Effect of Cholecalciferol Plus Calcium on Falling in Ambulatory Older Men and Women

A 3-Year Randomized Controlled Trial

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Background: A recent meta-analysis found that cholecalciferol (vitamin D) should reduce falls by more than 20%. However, little is known about whether supplemental cholecalciferol plus calcium citrate malate will lower the long-term risk of falling in men, active older individuals, and older individuals with higher 25-hydroxyvitamin D levels.

Methods: We studied the effect of 3-year supplementation with cholecalciferol-calcium on the risk of falling at least once in 199 men and 246 women 65 years or older and living at home. Individuals received 700 IU of cholecalciferol plus 500 mg of calcium citrate malate per day or placebo in a randomized double-blind manner. Subjects were classified as less physically active if physical activity was below the median level. Low 25-hydroxyvitamin D levels were classified as those below 32 ng/mL (<80 nmol/L).

Results: In 3 years, 55% of women and 45% of men reported at least 1 fall. Mean±SD baseline 25-hydroxyvitamin D levels were 26.6±12.7 ng/mL (66.4±31.7 nmol/L) in women and 33.2±14.2 ng/mL (82.9±34.9) in men. Cholecalciferol-calcium significantly reduced the odds of falling in women (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.30-0.97), but not in men (OR, 0.93; 95% CI, 0.50-1.72). Fall reduction was most pronounced in less active women (OR, 0.35; 95% CI, 0.15-0.81). Baseline 25-hydroxyvitamin D level did not modulate the treatment effect.

Conclusions: Long-term dietary cholecalciferol-calcium supplementation reduces the odds of falling in ambulatory older women by 46%, and especially in less active women by 65%. Supplementation had a neutral effect in men independent of their physical activity level.
calcium compared with placebo in older individuals living in the community. Subgroups of interest were men and women, active and less active individuals, and individuals with lower and higher baseline 25-OH-D levels.

METHODS

SUBJECTS

We enrolled healthy ambulatory men and women 65 years or older and living in the community. Of 848 persons who underwent prescreening with questionnaires, 545 were invited for screening. The final study sample included 445 individuals, of whom 430 were white, 11 were black, and 4 were Asian. All participants provided written informed consent, and the study protocol was approved by the Human Investigation Review Committee at Tufts University, Boston, Mass.

EXCLUSION CRITERIA

Subjects receiving therapy consisting of bisphosphonate, calcitonin, estrogen, tamoxifen citrate, or testosterone in the past 6 months or fluoride in the past 2 years; those with a history of renal disease or renal stone in the past 3 years; and those with current cancer, hyperparathyroidism, dietary calcium intake exceeding 1500 mg/d, or laboratory evidence of kidney (serum creatinine level, >1.2 mg/dL [>106.1 µmol/L]) or liver disease were excluded. Additional exclusion criteria were published previously.20

STUDY DESIGN

This was a 3-year double-blind placebo-controlled trial. The study was originally designed and powered to study the effect of cholecalciferol-calcium on bone mineral density.20 In this analysis, we study the effect of cholecalciferol-calcium on a secondary outcome of the original trial, a person’s risk of falling at least once during follow-up. Participants were randomly assigned to receive cholecalciferol (vitamin D3; 700 IU/d) plus calcium citrate malate (500 mg/d) or placebo. Random group assignment was performed with stratification according to sex, race, and decade of age.

Participants were asked to terminate any additional calcium or cholecalciferol supplements 2 months before the study start and throughout the study. Tablets in both groups had an identical appearance and were taken once daily at bedtime.

FOLLOW-UP AND COMPLIANCE

Of 445 subjects who were randomized, 389 attended the 3-year follow-up visit, and 318 were still receiving study medication at the 3-year follow-up visit. One hundred twenty-seven subjects had an identical appearance and were taken once daily at study start and throughout the study. Thirty-two subjects had fasted for at least 8 hours for measurement of plasma glucose (5 mmol/L). Baseline information on calcium and cholecalciferol intake was obtained by a food frequency questionnaire.22 For calcium intake, we used the average calcium intake across all follow-up visits. Baseline body mass index was measured as weight in kilograms divided by the square of the height in meters at the study center. Physical activity included leisure, household, and occupational activity as estimated by the Physical Activity Scale for the Elderly questionnaire.23 Scores on this questionnaire were previously found to be positively associated with grip strength \( r = 0.37 \), static balance \( r = 0.33 \), and leg strength \( r = 0.25 \) in older persons.23 We classified subjects as less physically active if their activity level was below the median of average physical activity (Physical Activity Scale for the Elderly score, 109) measured across time at each follow-up visit.

