Alfacalcidol Reduces the Number of Fallers in a Community-Dwelling Elderly Population with a Minimum Calcium Intake of More Than 500 Mg Daily

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OBJECTIVES: To study the effect of alfacalcidol ($1\alpha(OH)D_3$) on fall risk in community-dwelling elderly men and women.

DESIGN: Randomized, double-blind, placebo-controlled intervention trial.

SETTING: Basel, Switzerland.

PARTICIPANTS: Three hundred seventy-eight community-dwelling elderly (191 women/187 men).

INTERVENTION: Participants were randomly assigned to receive 1 μg of alfacalcidol or matched placebo daily for 36 weeks.

MEASUREMENTS: Serum 25-hydoxyvitamin D_3 (25(OH) D, 1,25-dihydroxyvitamin D_3 (D-hormone), and intact parathormone (iPTH) levels were measured using radioimmunoassay at baseline and every 12 weeks. Numbers of fallers and falls were assessed using a questionnaire during each study site visit. Dietary calcium intake was assessed at baseline using a food frequency questionnaire.

RESULTS: At baseline, participants had, on average, normal vitamin D and D-hormone serum levels. Over 36 weeks, alfacalcidol treatment was associated with fewer fallers (odds ratio (OR) = 0.69, 95% confidence interval (CI) = 0.41–1.16) than placebo. In a post hoc subgroups analysis by medians of total calcium intake, this reduction reached significance in alfacalcidol-treated subjects with a total calcium intake of more than 512 mg/d (OR = 0.45, 95% CI = 0.21–0.97, $P = .042$) but not in those who consumed less than 512 mg/d (OR = 1.00, 95% CI = 0.47–2.11, $P = .998$). Alfacalcidol treatment was also, independent of total calcium intake, associated with a significant 37.9% reduction in iPTH serum levels ($P < .0001$). No cases of clinically relevant hypercalcemia were observed.

CONCLUSION: Provided a minimal calcium intake of more than 512 mg/d, alfacalcidol treatment significantly and safely reduces number of fallers in an elderly community-dwelling population. **J Am Geriatr Soc 52:230–236, 2004.**

Key words: alfacalcidol; elderly; fallers; falls

Increased occurrence of falling in the elderly together with increased skeletal fragility may have a larger effect on age-related increased frequency of fractures than bone mass alone.[1,2] The age-related increase in falls is strongly associated with a decline in muscle strength and, combined with increased bone fragility, is responsible for at least 90% of all hip fractures.[3] Several studies have demonstrated a strong relationship between bone mineral density and muscle strength.[4,5] These results suggest that some aspects of the age-related decrease in bone quality and muscle strength may be due to a common pathophysiological mechanism such as low serum concentrations of calcitriol (D-hormone).[6]

Most of the previously accepted normal plasma values for vitamins, including 25-hydoxyvitamin D ($25(OH)D_3$) or vitamin D and D-hormone, were established based on the concept of prevention of the classic deficiency diseases and not necessarily on functional parameters, but results from recent studies suggest that serum concentrations of $25(OH)D_3$ that are significantly above the classically defined vitamin D deficiency level of less than 12 ng/mL (30 nmol/L) still have a negative effect on bone metabolism and muscle strength.[7,8]

In developed countries, elderly people are at high risk of vitamin D insufficiency[9] due to reduced exposure to sunlight, decreased synthesis of $25(OH)D_3$ in the skin, and low vitamin D content in diet.[10] Furthermore, there is evidence that a significant number of elderly people, even with normal vitamin D serum levels (>12 ng/mL), may

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suffer from D-hormone deficiency[11–13] due to age-related decreased activity of renal 1-hydroxylase,[14,15] decreasing cofactors for activation of sex hormones[16] and insulin-like growth factors,[17] drug interaction,[18] or cytokine-induced interaction in chronic inflammatory diseases.[19] Several studies have also observed an age-related reduction in D-hormone sensitivity due to decreased quality of D-hormone receptors.[20,21] Low vitamin D and D-hormone levels have been associated with myopathy in several diseases[22,23] and are common in patients with hip fractures.[24] Low D-hormone serum concentrations are an independent risk factor for hip fractures.[25]

Previous randomized, controlled trials reported a reduction in the frequency of falls in institutionalized or osteopenic elderly women supplemented with vitamin D and calcium[26] or with calcitriol alone.[27] The authors are not aware of an elderly population-based study on prevention of falls. This study investigated for the first time whether treatment with alfacalcidol, a prodrug of the D-hormone calcitriol, reduces the number of fallers and falls in community-dwelling men and women.

