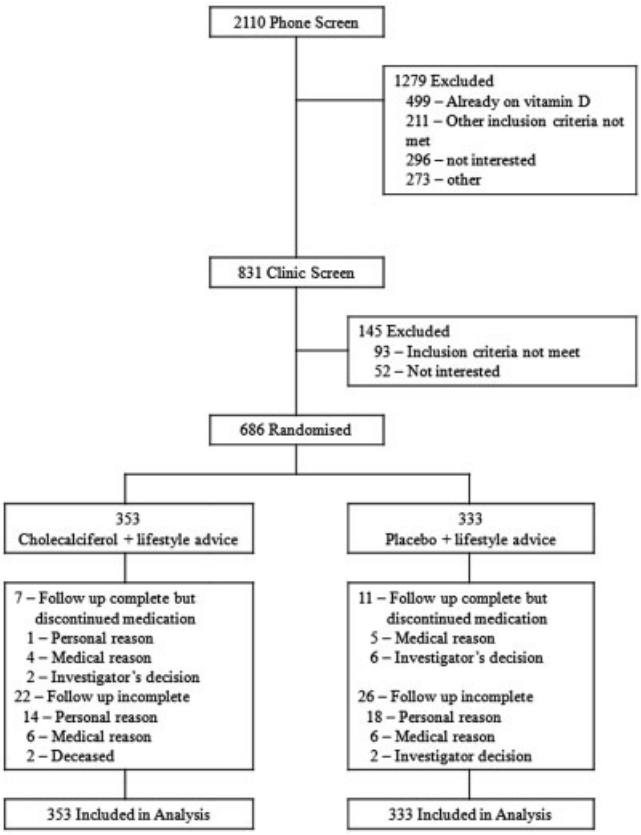

Fig. 1. Disposition of participants during the study.

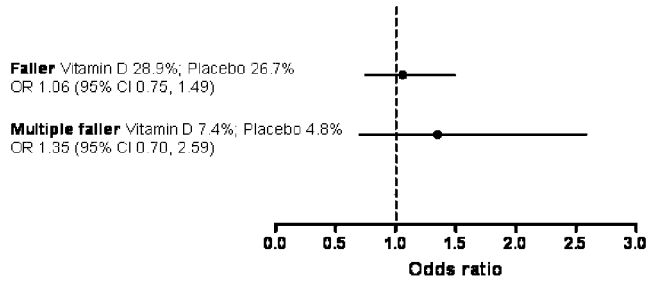

Fig. 2. Effects of cholecalciferol supplementation on falls. Faller refers to participants who had at least one fall and multiple faller refers to participants who had more than one fall during the study. Odds ratio (OR) obtained from logistic regression analysis adjusted for baseline age, falls in the previous 12 months, and length of follow-up.

$p > 0.05$). A higher percentage of participants in the cholecalciferol group had experienced at least one fall in the previous 12 months compared to the placebo group ($p = 0.01$), mainly because there were more multi-fallers in the cholecalciferol group (Table 1). There was no significant difference between the cholecalciferol group and the placebo group in the number of subjects who were lost to follow up or who discontinued the study medication (Figure 1; all $p > 0.05$). Because all study participants consumed test capsules at each clinic visit, adherence rates for those who remained active in the trial was 100%.

Effects on falls

During the 9 months study period, 102 (28.9%) subjects in the cholecalciferol group and 89 (26.7%) subjects in the placebo group experienced at least one fall and 26 (7.4%) subjects in the cholecalciferol group and 16 (4.8%) subjects in the placebo group experienced more than one fall (Fig. 2). The odds ratio for the cholecalciferol group compared with the placebo group was 1.11 (95% confidence interval [CI], 0.80–1.56) for experiencing at least one fall and 1.58 (95% CI, 0.83–2.99) for multiple falls. The higher percentage of participants recruited to the cholecalciferol group who experienced at least one fall in the previous 12 months compared to the placebo group, may have

