Effects of Calcium and Vitamin D Supplementation on Hip Bone Mineral Density and Calcium-Related Analytes in Elderly Ambulatory Australian Women: A Five-Year Randomized Controlled Trial

Kun Zhu, Amanda Devine, Ian M. Dick, Scott G. Wilson, and Richard L. Prince

School of Medicine and Pharmacology (K.Z., A.D., I.M.D., R.L.P.), University of Western Australia, Crawley 6009, Australia; Department of Endocrinology and Diabetes (K.Z., I.M.D., S.G.W., R.L.P.), Sir Charles Gairdner Hospital, Nedlands 6009, Australia; and School of Exercise, Biomedical, and Health Sciences (A.D.), Edith Cowan University, Joondalup 6027, Australia

Context: Effects of long-term calcium, with or without vitamin D, on hip bone mineral density (BMD) and bone turnover in sunny climates have not been reported.

Objective: The aim was to evaluate the effect of vitamin D added to calcium supplementation on hip dual-energy x-ray absorptiometry BMD and calcium-related analytes.

Design, Setting, and Participants: The study was a 5-yr randomized, controlled, double-blind trial of 120 community-dwelling women aged 70–80 yr.

Interventions: The interventions were 1200 mg/d calcium with placebo vitamin D (Ca group) or with 1000 IU/d vitamin D2 (CaD group), or double placebo (control).

Main Outcome Measures: Hip BMD, plasma 25-hydroxyvitamin D, biomarkers of bone turnover, PTH, and intestinal calcium absorption were measured.

Results: Hip BMD was preserved in CaD (−0.17%) and Ca (0.19%) groups but not controls (−1.27%) at yr 1 and maintained in the CaD group only at yr 3 and 5. The beneficial effects were mainly in those with baseline 25-hydroxyvitamin D levels below the median (68 nmol/liter). At yr 1, compared with controls, the Ca and CaD groups had 6.8 and 11.3% lower plasma alkaline phosphatase, respectively ($P \leq 0.02$), and 28.7 and 34.5% lower urinary deoxypyridinoline to creatinine ratio, respectively ($P \leq 0.05$). At 5 yr, this suppression was maintained only in the CaD group. CaD reduced PTH at 3 and 5 yr *cf.* controls (27.8 and 31.3%, $P \leq 0.005$) in those with baseline PTH levels above the median (3.6 pmol/liter). Therapy did not affect intestinal calcium absorption at high carrier loads.

Conclusions: Addition of vitamin D to calcium has long-term beneficial effects on bone density in elderly women living in a sunny climate, probably mediated by a long-term reduction in bone turnover rate. (***J Clin Endocrinol Metab* 93: 743–749, 2008**)

Osteoporosis and related fracture represent a significant public health burden globally. Postmenopausal women are at increased risk of structural deterioration of the skeleton because of loss of the beneficial effects of estrogen on stimulation of intestinal calcium absorption and reduction of renal calcium excretion (1) as well as direct skeletal effects (2). A metaanalysis of calcium supplementation studies, compared with placebo, showed a beneficial effect of 1.5% higher total hip site dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD) in the supplemented group (3), but most studies analyzed

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Abbreviations: BMD, Bone mineral density; CaD, calcium with vitamin D2; Cr, creatinine; DPD, deoxypyridinoline; DXA, dual-energy x-ray absorptiometry; 25OHD, 25-hydroxyvitamin D.

lasted 2 yr or less. Similarly, benefits of calcium and vitamin D, compared with placebo, on femoral neck of 0.98% higher BMD have been described (4). Interestingly the effects of vitamin D alone on hip DXA BMD have been compared only with placebo in two studies, neither of which showed any beneficial effect (5, 6). In light of evidence for short-term benefit of calcium and calcium and vitamin D on hip BMD, this study was designed to examine the relative effect of calcium compared with calcium and vitamin D over 5 yr.