METHODS

The participants of this study came mainly from the Basel Study,[28] a cohort study that has been running since 1959. During the summer of 2000, all Basel Study participants aged 70 and older (n = 410) received a written description of the study by mail and were invited to participate; 192 men and 82 women agreed to participate. Willing participants were followed up with a screening phone call to assess eligibility. Participants needed to be mobile and to have an independent life style to be included. Thirteen women and 11 men who volunteered met one or more exclusion criteria. Exclusion criteria were primary hyperparathyroidism (n = 0), polyarthritis or inability to walk (n = 3), calcium intake by supplement of more than 500 mg/d (n = 2), vitamin D intake of more than 200 IU/d (n = 10), active kidney stone disease (n = 1), history of hypercalcuria (n = 0) or cancer or other incurable diseases (n = 3), dementia (n = 1), elective surgery within the next 3 months (n = 4), severe renal insufficiency (creatinine clearance <20 mL/min) (n = 0), and fracture or stroke within the last 3 months (n = 0). Calcium supplementation of 500 mg/d or less was accepted (n = 10). Previous vitamin D supplementation of less than 200 IU/d was not an exclusion criteria, but participants were asked during the telephone interview 1 month before the study entry to stop their vitamin D supplementation, with the agreement of their physician. One hundred eighty-one men and 69 women satisfied the eligibility criteria and were enrolled. A sample size of 360 was required to detect a change of 20% with a error of 5%; therefore, the study recruited by means of a newspaper advertisement and follow-up telephone interview an additional 123 women and seven men aged 70 and older, who were selected according to the above-described inclusion and exclusion criteria. Thus, total number of recruited participants was 380: 192 women and 188 men. Two participants, one woman, and one man, refused after enrollment to take the drug and were excluded from the study. The intention-to-treat analysis included 191 women and 187 men.

The ethical review board of the University of Basel approved the study protocol. Written informed consent was obtained from each participant before enrollment. The Data, Safety and Monitoring Board, established by GWD Consult Germany, reviewed the conduct of the study.

Study Design

This was a 36-week double-blind, placebo-controlled, randomized trial. All investigators and staff conducting the study remained blinded throughout the treatment period. Participants were randomly assigned to 1 μg alfacalcidol (Alpha $D_3^{®}$ TEVA) or matching placebo once daily. Randomization was done using numbered containers. One hundred ninety-three participants were randomized to alfacalcidol and 187 to placebo. Administration of the prodrug alfacalcidol was deemed preferable to vitamin D supplementation for three reasons. First, its mechanism of action is independent of the renal 1-hydroxylase.[20] Second, alfacalcidol has been shown to be effective in the presence of vitamin D receptor (VDR) resistance.[20] Third, the risk of hypercalcemia appears to be lower with alfacalcidol than with calcitriol.[20] Calcium supplementation was not part of the intervention. An independent statistical group performed the blinding and randomization. None of the participants was receiving physical therapy or participating in training programs at study entry, and no attempt was made to alter subjects' diet or physical activity during the study. Baseline study site visit took place from September to October 2000 at the study center, University Hospital, Basel. After randomization (Day 0) participants began daily treatment with alfacalcidol or placebo and returned to the study center 4 and 12 weeks after randomization and every 12 weeks thereafter for a total of 36 weeks. Adverse reactions were reported to the study physician.

