Clinical and Laboratory Safety of One Year's Use of a Combination Calcium + Vitamin D Tablet in Ambulatory Elderly Women with Vitamin D Insufficiency: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Objective: This article presents the results of an evaluation of the clinical and laboratory safety of a 1-year course of treatment with a combination calcium and vitamin D tablet in ambulatory women aged >65 years with vitamin D insufficiency.

Methods: In a multicenter, randomized, double-blind, placebo-controlled study conducted in France, women with a 25-hydroxyvitamin D level ≤12 ng/mL were randomized to receive either a combination tablet containing calcium carbonate 500 mg and vitamin D_3 400 IU taken twice daily or a matching placebo tablet for 1 year. A complete clinical examination was performed at baseline and at 3, 6, 9, and 12 months of treatment; blood and urine samples were collected for laboratory analyses at the same time points. Safety was monitored based on adverse events recorded during the treatment period and on the results of laboratory tests, including measurement of creatinine and uric acid levels.

Results: The study included 192 women (mean [SD] age, 74.6 [6.9] years; mean weight, 64.0 [12.5] kg), 95 in the calcium + vitamin D group and 97 in the placebo group. Fifty women (21/95 [22.1%] calcium + vitamin D, 29/96 [30.2%] placebo) were prematurely withdrawn from the study for various reasons, with no difference in withdrawals between groups. Treatment-related adverse events were reported in 21 (22.1%) and 23 (24.0%) women in the respective treatment groups. These events consisted mainly of metabolic disorders (9 [9.5%] and 10 [10.4%], respectively), particularly hypercalcemia (6 [6.3%] and 8 [8.3%]) and gastrointestinal disorders (9 [9.5%] and 8 [8.3%]). No major complications directly related to calcium and vitamin D supplementation occurred during the course of treatment. Although renal function was not altered, the group who received calcium + vitamin D had significantly elevated concentrations of serum uric acid compared with those who received placebo (52.3% vs 37.2%; $P = 0.046$) but not urinary uric acid.

Conclusions: In these ambulatory elderly women with vitamin D deficiency, supplementation with calcium + vitamin D appeared to be well tolerated over 1 year of treatment. No significant effects on creatinine clearance were observed. However, the proportion of women with elevated serum uric acid concentrations was significantly greater in those who received calcium + vitamin D compared with those who received placebo. (*Clin Ther.* 2005;27:1885–1893)

Key words: calcium, vitamin D, aged, women, long-term effects.

INTRODUCTION

Calcium and vitamin D are essential to bone health. Low calcium intake is one of the main risk factors for

Accepted for publication October 3, 2005.
doi:10.1016/j.clinthera.2005.12.010
0149-2918/05/$19.00

osteoporosis,[1] and a lack of vitamin D can result in osteomalacia.[2] As a result of reduced exposure to ultraviolet light (<2 hours/d) and/or inadequate dietary intake of vitamin D (<400 IU/d), ~50% of women aged >65 years present with vitamin D insufficiency.[3,4] Osteoporosis and osteomalacia are associated with hip fracture, a major health problem among the elderly, particularly women.[5–7]

Long-term (1–3 years) supplementation with calcium and vitamin D delays the development of osteoporosis and prevents peripheral fractures in the elderly.[8–10] This antifracture effect is mediated mainly by an increase in bone mineral density[11] associated with a decrease in bone remodeling.[12] The prevalence of vitamin D insufficiency is well documented in France, as well as in countries at higher latitudes.[13,14] Linked to a lack of sun exposure, vitamin D insufficiency is common in elderly institutionalized patients but can begin earlier in adulthood, with a positive northward geographic gradient.[13,14] Despite the fact that regular calcium and vitamin D supplementation is common among both elderly and younger populations, a literature search identified few studies that focused on the long-term safety of such supplementation.[15,16] In the study by Honkanen et al,[16] administration of calcium 1.558 g/d and vitamin D 1800 IU/d for 11 weeks in 25 independently living and 30 institutionalized elderly women was associated with no adverse effects on safety indicators (serum calcium and creatinine).

This article assesses the clinical and laboratory safety of a 1-year course of treatment with a combination of calcium + vitamin D in ambulatory women aged >65 years with vitamin D insufficiency. Because of vitamin D's mechanism of action—strong urinary excretion of calcium and correction of secondary hyperparathyroidism—particular attention was paid to renal function.