Another study design question relates to the calcium and vitamin D status of the controls and the size of the calcium and vitamin D supplement provided. In this study, the participants were ambulant elderly women aged 70–80 yr living in Perth, Australia (latitude 32°), a sunny climate receiving on average a fairly high calcium intake of about 1000 mg/d. The calcium dose of 1200 mg in addition to normal dietary intake was selected on the basis of previous studies in which large doses of calcium have proved beneficial on bone mass in this population (7, 8). The vitamin D dose of 1000 IU was also selected on the basis of previous studies (9, 10) as a dose slightly larger than those shown to have beneficial effects on bone mass in combination with calcium.

Thus, the aim of the study was to evaluate the relative benefits of 5 yr of calcium supplementation of 1200 mg with or without 1000 IU vitamin D2, compared with placebo, on hip BMD and bone-related biochemistry in ambulant elderly women aged 70–80 yr living in a sunny climate.

Subjects and Methods

Study design

This study was nested within the larger Calcium Intake Fracture Outcome Study, a 5-yr double-blinded, randomized, controlled calcium supplementation study, in which 1500 community-living ambulant women over the age of 70 yr were randomized to received either 1200 mg calcium per day or identical placebo (11). The first 120 sequential patients presenting in September 1998 (end of winter in Western Australia) enrolled in this substudy and were randomized to receive either 600 mg calcium as calcium carbonate twice per day with food (Caltrate; Wyeth Consumer Healthcare, Baulkham Hills, New South Wales, Australia) and placebo vitamin D (the Ca group); 600 mg of calcium twice per day and 1000 IU of vitamin D as ergocalciferol once per day (Ostelin; Boots Healthcare, North Ryde, New South Wales, Australia) (the CaD group); or placebo calcium and placebo vitamin D (the control group).

Subjects

The subjects were recruited from the Australian electoral roll, which has contact details of more than 98% of subjects of this age, by means of a letter inviting participation in the study. The inclusion and exclusion criteria of this substudy were the same as the Calcium Intake Fracture Outcome Study, *i.e.* aged over 70 yr old, likely to survive a 5-yr study, and not receiving bone active agent. There were no other specific exclusions so that the results could be generalized to the whole ambulant population. One hundred twenty women were recruited to this substudy at the end of winter and had follow-up assessments at 1, 3, and 5 yr at the same time of year. Informed consent was obtained from each subject, and the study was approved by the Human Rights Committee of the University Western Australia. 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 Clinical Trials Registry (registration no. ACTRN012607000055404).

Randomization was undertaken by a computer-generated randomization sequence with a block size of 12 to the three groups in a ratio of 1:1:1 by an independent research fellow and was kept in the Pharmacy Department of the Sir Charles Gairdner Hospital, in which the bottles were labeled and dispensed to subjects. The study subjects and study staff remained blinded to the treatment code until all the data had been entered, evaluated for accuracy, and the *a priori* hypotheses reviewed. Adherence to the study medications was established by counting tablets returned every 12 months.

Bone measurements

DXA BMD was measured at the hip with an Acclaim 4500A fan beam densitometer (Hologic Corp., Waltham, MA) at baseline and yr 1, 3, and 5 using an identical protocol. The coefficient of variation at the total hip was 1.2%.

Biochemistry assessments

Venous blood and second morning void urine samples were collected between 0830 and 1030 h after overnight fasting at baseline and 1, 3, and 5 yr. Plasma 25-hydroxyvitamin D (25OHD) concentrations were measured by competitive protein binding assay after column extraction, which measures both 25 hydroxylated cholecalciferol and ergocalciferol equally (12). Plasma PTH concentrations were measured by immunochemiluminometric method (13). Urinary deoxypyridinoline (DPD) concentrations were measured by HPLC. Plasma concentrations of total alkaline phosphatase and albumin and plasma and urinary concentrations of total calcium and creatinine were measured by routine laboratory method.