MEASUREMENTS

Fallers

Comparison of number of fallers in each treatment group, instead of number of falls, was used as primary outcome measurement, because, similar to persons who sustained a fracture compared with number of fractures,[29] persons who fall (number of fallers) is a stronger outcome than number of falls. Nevertheless, the results for number of falls are also presented. Secondary outcome measurements included muscle strength, balance, blood pressure, and bone quality. The results of the secondary outcomes will be published separately.

Data were collected using a nonvalidated interview-administered questionnaire on the incidence of falls at each visit. Falls were defined as unintentionally coming to rest on the ground, floor, or other lower level. Participants were asked to keep a diary of fall incidence and to inform the study center by a telephone call within 48 hours of a fall. If available, all case reports of fall incidents were collected with the permission of the participants from the house physician or hospitals. The study nurses received training in the use of the fall protocol (date, time, circumstances, injuries).

Health Measurements

On study entry, all participants underwent a physical examination and detailed medical history. Information on social history; medicine use; alcohol and tobacco use; physical activity; and self-report of osteoarthritis, rheumatoid arthritis, and low-back pain was obtained using a questionnaire. Comorbid conditions were evaluated using the Charlson Comorbidity Index.[30] Dietary calcium intake was estimated using a self-administered shortened form of a validated food-frequency questionnaire.[31] Total calcium intake was defined as dietary calcium intake plus calcium supplementation.

Laboratory Studies

At each visit, blood samples were obtained, and serum calcium and phosphate levels were measured using automated serum chemical analysis. At baseline, Week 12, and Week 24, serum concentrations of $25(OH)D_3$, 1,25 dihydroxyvitamin D (D-hormone), and intact parathormone (iPTH) were measured using radioimmunoassay (Nichols, San Juan Capistrano, CA); intra-assay variation was 5.1%, 5.0%, and 1.8%, respectively, and interassay variation was 7.9%, 10.8%, and 5.6%, respectively. All samples were immediately frozen at $-80^{\circ}C$ and analyzed by the same person, who was blinded to treatment group, in one batch. Twenty-four-hour urine calcium excretion was not measured.

Statistical Analysis

T test, Wilcoxon rank sum test, chi-square test, Fisher exact test, and analysis of covariance were used for group comparison at baseline. Baseline characteristics of patients lost to follow-up and incomplete measures were compared with patients with a complete data set.

Univariate tests for follow-up data (Wilcoxon rank sum tests) were used to evaluate median difference from baseline for laboratory investigations. A one-sample *t* test was used to assess whether change was significantly different from baseline, and comparison between the rates of change between the two groups were made using analysis of variance.[32]

The main follow-up multivariate analysis compared the number of fallers in the two treatment groups. Factors that reached significance level of $P<.1$ in a screening regression model were entered into a logistic regression model. Multivariate differences in number of fallers between treatment groups in both study periods are given as odds ratio (OR) with 95% confidence intervals (CI). The results presented are from multivariate-controlled intention-to-treat analyses. A 5% significance level was maintained throughout this analysis, and all tests were two-sided.

SAS, version 8.2 (SAS Institute Inc., Cary, NC), licensed to the University of Basel, Switzerland, was used for all analyses.

RESULTS

Baseline

The two treatment groups were comparable at baseline. Significant differences were found for aspirin and phenprocoumon use (Table 1). Average dietary calcium intake was low, with a mean intake ± standard deviation (SD) of 507 ± 144 mg/d. The proportion of men to women was the same in each treatment group. Major comorbid conditions

Table 1. Characteristics of the Study Participants at Baseline by Treatment Group