Table 1. Baseline Characteristics of Participants

	Cholecalciferol ($n = 353$)	Placebo ($n = 333$)	p Value[a]
Age (year)	76.9 ± 4.0	76.5 ± 4.0	0.17
Weight (kg)	70.6 ± 13.0	70.7 ± 13.3	0.96
Height (cm)	160.4 ± 6.2	160.7 ± 6.1	0.55
Body mass index (kg/m^2)	27.5 ± 4.6	27.4 ± 4.9	0.81
Mini Mental State score	29.0 ± 1.2	29.0 ± 1.4	0.97
Ethnicity (%)			0.76
Caucasian	96.9	96.0	
Asian	2.9	3.4	
Other	0.3	0.6	
Calcium intake (mg/day)	862 ± 412	864 ± 413	0.94
Hand grip strength (kg)	19.9 ± 4.9	19.9 ± 5.2	0.93
Timed Up and Go (seconds)	8.4 ± 2.8	8.5 ± 2.9	0.64
Number of falls in the previous 12 months (%)			0.01
0	66.6	75.5	
1	15.1	15.0	
2	11.4	6.1	
≥ 3	6.9	3.4	

[a]By Student's t test or chi-square test.

predisposed the cholecalciferol group to the slightly higher falls risk. However, adjusting for this and other potential baseline confounding variables did not alter the outcome (Fig. 2).

Effects on physical performance and calcium intake

Table 2 shows that compared to baseline, hand grip strength increased in the placebo group at 3 months, but decreased in both groups at 9 months. TUG fell in both groups at 3 and 6 months and in the placebo group at 9 months. However, there were no significant differences between the two treatment groups in the change of these two physical performance measurements at each time point (Table 2). There were no significant changes in calcium intakes from baseline to 9 months in both treatment groups (Table 2).

Effects on vitamin D status

In the 40 randomly selected subjects at baseline the mean serum 25OHD concentration was 65.8 ± 22.7 nmol/L, and there was no significant difference between the two groups. At 3, 6, and 9 months, the vitamin D group had significantly higher serum 25OHD levels compared to the placebo group (Table 3). Serum 25OHD levels increased significantly in the vitamin D group between baseline, 3 and 9 months and decreased significantly in the placebo group between baseline, 3 and 6 months (Table 3). Overall the proportion of participants in the placebo group with 25OHD above 75 nmol/L fell from 30% at baseline to 20% at 9 months while the proportion participants in the vitamin D group with 25OHD over 75 nmol/L rose from 35% at baseline to 40% at 9 months.

Adverse events

During the study period, there were no significant differences between the vitamin D and the placebo groups in the rate of incident cancer (vitamin D 5.4%, placebo 4.5%, $p = 0.73$), type 2 diabetes (vitamin D 0.3%, placebo 0.5%, $p = 0.36$), stroke (vitamin D 0.8%, placebo 0.6%, $p = 1.00$), ischemic heart disease (vitamin D 0.6%, placebo 1.2%, $p = 0.44$), or fracture (vitamin D 2.8%, placebo 3.0%, $p = 1.00$).

Discussion

The multiple strengths of our study include the number of participants, the randomization process, the placebo control, the supervised administration of treatment, the high compliance, and the blinding of treatment allocation. Despite these strengths, vitamin D administered as oral cholecalciferol 150,000 IU every 3 months had no beneficial or adverse effect on falls rates in older females living independently. This lack of efficacy on balance, and associated falling, is supported by the lack of effect on hand grip strength and the TUG test.

As reported in the methods section the planned study had a power of 0.8, to show a 33% reduction in falls in the active compared to the placebo groups specified to be clinically significant. In our study, 686 individuals were recruited with a 7% loss to follow up and only a 2.6% lack of adherence to the intervention due to the supervised administration of the vitamin

Table 2. Effects of Cholecalciferol and Lifestyle Intervention on Physical Performance and Calcium Intake