Falls were defined as “unintentionally coming to rest on the ground, floor, or other lower level.”21 The primary analysis included any first fall event. In a sensitivity analysis, we restricted the analyses further to persons with a low-trauma fall. Low-trauma falls were defined as occurring from a standing or sitting position; while standing, sitting, walking; and while walking and turning on ground level.

For the total number of falls, predefined fall categories were used in addition to the total sum of falls, including 1, 2, 3 or 4, and more than 4 times during the 3-year follow-up.

MEASUREMENTS

Throughout the 3-year trial, subjects were invited to the study center every 6 months for a follow-up visit (6 visits). Information on calcium and cholecalciferol intake was obtained by a food frequency questionnaire.22 For calcium intake, we used the average calcium intake across all follow-up visits. Baseline body mass index was measured as weight in kilograms divided by the square of the height in meters at the study center. Physical activity included leisure, household, and occupational activity as estimated by the Physical Activity Scale for the Elderly questionnaire.23 Scores on this questionnaire were previously found to be positively associated with grip strength \( r = 0.37 \), static balance \( r = 0.33 \), and leg strength \( r = 0.25 \) in older persons.23 We classified subjects as less physically active if their activity level was below the median of average physical activity (Physical Activity Scale for the Elderly score, 109) measured across time at each follow-up visit.

Tobacco use and use of alcoholic beverages were assessed by a questionnaire at baseline.

Comorbid conditions assessed at baseline with a questionnaire were summarized with a comorbidity score, which represents the sum of the following conditions: diabetes mellitus, hyperthyroidism, hypertension, cancer, low back surgery, previous hip fracture, and stomach surgery.

LABORATORY INVESTIGATIONS

Venous blood was collected between 7 and 9:30 AM, after the subjects had fasted for at least 8 hours for measurement of plasma 25-OH-D levels (by a competitive protein binding assay as described by Preece et al24) and serum intact parathyroid hormone levels (by immunometric assay; Nichols Institute, San Juan Capistrano, Calif). For the stratified analysis on baseline 25-OH-D levels, low serum 25-OH-D levels were defined as below 32 ng/mL (<80 nmol/L), which is a commonly used cutoff level.25,26 Baseline creatinine clearance was calculated as urinary creatinine concentration (in milligrams per deciliter) \times \text{urine volume (in milliliters)} /[\text{plasma creatinine (in milligrams per deciliter)} \times 1440 \text{minutes}].

STATISTICAL ANALYSIS

The main intent-to-treat analysis included 445 subjects. We used logistic regression to evaluate the effect of cholecalciferol-calcium compared with placebo on a person’s risk of falling at least once during the 3-year follow-up. This approach was chosen to be consistent with the outcome evaluated in the recent meta-analysis from our group.2 All analyses controlled for age in years, sex, baseline body mass index (<23, 23-29, or ≥30), average dietary calcium intake across time, baseline plasma 25-OH-D levels, baseline plasma intact parathyroid hormone levels, being less vs more active, baseline smoking status (never, current, or former smoker), baseline use of alcoholic beverages (yes or no), baseline use of tobacco products (yes or no), and use of hormone replacement therapy (yes or no) in the multivariate analysis. These factors were selected based on previous reports of their association with risk of falling. The statistical package used was SAS (version 8.2; SAS Institute, Cary, NC).
number of comorbid conditions, baseline creatinine clearance, and length of follow-up (in days). All 445 subjects underwent analysis, followed by subgroup analyses by sex, activity level, and baseline serum 25-OHD levels. Subgroup analyses were predefined on the basis of clinical considerations and previous findings. Because the study was not powered to detect effect modification, the interaction terms for sex, activity level, and baseline 25-OHD level did not reach statistical significance (treatment × sex, \( P = .25 \); treatment × activity level, \( P = .29 \); treatment × 25-OHD level, \( P = .71 \)).