PATIENTS AND METHODS

Patients

This study included community-dwelling ambulatory women aged >65 years who spontaneously consulted a practitioner and presented with vitamin D insufficiency (ie, serum 25-hydroxy vitamin D [25(OH)D] ≤12 ng/mL). Exclusion criteria were hypercalcemia (serum calcium [sCa] >2.62 mmol/L), primary hyperparathyroidism, renal insufficiency (serum creatinine [sCr] >130 μmol/L), or hepatic insufficiency. In addition, women who had received a bisphosphonate, calcitonin, vitamin D or its metabolites, estrogen, raloxifene, fluoride, anticonvulsives, or any other treatment acting on bone metabolism (eg, glucocorticoids) in the past 6 months were excluded from the study.

Each woman provided written informed consent before being included in the study. A local ethics committee approved the protocol, and the trial was conducted in accordance with the Declaration of Helsinki, the Huriet law, and good clinical practice guidelines.

Study Design

This randomized, double-blind, placebo-controlled trial was conducted at 50 centers in 10 administrative regions throughout France. At each center, women were randomly allocated (4-block equilibrated randomization) to receive a single tablet* containing elemental calcium (calcium carbonate 500 mg) + vitamin D_3 (cholecalciferol 400 IU) or a placebo tablet twice daily for 1 year. The primary objective of the study was to assess the effects of treatment on bone mineral density and biochemical markers of bone formation and resorption. Its secondary objective was to evaluate the clinical and laboratory safety of treatment. This article presents the results of the safety evaluation.

Immediately before their inclusion in the study, participants' daily dietary calcium and vitamin D intakes were assessed using validated food-frequency questionnaires.[17,18] Treatment compliance was assessed at each visit based on counts of the number of tablets taken compared with the number that was to be taken.

Clinical Safety Assessment

Clinical safety was evaluated in terms of spontaneously reported and observed adverse events. The investigators assessed the causal relationship between each adverse event and study treatment. Adverse events leading to premature discontinuation and serious adverse events were recorded, even if they were not considered possibly related to treatment. Hypercalcemia (sCa >2.7 mmol/L), hypercreatininemia (sCr >130 μmol/L), and calcic lithiasis were considered adverse events and constituted cause for withdrawal from the study. All adverse events occurring during treatment were required to be reported immediately to a central site.

*Trademark: Ideos® (Innothera Laboratories, Arcueil, France).

A complete clinical examination (height, weight, vital signs) was performed at baseline and at 3, 6, 9, and 12 months of treatment. Blood pressure was measured using a sphygmomanometer on the dominant arm with the patient in a resting position. Grip strength in the dominant arm was measured using a dynamometer (Martin-Vigometer, Paris, France).

Laboratory Safety Assessment

The laboratory parameters focused on measures of renal function—sCr, urinary creatinine (uCr), serum uric acid (sUA), and urinary uric acid (uUA) levels. However, measures of calcium homeostasis were also assessed—serum 25(OH)D, intact parathyroid hormone (i-PTH), sCa, and urinary calcium (uCa) levels.

Blood and urine samples were collected at baseline and after 3, 6, 9, and 12 months of treatment. Fasting blood samples were obtained by venipuncture. Serum was separated and frozen at –80°C until assayed. The previous day's 24-hour urine samples were collected, frozen, and stored at –80°C until assayed.

Serum 25(OH)D was measured using a competitive protein-binding assay after ethanol extraction followed by chromatographic purification.[19] Serum i-PTH was measured using an immunoluminometric assay (Magic Lite intact PTH, Ciba-Corning, Cergy Pontoise, France). sCa, sCr, and sUA were measured by colorimetric methods using an automated system (Ektachem 500 autoanalyzer, Johnson & Johnson, Rochester, New York). sCa was expressed as mmol/L (1 mmol/L = 4 mg/dL). Interassay reproducibility, expressed as percent coefficient of variation, was 10.8% for 25(OH)D and <2% for the other parameters. uCa, uCr, and uUA were measured in 24-hour samples. Calcium excretion was expressed as the ratio of 24-hour uCa to uCr (uCa:uCr), and true creatinine clearance (CrCl) and uric acid clearance (UA Cl) were calculated as 24-hour urinary flow × serum/urine concentration. These assays were performed by colorimetric methods using an automated system (Ektachem 500 autoanalyzer). The interassay reproducibility, expressed as percent coefficient of variation, was <5%.