	Baseline values (mean ± SD)[a]		Difference to baseline (mean ± SE)					
			3 months		6 months		9 months	
	Vitamin D	Placebo	Vitamin D	Placebo	Vitamin D	Placebo	Vitamin D	Placebo
Hand grip strength (kg)	20.2 ± 4.9 ($n = 311$)	20.0 ± 5.1 ($n = 288$)	0.12 ± 0.18	$0.64 \pm 0.21^*$	-0.26 ± 0.20	0.12 ± 0.23	$-1.05 \pm 0.20^*$	$-0.65 \pm 0.21^*$
Timed Up and Go (seconds)	8.23 ± 2.61 ($n = 325$)	8.32 ± 2.67 ($n = 302$)	$-0.22 \pm 0.08^*$	$-0.32 \pm 0.10^*$	$-0.21 \pm 0.08^*$	$-0.32 \pm 0.09^*$	-0.02 ± 0.08	$-0.12 \pm 0.09^*$
Calcium intake (mg/day)	868 ± 413 ($n = 325$)	869 ± 420 ($n = 298$)	–	–	–	–	-19.3 ± 19.2	-11.4 ± 21.4

There were no significant treatment effects.
[a]n is the number of subjects for each test.
*Significant change from baseline $p < 0.05$, one-factor repeated measures ANOVA.

Table 3. Effects on Serum 25OHD Levels in 40 Randomly Selected Participants

	Cholecalciferol ($n = 20$)	Placebo ($n = 20$)	p^a
Baseline (nmol/L)	65.0 ± 17.8	66.5 ± 27.1	0.425
3 month (nmol/L)	$74.0 \pm 21.6^*$	$59.8 \pm 20.5^{**}$	0.001
6 month (nmol/L)	69.1 ± 25.9	$53.2 \pm 22.8^*$	0.004
9 month (nmol/L)	$74.6 \pm 25.8^*$	60.2 ± 26.3	0.006

Values are mean $\pm$ SD.

[a]Student's *t* test for baseline and two-factor repeat-measures ANOVA for 3, 6, and 9 months.

[*]Significantly different from baseline, $p \leq 0.001$, one-factor repeated measures ANOVA.

[**]Significantly different from baseline, $p < 0.05$, one-factor repeated measures ANOVA.

D and placebo. The falls rate was slightly lower than anticipated at 26.7%. Recalculation of the power using these data demonstrated a power of 0.8 to detect a 34% reduction in falls. However, the falls rate in the active treatment group was higher than in the placebo group, suggesting that there was no beneficial effect and arguing against a Type 2 error.

A review of previous studies is instructive regarding the frequency and dosage of cholecalciferol chosen in our study and the lack of efficacy demonstrated. The data in this study of 150,000 IU of cholecalciferol administered every 3 months (daily average intake 1667 IU) can be compared to previous studies that prescribed up to 1000 IU per day of vitamin D[15] and three studies using higher-dose, intermittent vitamin D therapy.[8,10,16] The majority of studies of daily vitamin D replacement have demonstrated beneficial effects on falls with an approximately 20% to 30% reduction in event rates[6,15] and, with calcium, a reduction in fractures of about 26%.[17]. However, three studies of intermittent high-dose vitamin D that have been published have variable results depending on the dose.[8,10,16] A fracture endpoint study of oral cholecalciferol 100,000 IU every 4 months for 5 years in 2500 community-dwelling British men and women aged 65 to 85 years demonstrated a 22% reduction of first fracture events and 33% reduction in first hip, wrist, or vertebral fractures.[8] Falls rates were not measured in this study.[8] A study of 9000 British community-dwelling men and women randomized to 300,000 IU of intramuscular ergocalciferol or placebo annually for 3 years reported an increased risk of hip fractures but not total fracture in women treated with ergocalciferol.[16] Falls data were collected yearly by recall but no effect of vitamin D on falls was reported.[16] Finally, a study of 2200 community-dwelling women aged over 70 years at high risk of fracture demonstrated that 500,000 IU of cholecalciferol administered as an annual oral dose was associated with a 26% increased risk of fracture and a 15% increased risk of falling compared to placebo.[10] The majority of the deleterious effects in the latter study occurred in the first 3 months when 25OHD levels were highest.[10] In this context, the findings of our current study using 150,000 IU of cholecalciferol replacement every 3 months showing no overall beneficial or adverse effect are consistent with the concept that doses of vitamin D replacement over 100,000 IU should be considered ineffective or, at higher dose, deleterious.