We considered as a secondary outcome the occurrence of any low-trauma fall. Because the effect of cholecalciferol was similar to that of the analyses including all falls, only the results for the primary outcome are presented. All analyses were conducted with SAS statistical software (version 8.2; SAS Institute Inc, Cary, NC). All \( P \) values were 2 sided.

### RESULTS

Baseline characteristics were similar between assigned treatment groups among men and women (Table 1). Changes in plasma 25-OHD levels over time are presented by sex, activity level, and treatment in Table 2.

#### FALLS DURING FOLLOW-UP BY SEX AND ACTIVITY LEVEL

Overall, 97 men (49%) and 134 women (55%) fell during the 3-year follow-up. Of these, 123 (53%) of all first falls occurred in the first year, 62 (27%) in the second year, and 46 (20%) in the third year. Among women, 69...
(50%) of the less active and 65 (61%) of the more active individuals fell. Among men, 36 (46%) of the less active and 60 (50%) of the more active individuals fell.

**TREATMENT EFFECT DURING THE 3-YEAR FOLLOW-UP**

**Intent-to-Treat Analysis**

In 3 years, including men and women, 231 of 445 individuals reported at least 1 fall. Of these, 107 were in the cholecalciferol-calcium group and 124 were in the placebo group. In the multivariate analysis (Table 3), cholecalciferol-calcium did not significantly reduce the odds of falling compared with placebo in the total sample (odds ratio [OR], 0.77; 95% confidence interval [CI], 0.51-1.15).

Among women, 134 of 246 individuals reported at least 1 fall. Of these, 59 were in the cholecalciferol-calcium group and 75 were in the placebo group. In the multivariate analysis, cholecalciferol-calcium significantly reduced the odds of falling in women by 46% compared with placebo (OR, 0.54; 95% CI, 0.30-0.97). Fall reduction was most pronounced in less active women (OR, 0.35; 95% CI, 0.15-0.81) rather than in active women (OR, 1.06; 95% CI, 0.42-2.66).

Among men, 97 of 199 individuals reported at least 1 fall. Of these, 48 were in the cholecalciferol-calcium group and 49 were in the placebo group. In the multivariate analysis, cholecalciferol-calcium did not reduce the odds of falling in men compared with placebo (OR, 0.93; 95% CI, 0.50-1.72). Unlike the findings in women, we found no appreciable impact regarding the level of responsiveness to treatment in less active men (OR, 0.96; 95% CI, 0.34-2.67) compared with more active men (OR, 1.06; 95% CI, 0.42. 2.60).

Fall reduction by cholecalciferol-calcium was not enhanced further in individuals with low 25-OHD levels. If only subjects with 25-OHD levels of less than 32 ng/mL (<80 nmol/L) underwent analysis (64% of participants), this corresponded to an OR of 0.73 (95% CI, 0.43-1.25) vs 0.77 for the total sample. If only women with 25-OHD levels of less than 32 ng/mL underwent analysis (74% of women), this corresponded to an OR of 0.55 (95% CI, 0.28-1.10) vs 0.54 in all women. Similar results were achieved using a lower cutoff of 24 ng/mL (59.9 nmol/L) (39% of all participants).

**Per Protocol Analysis**

If analyses were restricted to individuals who continued to receive the study medication until the end of follow-up, the study sample included 318 subjects. In the per protocol analysis, receiving treatment enhanced the cholecalciferol-calcium benefit significantly for less active individuals, women, and especially less active women (Table 3).

### Creatinine Clearance, Intact Parathyroid Hormone Level, and Risk of Falling

Using creatinine clearance as a linear variable and a dichotomized variable (<65 or ≥65 mL/min | <1.1 or ≥1.1 mL/s], as suggested by Dukas et al27,28), we could not find that creatinine clearance predicted the risk of falling or modified the treatment effect of cholecalciferol-calcium. Similarly, we found no independent effect of parathyroid hormone on the incidence of falls.

**Time Course of Response to Treatment**

In Figure 1 and Figure 2, the time course of response to treatment is illustrated in 318 subjects who continued to receive treatment until the end of follow-up. Women and especially less active women who received cholecalciferol-calcium had lower rates of falls after 12 months of treatment.