Intestinal calcium absorption

Gut calcium absorption was measured using Ca^{45} as calcium chloride as previously reported (14). At baseline and 2 yr, 10 mg calcium chloride containing 5 μCi calcium chloride tracer was administered with 140 ml deionized water. At 4 months 600 mg calcium chloride containing 10 μCi calcium chloride tracer was administered in 140 ml deionized water followed by a standard breakfast consisting of one piece of toast with one serving of butter and jam and one cup of tea. A blood sample was collected 2 h later and counted in a β-counter. The absorbed fraction was calculated from the total counts administered and measured in the circulation at 2 h corrected for the specific activity and the extracellular volume estimated as 15% of the individual's body weight. The 10-mg calcium load was selected to measure the active fraction of gut calcium absorption, and the 600-mg calcium load was selected to reflect the normal circumstances that participants randomized to the calcium groups would consume their morning dose of calcium.

Other assessments

Weight and height were measured with light clothes and without shoes. Nutrient intakes were determined from a self-administered semiquantitative food frequency questionnaire (15, 16). Physical activity level was assessed by a questionnaire (17, 18), and activity levels were calculated in kilocalories per day using a validated method using body weight, questions on the number of h and type of physical activity, and energy costs of such activities (19, 20).

Adverse event recording

During the study, participants were asked to fill out an adverse event diary in which each contact with a health care provider was recorded.

Statistical analysis and power calculation

To detect a difference in the rate of bone loss between groups of 1.8% over the study period, with a within group measurement error of 2%, 26

subjects per group were needed at an alpha of 0.05 and 90% power. Allowing for a 30% dropout rate, 40 subjects were recruited per group.

Descriptive statistics are reported as mean ± SD and differences as mean ± SEM for all variables unless otherwise stated. Baseline characteristics between the groups were compared by one-factor ANOVA. *Post hoc* multiple comparisons were made by Tukey's honestly significant difference test.

The main intention-to-treat analysis included all subjects who entered the study and had at least one follow-up measurement. Treatment, time, and interaction effects during the 60-month study period were examined using linear mixed-effects model analysis using the raw data with subjects defined as random effects and a first-order autoregressive covariance structure. This structure was chosen because correlations between measurements made at different time points decline with distance and by checking of AIC of different models, this covariance structure provides the best-fitted model. The advantage of mixed-effects model is that it accounts for highly correlated repeated measurements from single individuals and allows the inclusion of data from all subjects, regardless of the number of study visits. If the linear mixed-effect model analysis of actual values at the various time points indicated a significant treatment and time interaction, the treatment effects at each follow-up time points (1, 3, and 5 yr) were analyzed with linear regression models, in which outcomes (measurements of each follow-up point) were analyzed first with adjustment for baseline values and treatment groups and then further adjusted for baseline age, height, and body weight for hip BMD or age only for bone-related biochemistry variables. In a further analysis, baseline calcium intake and vitamin D status were added as covariates in addition to treatment effects on hip BMD, and the significance of relevant interaction terms were tested in the model. The normality and independence of the residuals and the homogeneity of variance of each model were checked by residual plots (normal probability plot and plot of residuals *vs.* treatment, subject, and predicted values). $P < 0.05$ (two tailed) was regarded as statistically significant. The data analyses were performed with SPSS PC for Windows (version 15; SPSS, Chicago, IL).

Results

Participant characteristics (Tables 1 and 2)

At study entry, the mean age of participants was 74.8 ± 2.6 yr, and the mean plasma 25OHD concentration was 68.0 ± 28.7 nmol/liter. Four participants had 25OHD levels between 12.5 and 25 nmol/liter (3.3%) and 31 participants (25.8%) had 25OHD levels between 25 and 50 nmol/liter. Seventy-four participants (61.7%) had a plasma 25OHD concentration less than 75 nmol/liter. The average calcium intake at baseline was 1010 ± 349 mg/d, and 74.8% participants had a calcium intake less than 1300 mg/d. The only difference between the groups at baseline was that the CaD group was significantly shorter than the Ca group (Table 1).