The mechanism of the deleterious effect of high-dose vitamin D replacement remains uncertain. However, the frequency of hormone administration is recognized to modulate biological effects. For example, parathyroid hormone when given as an intermittent daily dose has anabolic skeletal effects,[18] but when given in a continuous fashion, the opposing catabolic skeletal effect is seen.[19] It is therefore, hypothesized that infrequent high-dose administration of cholecalciferol could negate any beneficial effect on muscle metabolism due to differential effects on gene regulation.

Weaknesses of our study include; first, the suboptimal dietary calcium intake of the participants who did not comply with the request to increase calcium intake to 1300 mg per day. Because the published literature demonstrates the benefit of vitamin D in combination with calcium in the prevention of falls and fractures,[17] calcium supplementation should be added to vitamin D supplementation in future randomized controlled trials. Second, a higher percentage of participants in the cholecalciferol group had experienced at least one fall in the previous 12 months compared to the placebo group. However, adjustment for this factor in the logistic regression analysis did not alter the study outcome. Third, the effectiveness of cholecalciferol replacement in our study may have been negated by the high mean baseline serum 25OHD values of 65.8 nmol/L. Fourth, at the 9-month study visit, 60% of participants in the vitamin D group had a 25OHD nadir value less than 75 nmol/L, an optimal threshold level considered by some to prevent falls and fractures. However, a previous study, used as one basis for our study, reported that 100,000 IU oral cholecalciferol every 3 months resulted in a serum 25OHD levels of 124.0 ± 27.9 nmol/L 1 week after the third dose administration.[9] Furthermore, a previous published study demonstrated protection against falls risk (odds ratio 0.61) with a serum 25OHD level of 60 ± 14 nmol/L.[6] Fifth, our study used a diary method to collect falls events that may have missed or misclassified some falls compared to more intensive methods. This is, however, unlikely because the event rates reported by more intensive ascertainment of falls were no different from that of the present study. Furthermore, the main outcome, a comparison of fall frequency in the two groups, would not be affected by any potential underestimation of event rates equally in both groups. Finally, more than 96% of the study subjects were Caucasian community-dwelling older women. Therefore, the interpretation of these findings is limited to this population.

In conclusion, these data and other studies of high dose intermittent vitamin D therapy, support the concept that dosing above 100,000 IU every 3 to 4 months is ineffective or deleterious. Thus, intermittent high dose vitamin D supplementation with or without daily oral calcium replacement cannot be currently advocated as an effective strategy to reduce falls and fractures, despite previously recognized adherence problems with daily regimens.

Disclosures

All the authors state that they have no conflicts of interest.

Acknowledgments

The study was supported by the Department of Health, Western Australia State Health Research Advisory Council Research Translation Project Grant, Sir Charles Gairdner Hospital Research Advisory Committee Grant, and Royal Perth Hospital Medical Research Foundation Grant.

We thank all study participants for their diligence and cooperation. We are grateful to Burslem, Parkwood, and Applecross Medical Centres and Victoria Medical Group for their help with the recruitment of study participants, the Data Linkage Unit Department of Health Western Australia for providing the electoral roll name list, and Captain Stirling Pharmacy for formulating the test capsules. None of the funding agencies had any role in the conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Australian New Zealand Clinical Trials Registry Registration number: ACTRN12609000748213 (Date of registration: 28 August 2009).

Authors' roles: Study design: PG, KZ, CI, PH, and RLP. Study conduct: KZ, JRL, and RLP. Data collection: KZ, JRL, and RLP. Data analysis: KZ. Data interpretation: PG, KZ, CI, PH, and RLP. Drafting manuscript: PG, KZ, and RLP. Revising manuscript content: PG, KZ, CI, PH, JRL, and RLP. Approving final version of manuscript: PG, KZ, CI, PH, JRL, and RLP. KZ takes responsibility for the integrity of the data analysis.

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