Characteristic	Placebo (n = 186)	Alfacalcidol (n = 192)	*P*-value
Male/female, n	90/96	93/99	.678
Age, mean ± SD	75.0 ± 4.1	75.0 ± 4.4	.961
Body mass index, kg/m^2, mean ± SD	26.7 ± 4.1	26.0 ± 3.6	.074
Laboratory, mean ± SD			
Intact parathormone, pg/mL	39.1 ± 24.5	36.9 ± 16.6	.303
D-hormone, pg/mL	39.1 ± 10.9	39.5 ± 12.0	.905
Calcidiol, ng/mL	28.3 ± 10.7	29.9 ± 11.6	.165
Albumin, g/L	42.3 ± 3.1	42.2 ± 2.7	.541
Creatinine clearance, mL/min.	78.0 ± 20.3	76.4 ± 19.3	.440
Drug intake, %			
Multivitamin use before the study	17.7	12.5	.155
Estrogen use	10.9	9.8	.656
Aspirin cardiac 100 mg	26.3	16.2	.015
Phenprocoumon	3.2	9.9	.009
Other variables			
Experiencing a fall or falls 3 months before study entry, %			
1 fall	13.4	5.2	.148
≥2 falls	1.6	2.1	
Daily dietary calcium intake, mg, mean ± SD	502 ± 138	512 ± 149	.499
Bone quality quantitative ultrasound,* T-score, mean ± SD	−0.66 ± 1.52	−0.94 ± 1.41	.057
Timed up and go test, seconds, mean ± SD	6.9 ± 1.6	6.9 ± 1.9	.918

* Calcaneus.
SD = standard deviation.

Table 2. Alfacalcidol Versus Placebo: Odds Ratio (OR) of Fallers and Falls Stratified by Medians of Total Daily Calcium Intake

Total Daily Calcium Intake*	Parameter Adjusted OR†	Multivariate Alfacalcidol vs Placebo	Number of Fallers/Falls (95% Confidence Interval)	*P*-value
Upper median	Fallers	0.45 (0.21–0.97)	16/26	.042
≥ 512 mg/d	Falls	0.46 (0.22–0.99)	18/29	.045
Lower median	Fallers	1.00 (0.47–2.11)	24/20	.998
<512 mg/d	Falls	1.09 (0.53–2.30)	28/22	.794

* Total daily calcium intake = daily dietary calcium intake plus calcium supplementation.
† Adjusted for age, sex, body mass index, creatinine, creatinine clearance, intact parathormone and albumin serum levels, comorbidities, coffee intake, and previous falls.

were equally distributed between treatment groups (data not shown).

A small number of participants (1.6% of the women and 3.7% of the men) had $25(OH)D_3$ serum levels below 12 ng/mL (30 nmol/L), which is the accepted threshold for vitamin D deficiency;[11,33,34] 15.1% of the women and 29.3% of the men were calcitriol deficient, defined according to the laboratory of the University Hospital, Kantonsspital, Basel, as calcitriol serum levels below 30 pg/mL; and 4.2% of the women and 6.9% of the men fulfilled criteria for secondary hyperparathyroidism, namely increased iPTH levels (iPTH ≥65 pg/mL) and normal serum calcium levels (data not shown). Three men and seven women reported calcium supplementation of 500 mg/d at study entry.

Follow-Up

Of the 378 participants enrolled, 321 (84.3%; 158 women (82.7%) and 163 men (87.2%)) completed the study, with no difference in completion rate between treatment groups (placebo 83.3% vs alfacalcidol 86.5%, $P = .649$). There were two deaths during the study: one man on placebo, who had long-standing heart disease and died from myocardial infarction, and one man on alfacalcidol, who had influenza and died from pneumonia and subsequent hepatitis ($P = .982$).

Fallers

The multivariate analyses included predictors that have been shown to be associated with increased risk of falling or variables that were significantly different between treatment groups. These variables were age, sex, body mass index, serum creatinine, creatinine clearance (mL/min), number of falls in previous 3 months, physical activity (sport:yes/no), Charlson Comorbidity Index, number of medications at baseline, dietary calcium intake, heart rate at baseline (<80 beats/min vs ≥80 beats/min), serum iPTH (pg/mL) and albumin (g/L) at baseline, and coffee intake. Number of falls in the 3 months before study entry did not reach significance.