Retention and compliance

Patient withdrawals were not significantly different among the three groups. During the study, two patients withdrew from the Ca group, six from CaD group, and five from the control group. The reasons for the two withdrawals in the Ca group were concurrent illnesses or health concerns; in the CaD group, the reasons for withdrawal were personal reasons not related to the study (n = 3), concurrent illnesses or health concerns (n = 2), and investigator's decision (n = 1). In the control group, the reasons for withdrawal were personal reasons not related to the study (n = 1), death (n = 2), and investigator's decision (n = 2). There were no significant differences among the three groups in the compliance rates determined by tablet counting for calcium or placebo in the Ca, CaD, and control groups (80.9, 80.7, and 86.9%, respectively) or for vitamin D or placebo (84.2, 86.9, and 89.8%, respectively).

Effects of treatment on vitamin D status (Table 2)

With supplementation, the plasma 25OHD concentrations were significantly higher in the CaD group than the Ca and control groups at yr 1, 3, and 5.

Effects of treatment on total hip BMD (Figs. 1 and 2)

Both Ca and CaD groups had significantly better maintenance of hip BMD than the control group at yr 1 (Ca-control: 1.5 ± 0.5%, $P = 0.007$; CaD-control: 1.2 ± 0.6%, $P = 0.04$). However, only the CaD group had significantly better maintenance of hip BMD, compared with the control group, at yr 3 (CaD-control: 2.8 ± 1.1%, $P = 0.01$) and 5 (CaD-control: 2.2 ± 1.1%, $P = 0.05$). In the CaD group, there was no bone loss over

TABLE 1. Baseline characteristics of subjects

	Ca group (n = 40)	CaD group (n = 39)	Control group (n = 41)
Demography			
Age (yr)	74.1 ± 2.0	75.4 ± 2.7	74.8 ± 2.8
Weight (kg)	72.3 ± 12.4	68.0 ± 12.0	70.9 ± 13.5
Height (cm)	160.7 ± 7.4	157.1 ± 6.3[a]	159.9 ± 5.9
Calcium intake (mg/d)	1053.8 ± 398.2	926.7 ± 295.2	1046.1 ± 340.3
Physical activity (kcal/d)	147.7 ± 128.0	129.8 ± 168.4	121.2 ± 125.4
BMD			
Total hip BMD (mg/cm^2)	833.5 ± 92.9	782.9 ± 88.8	827.8 ± 125.4
Biochemistry			
PTH (pmol/liter)	3.9 ± 1.7	3.7 ± 1.3	3.9 ± 1.2
Total Ca (mmol/liter)	2.32 ± 0.09	2.34 ± 0.07	2.36 ± 0.12
Total alkaline phosphatase (U/liter)	84.4 ± 17.6	80.2 ± 21.4	83.3 ± 18.4
Urinary Ca to Cr (mmol/mol)	304.0 ± 238.7	311.3 ± 191.4	318.7 ± 226.6
Urinary DPD to Cr (nmol/mmol)	28.9 ± 9.7	31.9 ± 13.5	26.8 ± 11.3

Values are mean ± SD.

[a] Significantly lower than that of the Ca group ($P = 0.036$).

TABLE 2. Effects of treatment on 25OHD and intestinal calcium absorption

	Ca group	CaD group	Control group
Plasma 25OHD (nmol/liter)			
Baseline (n)	40	39	41
25OHD	66.6 ± 25.9	70.2 ± 25.6	67.3 ± 34.2
Year 1 (n)	37	34	38
25OHD	64.5 ± 26.5	97.8 ± 31.8[a,b]	59.7 ± 28.8
Year 3 (n)	35	32	32
25OHD	74.6 ± 23.8	118.4 ± 44.38[a,b]	63.6 ± 32.3
Year 5 (n)	34	29	30
25OHD	63.7 ± 28.7	106.4 ± 29.0[a,b]	61.5 ± 23.0
Intestinal calcium absorption (%)			
Baseline, 10-mg carrier load (n)	40	39	41
Fractional rate of absorption	0.45 ± 0.11	0.41 ± 0.11	0.41 ± 0.11
Month 4, 600-mg calcium load (n)	39	36	38
Fractional rate of absorption	0.11 ± 0.03	0.10 ± 0.03	0.11 ± 0.03
Year 2, 10-mg calcium load (n)	37	32	37
Fractional rate of absorption	0.40 ± 0.11[b]	0.36 ± 0.09[b,c]	0.41 ± 0.13

Results are mean ± SD.