**Treatment Effect on Total Number of Falls in 445 Individuals**

The total number of falls was similar between treatment groups for women (cholecalciferol-calcium, 164 falls among 121 women; placebo, 142 falls among 125 women) and men (cholecalciferol-calcium, 110 falls among 98 men; placebo, 110 falls among 101 men). The results in women are primarily due to the fact that most women who had more than 4 falls were in the cholecalciferol-calcium group. Those who fell frequently were equally distributed in the active women (2 women in the cholecalciferol-calcium group and 2 in the placebo group), whereas of the 6 inactive women who had more than 4 falls, 5 were in the cholecalciferol-calcium group.

**Table 3**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Intent-to-Treat Analysis (n = 445)</th>
<th>Per Protocol Analysis (n = 318)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample</td>
<td>0.77 (0.51-1.15) (n = 416)</td>
<td>0.68 (0.43-1.08) (n = 318)</td>
</tr>
<tr>
<td>Less active</td>
<td>0.60 (0.33-1.07) (n = 204)</td>
<td>0.42 (0.20-0.87) (n = 146)</td>
</tr>
<tr>
<td>More active</td>
<td>0.98 (0.54-1.77) (n = 212)</td>
<td>0.88 (0.46-1.68) (n = 172)</td>
</tr>
<tr>
<td>Women</td>
<td>0.54 (0.30-0.97) (n = 229)</td>
<td>0.44 (0.21-0.90) (n = 170)</td>
</tr>
<tr>
<td>Less active</td>
<td>0.35 (0.15-0.81) (n = 130)</td>
<td>0.26 (0.09-0.83) (n = 91)</td>
</tr>
<tr>
<td>More active</td>
<td>1.06 (0.42-2.66) (n = 99)</td>
<td>0.88 (0.31-2.35) (n = 79)</td>
</tr>
<tr>
<td>Men</td>
<td>0.92 (0.50-1.72) (n = 187)</td>
<td>0.84 (0.42-1.68) (n = 148)</td>
</tr>
<tr>
<td>Less active</td>
<td>0.96 (0.34-2.67) (n = 74)</td>
<td>0.65 (0.18-2.29) (n = 55)</td>
</tr>
<tr>
<td>More active</td>
<td>1.01 (0.43-2.40) (n = 113)</td>
<td>0.94 (0.37-2.38) (n = 93)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

*Controlling for age, sex, body mass index, average dietary calcium intake, baseline 25-hydroxyvitamin D levels, baseline intact parathyroid hormone level, activity level, smoking status, use of alcoholic beverages, number of comorbid conditions, creatinine clearance, and length of follow-up.

**COMMENT**

During this 3-year community-based study, supplementation with cholecalciferol-calcium significantly reduced the odds of falling by 46% among women, whereas no appreciable benefit was observed in men. This sex difference in response to cholecalciferol-calcium has not been addressed specifically in previous trials because primary...
ily women were studied. One explanation may be that ambulatory women have lower muscle strength and an increased susceptibility to falls than ambulatory men. Only among less active men who stayed on treatment could a possible benefit not be excluded. However, this result was not significant.

Cholecalciferol-calcium supplementation was more successful in reducing falls among less active individuals, and primarily among less active women with a 65% fall reduction. This benefit was enhanced among less active women who continued to receive treatment throughout the 3-year follow-up, leading to a 74% fall reduction. This may pos-

Figure 1. Cumulative percentage of falls by treatment group and sex. A. The women who received cholecalciferol (vitamin D) plus calcium citrate malate had lower rates of falls starting after 12 months and then throughout the follow-up compared with women in the placebo group. B. In men, both groups had similar rates of falls throughout the study.

Figure 2. Cumulative percentage of falls by treatment group and activity level. A. Less active women who received cholecalciferol (vitamin D) plus calcium citrate malate had lower rates of falls starting after 12 months and then throughout the follow-up compared with women in the placebo group. B. In more active women, both groups had similar rates of falls throughout the study. C and D. In less active (C) and more active (D) men, the rate of falls was not consistently lower in the cholecalciferol-calcium group or the placebo group.
sibly be related to lower muscle strength in less active women, but it cannot be attributed to lower 25-OHD levels because less active women did not have lower baseline 25-OHD levels than more active women. On the other hand, the relationship between activity level and treatment response is somewhat complicated by the observed increased frequency of falls in more active individuals in our study. An increased risk of falling in more active community-dwelling older persons has been described before, suggesting that more active older persons may put themselves at increased risk for falls simply through being more active, a mechanism that may not be affected significantly by cholecalciferol-calcium supplementation.