In the multivariate-adjusted logistic regression analyses, treatment with alfacalcidol over 36 weeks was associated with nonsignificant fewer fallers (OR = 0.69, 95% CI = 0.41–1.16) than placebo. In subgroup analyses, subjects were stratified according to medians of total daily calcium intake. In subjects who consumed more than 512 mg of calcium daily, alfacalcidol was associated with significantly fewer fallers than placebo (OR = 0.45, 95% CI = 0.21–0.97, $P = .042$). This relationship was not seen in subjects consuming less than 512 mg/d of calcium (OR = 1.00, 95% CI = 0.47–2.11, $P = .998$) (Table 2 and Figure 1). Similar results were found for number of falls (Table 2). In the sex-stratified analyses of the subgroups of total calcium intake, no significant difference was found between women and men in number of fallers (data not shown).

Effect of Alfacalcidol on Metabolism

After 12 weeks an average significant decrease of serum iPTH levels of 32.5% ($P < .0001$) was observed in all participants treated with alfacalcidol, followed, after another 12 weeks of observation, by a further significant 5.4% decrease ($P < .01$) (iPTH decrease baseline to week 24: 37.9%, $P < .0001$) (Figure 2). However, in the placebo group, a significant increase of iPTH levels of +5.4% ($P < .0001$) during 24 weeks of observation was observed (Table 3 and Figure 2). This observed effect of alfacalcidol on serum iPTH levels was independent of daily calcium intake. In both subgroups, after 24 weeks of intervention with alfacalcidol treatment, a significant decrease in serum

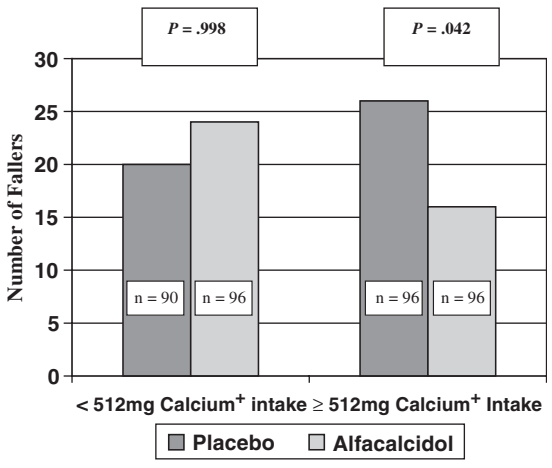

Figure 1. Number of fallers in 36 weeks according to treatment group by total calcium intake.

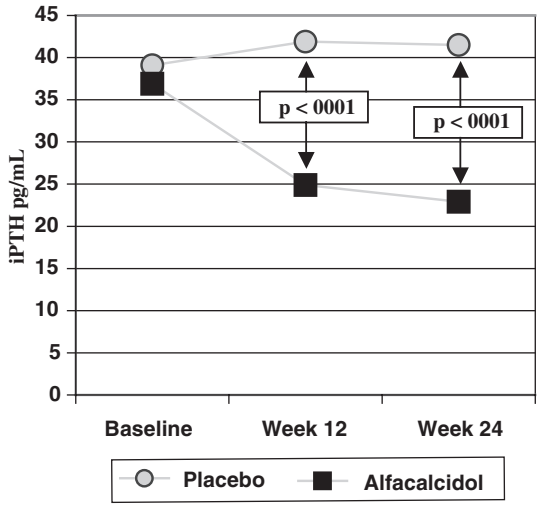

Figure 2. Intact parathormone (iPTH) serum levels during 24 weeks of observation according to treatment group.

iPTH levels ($\geq$512 mg/d calcium intake: iPTH mean $\pm$ standard deviation from 37.7 ± 19.0 to 24.1 ± 11.8 pg/mL, $P < .0001$; $<$512 mg/d calcium intake: iPTH mean from 36.0 ± 13.9 to 21.1 ± 7.5 pg/mL, $P < .0001$) and, with placebo, a significant increase of iPTH levels ($\geq$512 mg/d calcium intake: iPTH (mean from 38.9 ± 26.7 to 40.6 ± 27.8 pg/mL, $P = .005$; $<$512 mg/d calcium intake: iPTH (mean from 39.2 ± 17.4 to 42.4 ± 18.2 pg/mL, $P < .001$) were observed. Treatment with alfacalcidol was also associated with a significant increase in serum calcium levels within the normal range, whereas in the placebo group, serum calcium levels did not change. In both treatment groups a significant increase in phosphate serum levels was observed (Table 3). Similar results were observed in changes of serum levels of calcium and phosphate when stratified by medians of total calcium intake and by sex (data not shown).