[a] Significantly higher than that of the Ca and control groups ($P < 0.001$).

[b] Significantly different from that of baseline ($P < 0.01$).

[c] Significantly lower than that of the control group ($P < 0.05$).

the 5 yr of the study. The results were unchanged after being adjusted for baseline age, height, and body weight. Because there was a significant interaction between baseline 25OHD concentrations and treatment on hip BMD, further analysis was carried out by grouping subjects according to the median of the baseline 25OHD values (68 nmol/liter). In those patients with 25OHD concentrations below the median, the hip BMD was maintained, compared with controls, whereas in those with higher baseline 25OHD levels, there was no treatment effect (Fig. 2).

Effects of treatment on bone-related biochemistry (Fig. 3)

Alkaline phosphatase

At yr 1, compared with the control group, total alkaline phosphatase concentrations were 6.8 ± 2.7% lower in the Ca group ($P = 0.02$) and 11.3 ± 2.9% lower in the CaD group ($P < 0.001$). At yr 3 and 5, compared with the control group, the alkaline phosphatase concentrations were 8.7 ± 3.9% ($P = 0.03$) and 11.3 ± 5.7% ($P = 0.05$) lower in the CaD group, respectively. At 3 yr, the CaD group results were also 8.8 ± 3.8% ($P = 0.03$) lower than the Ca group.

DPD to creatinine (Cr)

At yr 1 and 3, compared with the control group, urinary DPD to Cr ratios were significantly lower in both the Ca and CaD

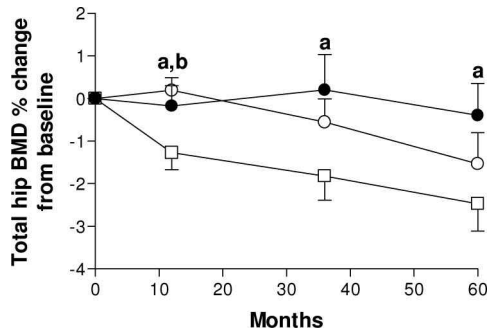

FIG. 1. Percentage change (mean ± SE) relative to baseline in total hip BMD. ○, Ca group; ●, CaD group; □, control group; significance values were obtained from a linear mixed-effect model analysis using the raw values: a, $P < 0.05$, CaD group *cf.* control group; b, $P < 0.05$, Ca group *cf.* control group.

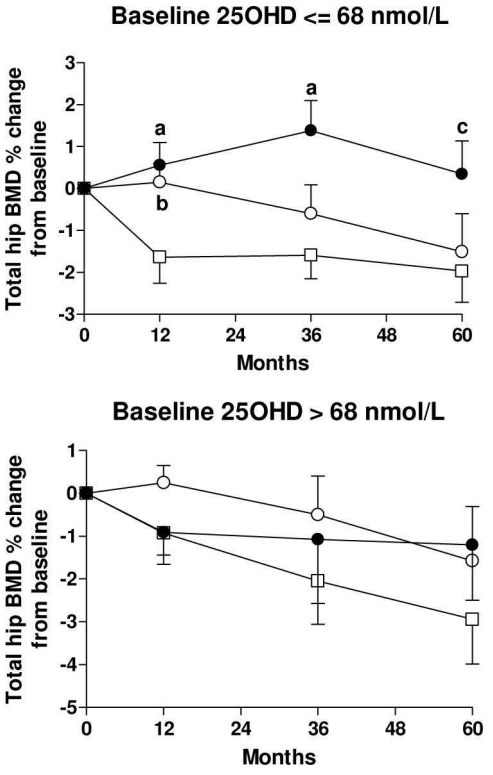

FIG. 2. Percentage change (mean ± SE) relative to baseline in total hip BMD by baseline vitamin D status. ○, Ca group; ●, CaD group; □, control group; significance values were obtained from a linear mixed-effect model analysis using the raw values: a, $P < 0.05$, CaD group *cf.* control group; b, $P < 0.05$, Ca group *cf.* control group; c, $P = 0.06$, CaD group *cf.* control group.