Statistical Analysis

Statistical analysis was carried out using SAS version 6.12 (SAS Institute Inc., Cary, North Carolina). The results are expressed as numbers and percentages for qualitative variables, and as mean (SD), median, first quartile, and third quartile for quantitative variables. Medians were preferred to means in the case of nonnormal distribution (all laboratory values were considered to have nonnormal distribution). Comparisons between groups were performed using parametric tests (Student t test and χ^2 test) and nonparametric tests (Wilcoxon signed-rank test and Wilcoxon rank sum test). The correlations between laboratory parameters were studied. Two-sided tests were performed with a type 1 error set at 5%. The study had 73% power to detect a significant difference in bone mineral density at L2-L4.

The reference values for calcium homeostasis (25[OH]D, i-PTH, sCa, and uCa) had been determined previously in a similar population (women aged >65 years with vitamin D insufficiency),[20,21] and values outside the normal range were defined by the usual upper or lower thresholds of the laboratory. Threshold values were as follows: 25(OH)D ≤12 ng/mL; i-PTH >54 pg/mL; sCa >2.62 mmol/L; sUA >340 µmol/L; sCr >130 µmol/L; 24-hour uCa:uCr >6.25 mmol/24 hours; uUA >3.5 mmol/L; CrCl <80 mL/min; and UA Cl <6 mL/min or >9 mL/min.

RESULTS

Patient Population

Of the 360 women recruited, approximately half were excluded from the study, mainly because baseline 25(OH)D levels were above the threshold of ≤12 ng/mL for hypovitaminosis D (**Figure**). The study included 192 women who met all inclusion criteria, 95 in the group that received calcium + vitamin D and 97 in the group that received placebo (**Table I**). Baseline characteristics were comparable in the 2 study groups. Vitamin D and calcium intakes were low in both groups, usually lower than the recommended daily intake (at least 200 IU/d and 1500 mg/d, respectively). Premature withdrawal occurred in 21 (22.1%) women who received calcium + vitamin D and 29 (30.2%) women who received placebo (n = 96 in the placebo group, as 1 woman did not receive at least 1 dose), with no difference in withdrawals between groups. The withdrawals were mainly the result of adverse events or the patient's request.

Compliance at each visit ranged from a median of 93.0% to 94.0% in the calcium + vitamin D group and from 93.0% to 96.5% in the placebo group. Global compliance was 92.0% in the calcium + vitamin D group and 92.5% in the placebo group. No significant difference in compliance was observed between the 2 groups at any visit.