Adverse Events and Side Effects

During the 36 weeks of intervention, six cases (1 in the placebo group and 5 in the alfacalcidol group) of slight transient hypercalcemia (one measurement of serum calcium above normal with subsequent (1 week later) control measurement within normal ranges) were observed, the highest value measured being 2.73 mmol/L (normal range 2.10–2.65 mmol/L). Two participants in the alfacalcidol group after 12 weeks of intervention continuously until the end of the study developed elevated calcium levels (highest value 3.00 mmol/L), without clinical symptoms. One of these participants admitted at the end of the study to having taken supplementary calcium (1,000 mg/d). The difference in the incidence of hypercalcemia between study groups was not significant ($P = .0621$). Furthermore, no differences were observed in the frequency of major diseases occurring during the 36 weeks between treatment groups and no cases of serious adverse events attributable to alfacalcidol treatment. Frequency of reported side effects was equally distributed between treatment groups (82 cases in placebo vs 75 cases in alfacalcidol, $P = .850$). The most common side effects were itching (placebo treatment group: 23 cases; alfacalcidol treatment group: 22 cases) and skin eruption (placebo treatment group: 11 cases; alfacalcidol treatment groups: 15 cases).

DISCUSSION

The results of this study show for the first time that treatment with alfacalcidol reduces the number of fallers and number of falls in an elderly population with a minimum calcium intake of 512 mg/d or more, and independent of calcium intake, decreases parathyroid hormone secretion, increases serum calcium concentrations within the normal range, and is safe.

Because, in the elderly population within industrial countries, low bone mineral mass is universal, it can be argued that falling becomes the major determinant of fractures in these subjects.[35] Among the most important mechanisms involved in locomotoric nonsyncopal falls in

Table 3. Serum Biochemical Values at Baseline and After Follow-Up According to Treatment Groups

Characteristic	Baseline	Follow-Up	*P*-value*
	Mean $\pm$ Standard Deviation		
Serum intact parathormone, pg/mL (normal $<$65 pg/mL)			
Placebo	39.1 $\pm$ 24.5	41.2 $\pm$ 23.3	$<$.0001
Alfacalcidol	36.9 $\pm$ 16.6	23.2 $\pm$ 10.1	
Serum calcium, mmol/L (normal 2.10–2.65 mmol/L)			
Placebo	2.31 $\pm$ 0.10	2.31 $\pm$ 0.09	$<$.001
Alfacalcidol	2.31 $\pm$ 0.10	2.36 $\pm$ 0.13	
Serum phosphate, mmol/L (normal 0.80–1.50 mmol/L)			
Placebo	1.00 $\pm$ 0.19	1.06 $\pm$ 0.17	.458
Alfacalcidol	0.99 $\pm$ 0.20	1.07 $\pm$ 0.18	

* *P*-value for differences in changes over time between treatment groups, controlled for age and sex.

the elderly are probably vitamin D insufficiency, low calcitriol serum concentrations, reduced calcitriol action,[20,36] high serum iPTH levels, and calcium deficiency. The response to D-hormone deficiency is a negative calcium balance that stimulates iPTH secretion. Several,[37–40] but not all, studies[41] have demonstrated a beneficial effect of vitamin D[37,38] and its metabolites[39,40] on muscle strength and balance. This inconsistency may be due to differences in the amount of daily calcium intake, which was supplemented in two of these studies[37,39] but not assessed in the two other studies.[38,40] Similar to the current study, daily calcium intake was low in another study,[41] which did not find an association between calcitriol and muscle strength. Calcitriol, the active metabolite of vitamin D, mediates the effects of vitamin D on muscle because there are specific receptors for calcitriol in muscle tissue.[21,42] The results of the current study suggest that a synergistic effect of calcitriol and a minimal intake of calcium, which in this study was 512 mg/d or greater, is required to observe an effect on muscle. In calcium-replete subjects, the role of a synergistic effect of calcitriol and calcium may explain the prevention of falls.