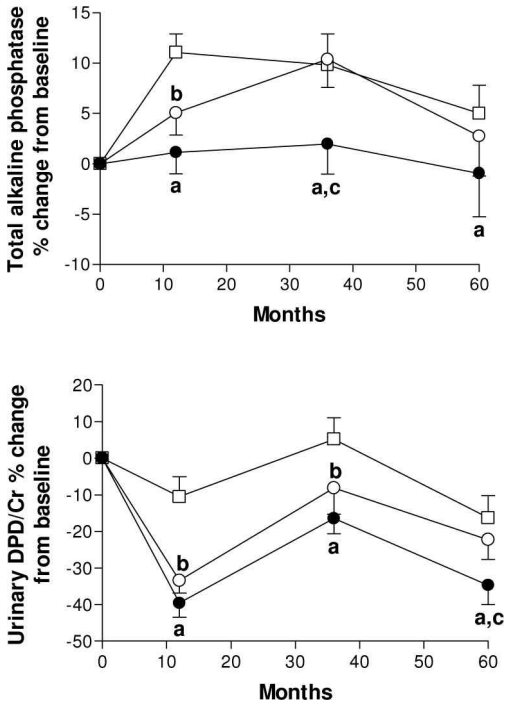

FIG. 3. Percentage change (mean ± SE) relative to baseline in total alkaline phosphatase and urinary DPD to Cr ratio. ○, Ca group; ●, CaD group; □, control group; significance values were obtained from a linear mixed-effect model analysis using the raw values: a, $P < 0.05$, CaD group *cf.* control group; b, $P < 0.05$, Ca group *cf.* control group; c, $P < 0.05$, CaD group *cf.* Ca group.

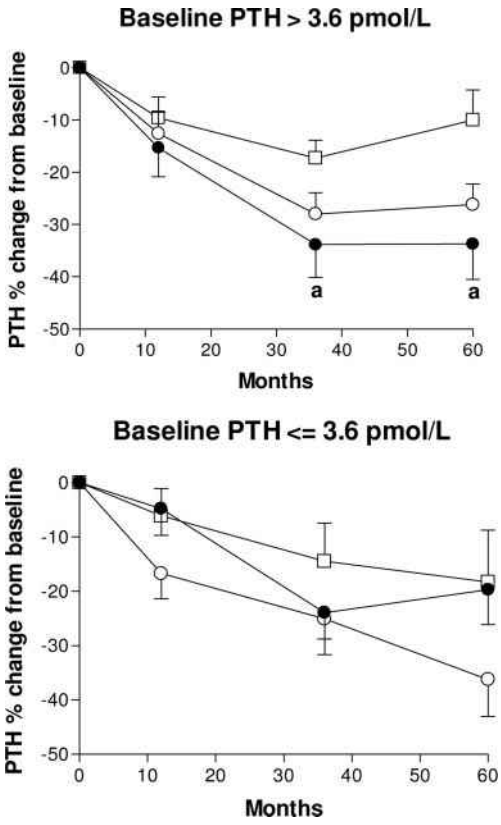

FIG. 4. Percentage change (mean ± SE) relative to baseline in PTH according to median value of baseline PTH. ○, Ca group; ●, CaD group; □, control group; significance values were obtained from a linear mixed-effect model analysis using the raw values: a, $P < 0.05$, CaD group *cf.* control group.

groups (yr 1: Ca-control: −28.7 ± 8.1%, $P = 0.001$; CaD-control: − 34.5 ± 8.6%, $P < 0.001$; yr 3: Ca-control: −15.6 ± 7.7%, $P = 0.05$; CaD-control: − 16.3 ± 8.0%, $P = 0.05$). The CaD group also had significantly lower DPD to Cr ratios at yr 5 than both the control group (−27.6 ± 8.6%, $P = 0.002$) and the Ca group (−17.5 ± 7.7%, $P = 0.03$).