Based on our results, length of treatment with cholecalciferol-calcium may be an important factor. The treatment effect in women in our study increased with time and occurred primarily after 12 months of treatment. On the other hand, the short-term benefits of cholecalciferol-calcium on the risk of falling observed in 2 previous European RCTs may be explained by a combination of older age, increased frailty, and significantly lower baseline 25-OHD levels in their participants. In those 2 studies, with follow-up ranging from 3 to 12 months and including a total of 259 elderly women, a similar dose of cholecalciferol (800 IU/d) plus a higher dose of calcium carbonate (1200 mg/d) reduced the odds of falling by 33% (pooled OR, 0.65; 95% CI, 0.40–1.00) compared with calcium carbonate alone (1200 mg/d). With a 3-year follow-up, we documented a greater effect of cholecalciferol-calcium with a significant 46% fall reduction among women.

We did not find that lower baseline 25-OHD levels at any cutoff level (<24 ng/mL [<59.9 nmol/L] or <32 ng/mL [<80 nmol/L]) modified the treatment response of cholecalciferol-calcium in our study. This may be explained by the rather high mean baseline 25-OHD levels observed in our participants, which is likely owing to vitamin D fortification of dairy products and activity level of our healthy and relatively young community-dwelling older participants.

Total number of falls was not significantly reduced by cholecalciferol-calcium treatment in men or women. However, among women, this was primarily influenced by those who fell frequently and did not seem to benefit from treatment. Most women who fell more than 4 times during treatment were in the less active subgroup, suggesting that these women may have additional problems that make them fall independent of cholecalciferol-calcium therapy.

The strengths of this study include its double-blind, randomized, placebo-controlled design and its long-term follow-up. Although falls were a secondary outcome of the original trial, this end point was ascertained comprehensively through postcards and at every 6-month follow-up visit. This is important because falls tend to be forgotten if no injuries are involved. Our result for the overall sample is consistent with the previous crude findings based on 389 subjects in the original publication that found no significant benefit of cholecalciferol-calcium on the percentage of persons who fell. However, by focusing on predefined subgroups, we have demonstrated that women, and especially less active women, benefit significantly from cholecalciferol-calcium supplementation. The frequency of falls in our ambulatory study sample is representative of what has been reported in the literature. Also, the median level of physical activity is similar to what has been described before in the community-dwelling elderly population. Furthermore, in addition to the protection conferred by randomization, we were able to control for several potential confounders and variables known to influence the risk of falling in older persons. In addition, the per protocol analysis shows an enhanced treatment effect for the less active individuals, women, and especially less active women, which would be expected if there is a true treatment effect by cholecalciferol-calcium.

There are also limitations to our study. Our main findings pertain to subgroups, which is an approach that may be questioned because the trial was not originally powered to detect effect modification by sex, activity level, and baseline 25-OHD level. However, as stated in the introduction, our focus on these subgroups was based on previously reported data indicating that these subgroups may benefit differently from treatment. Moreover, generalizability may be limited to community-dwelling older persons.

Our results have clinical significance. First, we show a significant reduction in the odds of falling in ambulatory older women with a very inexpensive, well-tolerated, and simple supplementation with cholecalciferol-calcium. Second, our findings fit well with the results of the original trial, which showed a significant 60% reduction of osteoporotic fractures with cholecalciferol-calcium compared with placebo, with most of the fractures occurring in women. Third, the benefits of this intervention are similar to or greater than those of more expensive and more time-intensive interventions, such as medication adjustments and occupational therapy, and single-intervention strategies, such as tai chi balance training and exercise, that reduced the risk of falling from 23% to 50%.

In conclusion, cholecalciferol-calcium supplementation reduces falls by 46% to 63% in community-dwelling older women, but has a neutral effect on falls in men.

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