Another randomized, controlled trial found an association between supplementation of vitamin D with calcium and the reduction of number of fallers or falls in institutionalized women.[26] Two recent studies described a significant decrease in the number of falls and the incidence rate of falls after 3 years of treatment with 0.5 μg calcitriol daily in osteopenic elderly women without vitamin D deficiency and with a daily calcium intake greater than 750 mg.[27,43]

In this study, for the first time, the efficacy of D-hormone on reduction of number of fallers was investigated in both sexes. No significant difference between women and men in subgroups of calcium intake was observed in response to alfacalcidol treatment.

Interestingly, in this study, a significant effect of alfacalcidol treatment on prevention of fallers and falls was observed only in participants with a daily calcium intake of 512 mg or more. Dietary calcium intake in this study group was generally low, with an average intake of 507 mg/d. Reduced dietary calcium intake is common in the elderly.[44] A double-blind, randomized trial[45] compared the effect of vitamin D supplementation without calcium with placebo and found no difference in fracture incidence in elderly women. In another study,[46] vitamin D plus calcium supplementation reduced fracture incidence in elderly institutionalized women with marked vitamin D deficiency. It is not clear whether the difference in outcome is primarily due to calcium supplementation, because the vitamin D dosage and $25(OH)D_3$ serum levels at baseline also differed in the two studies, but these results,[45,46] as well as the data presented in this paper, support the physiologically plausible hypothesis that treatment with vitamin D or D-hormone analogs requires a minimum daily calcium intake of more than 500 mg/d to modify calcium metabolism sufficiently to demonstrate clinically significant effects.

The expected effect of D-hormone supplementation on parathyroid metabolism was observed, in that significant iPTH levels decreased in all participants treated with alfacalcidol, independent of daily calcium intake. In addition to providing evidence of good compliance with the intervention, an increasing body of evidence[47,48] suggests that the observed decrease in serum iPTH levels may have a direct relationship with the improved outcome seen in the treatment group with a minimal total calcium intake of 512 mg/d or more; serum iPTH levels have been shown to be inversely related to muscle strength and endurance, because of atrophy of fast-twitch muscle fibers, decrease of energy metabolism in skeletal muscle, and proteolysis of muscle proteins.[47,48] High normal iPTH levels have been associated with subclinical myopathy.[7] These findings[7,47,48] suggest that PTH is an independent risk factor for decreased muscle strength and for falls,[49] but the current study's results suggest that a positive effect of decreasing iPTH serum levels on falls is dependent on a minimal calcium intake of 512 mg/d or more, because in the current study, a decrease of serum iPTH levels in participants with calcium intake of less than 512 mg/d was not associated with a decrease in number of fallers or falls.

The positive effect of alfacalcidol on reduction of number of fallers was not due to correction of age-related clinical vitamin D deficiency as seen in many other studies, because nearly all participants had "normal" vitamin D serum levels at baseline. Rather, alfacalcidol in combination with a minimum calcium intake of 512 mg/d or more seems to act as a pharmacological treatment with an effect on muscle power or neuromuscular coordination, as has been demonstrated by other authors.[38,39,50] Future investigations should focus on understanding the precise mechanism of this effect.

This study had several limitations. The participants were Caucasian community-dwelling men and women aged 70 and older, so the findings are not generalizable to a younger population, to institutionalized elderly, or to men and women of other races. The study had limited power to evaluate the risk of falling according to quartiles and tertiles of calcium intake or changes in iPTH. Assessment of risk factors for falls and the large majority of incidence of falls during the study were based only on the participant's own report. Finally, significant results were found only in subgroup analyses.

In conclusion, 36 weeks of daily treatment with alfacalcidol was safe and, with a minimum calcium intake of 512 mg/d, decreased the number of fallers in a community-dwelling elderly population.

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