Plasma and urine Ca

Both the Ca and the CaD groups had significantly higher fasting plasma calcium concentrations than the control group at yr 1 (Ca-control: 1.5 ± 0.7%, $P = 0.03$; CaD-control: 1.8 ± 0.7%, $P = 0.01$) and yr 3 (Ca control: 3.8 ± 0.8%, $P < 0.001$; CaD-control: 2.6 ± 0.8%, $P = 0.001$) but not at yr 5. There were no effects of the interventions on the fasting urinary Ca to Cr ratio (data not shown).

Effects on PTH (Fig. 4)

Because there was a significant interaction of the effects of treatment and baseline values on PTH, participants were grouped according to the median of baseline PTH concentration of 3.6 pmol/liter. In women with baseline PTH levels above the median, the CaD group had significantly lower PTH concentrations at yr 3 (−27.8 ± 9.4%, $P = 0.005$) and 5 (−31.3 ± 9.9%, $P = 0.003$), compared with the control group. The results remained unchanged after being adjusted for age.

Effects on gut calcium absorption (Table 2)

Compared with that of baseline, at 24 months the fractional rate of absorption of the 10 mg radiocalcium load was significantly lower in the Ca and CaD groups but not the control group. At 24 months the fractional rate of radiocalcium absorption was significantly lower in the CaD group than the control group. At 4 months, using the 600-mg calcium load test, there were no significant differences among the three groups in the fractional rate of radiocalcium absorption.

Adverse events

During the 5-yr study period, there were no significant differences among the three groups in the rate of incident cancer or vascular disease. No case of kidney stones was reported. In six cases the calcium level was noted to be above 2.55 mmol/liter, the upper limit of our reference range (three Ca, one CaD, and two control). These episodes were not associated with adverse clinical outcomes as determined by a documented clinical intervention. There were no significant differences in compliance between those who had or did not have adverse events while in the study.

Discussion

At the clinically important hip site, calcium therapy with an additional 1200 mg of calcium as calcium carbonate a day, although initially successful at stopping bone loss, was not different from placebo at 3 or 5 yr. These results are similar to one 4-yr study (21) but differ from two others (6, 22), which showed continuing benefit from a calcium alone at 4 yr. One used a

supplement of 1600 mg in younger women (22), and the other studied both men and women, although no gender difference was detected (6). In contrast to the calcium-alone findings, the addition of 1000 IU vitamin D to calcium supplementation maintained hip BMD constant for 5 yr, especially in individuals with low 25OHD levels at baseline. Despite the beneficial effects of the combination of calcium and vitamin D on bone density, it should be pointed out that a recent metaanalysis of clinical trials has not demonstrated increased efficacy of the combination of calcium and vitamin D, compared with calcium alone on the important fracture prevention endpoint (23).

Although the participants were ambulant older women living in a sunny climate, about one third of them had vitamin D insufficiency or deficiency in winter and only 38% of participants had a plasma 25OHD concentration greater than 75 nmol/liter, the level suggested by some studies to optimize intestinal calcium absorption and prevent a rise in PTH (24–26). The basis of these suboptimal vitamin D levels is likely to be due to reduced sun exposure and the reduced ability of the skin to synthesize vitamin D (27), causing older people to be at increased risk of inadequate vitamin D production in the skin. Thus, these data support the concept of supplementation of calcium and vitamin D in elderly women, even in sunny climates such as Perth at 32° south, a similar latitude to San Diego in the Northern Hemisphere.

Mechanism

The mechanism of the effect of calcium and vitamin D is considered to be related to reducing bone turnover and suppressing PTH in individuals with relatively high PTH levels at baseline (28). Indeed, at 5 yr calcium alone was not as effective as the combination therapy in achieving either of these end points. It is possible that the lack of continued effectiveness was due to a bone remodeling transient (29). However, a previous report of beneficial effects of calcium on reducing fracture rates in the per protocol group consuming calcium argues against this (11). It is also possible that the beneficial effects of vitamin D in people with high calcium intake resulted from specific effects of 25OHD on reducing PTH production (30) or an effect on local formation of calcitriol in bone cells (31).

Intestinal calcium absorption

There were no significant differences among the three groups in fractional calcium absorption efficiency at baseline using a 10-mg carrier load reported previously as ungrouped data (14) or 4 months using a 600-mg calcium load test. Thus, increasing daily calcium intake and improving vitamin D status did not alter fractional calcium absorption at high calcium intakes. Because the calcium-supplemented patients were regularly exposed to higher calcium intakes than controls, the absolute amount of calcium absorbed was substantially greater, probably accounting for higher plasma calcium levels, lower fasting PTH, and lower bone turnover levels in these subjects.

At 24 months, the fractional absorption of the 10-mg calcium load was substantially lower in the CaD group than the control group. This is somewhat counterintuitive because reduced intestinal calcium absorption is considered to be one of the causes of age-related bone loss (32). One possible explanation is that in this study the reduction in active calcium absorption resulted from lower renal formation of calcitriol under the influence of lower PTH levels. Previously we reported that in a cross-sectional study, the 25OHD level was a major determinant of active intestinal calcium absorption (14). However, the current data argue against an effect of 25OHD on intestinal calcium absorption in calcium-supplemented patients. The current data are also different from findings by Heaney *et al.* (24), who reported substantially increased calcium absorption when vitamin D status was improved from 50.2 to 86.5 nmol/liter using supplemental 25OHD. Because the 25OHD levels in the study by Heaney *et al.* were about 20 nmol/liter lower than in the current study, it could be that the improvement observed in intestinal absorption by Heaney *et al.* was due to a shift of vitamin D status up to the level at which the current participants entered the study, thus supporting the known multifactorial nonlinear regulation of active calcium absorption.

There are several limitations to this study. Calcium absorption did not take account of losses of absorbed calcium to bone and urine. However, the lower bone turnover in the CaD group would, if anything, have reduced dilution of the tracer by bone calcium, giving a higher apparent calcium absorption. A lower circulating PTH in the CaD group would also allow a larger calciuresis, perhaps accounting for the lower tracer activity in the circulation. However, the higher concentrations of plasma calcium of the Ca and CaD groups, compared with the control group, at yr 1 and 3 indicated that these two treatment groups had higher circulating calcium levels as a result of supplementation.

The lack of a supplementation effect on the urine calcium creatinine ratio could be due to the ratio being determined from a second morning void urine sample taken after an overnight fast, and the calcium supplements were consumed with the morning and evening meals. Thus, the effect of the supplement may not be detectable at this time.

Another limitation of the study is that there was no vitamin D and placebo calcium group, and therefore, we cannot know whether the effects on hip BMD were due to the vitamin D alone or an interaction of vitamin D and calcium. However, a study in younger women aged 47–70 yr showed that 800 IU cholecalciferol per day for 2 yr had no effects on hip and spine BMD and heel ultrasound, compared with placebo (33). It should be noted that our study used ergocalciferol rather than cholecalciferol. Ergocalciferol has been reported to be less potent, unit for unit, in maintaining 25OHD levels in the circulation; therefore, the effect cholecalciferol on bone density could be greater (34).

Based on the findings of this study, we conclude that even in sunny climates the addition of vitamin D to high-dose calcium alone has long-term beneficial effects on bone density and turnover in elderly women.

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Address all correspondence and requests for reprints to: R. L. Prince, M.D., Department of Endocrinology and Diabetes, Sir Charles Gairdner

Hospital, Nedlands, Western Australia 6009, Australia. E-mail: rlprince@cyllene.uwa.edu.au.

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