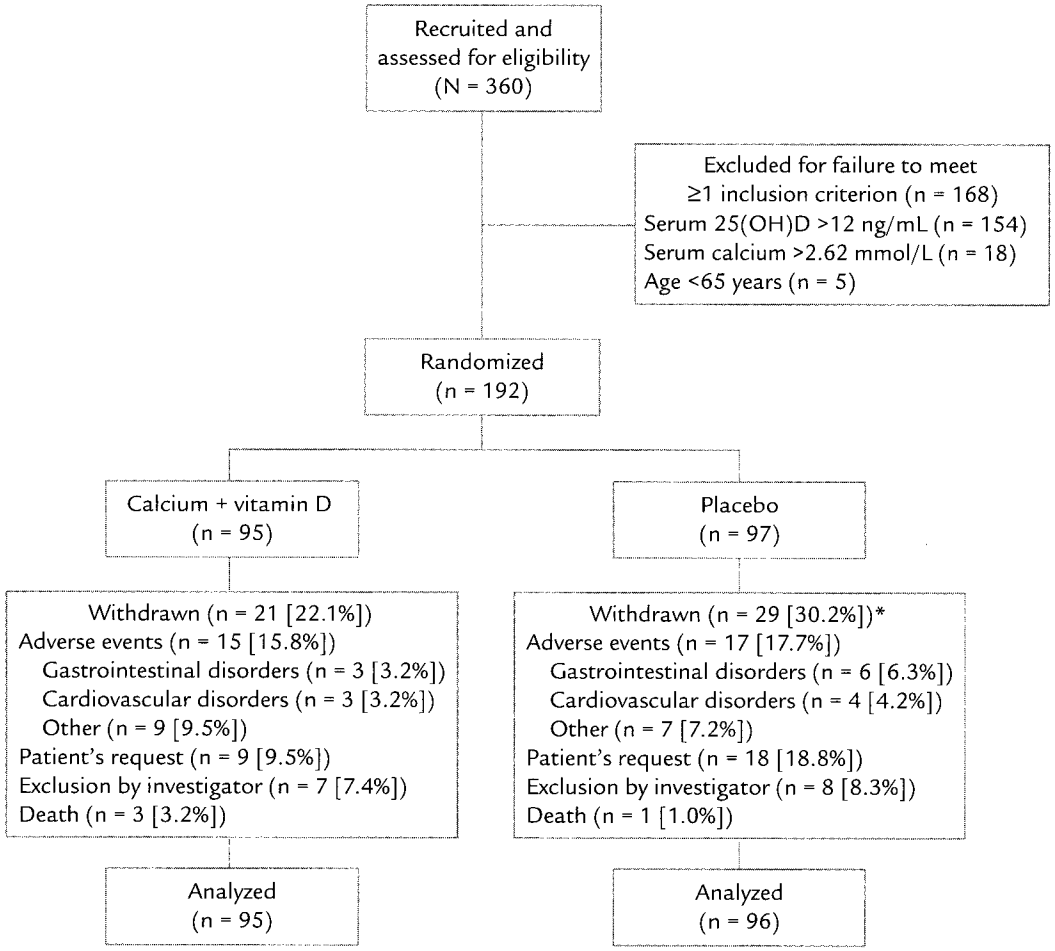

Figure. Flow of subjects through the study. 25(OH)D = 25-hydroxyvitamin D. *One patient in the placebo group was withdrawn from the study before intake of the first dose and was excluded from analysis. Therefore, the percentages that follow were calculated based on 96 patients.

Clinical Safety

The number of adverse events overall was 187 in the calcium + vitamin D group and 170 in the placebo group. There was no significant difference between groups in terms of the number of patients who experienced ≥1 adverse event (mean [SD], 69 [72.6%] calcium + vitamin D, 70 [72.9%] placebo), ≥1 serious adverse event (14 [14.7%] and 12 [12.5%], respectively), ≥1 adverse event leading to premature study discontinuation (15 [15.8%] and 17 [17.7%]), or ≥1 adverse event possibly related to study treatment (21 [22.1%] and 23 [24.0%]) (**Table II**).

Adverse events leading to premature discontinuation mainly affected the gastrointestinal and cardiovascular systems (**Figure**). Gastrointestinal adverse events in the calcium + vitamin D group included 2 cases of dyspepsia and 1 of abdominal pain; in the placebo group, there were 2 cases of nausea, 2 of gastrointestinal bleeding, 1 of dyspepsia, and 1 of gastritis. Cardiovascular adverse events leading to premature discontinuation in the calcium + vitamin D group included 2 cases of myocardial infarction and 1 case of stroke; in the placebo group, there were 2 cases of pulmonary edema, 1 of auricular fibrillation, and 1 of stroke. Two women from the calcium + vitamin D group and none in the placebo group were withdrawn from the study because of hypercalcemia. Three deaths occurred in the calcium + vitamin D group: a 93-year-old woman died suddenly at home, and a 91-year-old woman with angina pectoris and a 71-year-old woman died of myocardial infarction. The latter patient had previously under-

Table I. Baseline characteristics of study participants. Values are mean (SD), with the exception of laboratory parameters, which are medians.

Characteristic	Calcium + Vitamin D (n = 95)	Placebo (n = 97)	Overall (N = 192)
Age, y	74.2 (6.4)	75.0 (7.3)	74.6 (6.9)
Weight, kg	65.2 (12.4)	62.8 (12.6)	64.0 (12.5)
Body mass index, kg/m^2	27.0 (4.4)	26.4 (4.3)	26.7 (4.3)
Systolic blood pressure, mm Hg	138.5 (11.3)	138.0 (13.8)	138.3 (12.6)
Diastolic blood pressure, mm Hg	77.9 (8.7)	77.1 (9.4)	77.5 (9.1)
Heart rate, beats/min	72.4 (7.2)	72.7 (9.0)	72.6 (8.2)
Grip strength (dominant hand), kPa	63.6 (16.2)	62.3 (17.2)	62.9 (16.7)
Dietary calcium intake, mg/d	751.7 (382.7)	720.8 (337.1)	736.0 (369.6)
Dietary vitamin D intake, IU/d	84.9 (74.3)	83.9 (66.9)	84.4 (70.4)
Bone mineral density at L2-L4,* g/cm^2	0.937 (0.169)	0.889 (0.155)	Not calculated
Laboratory parameters†			
25(OH)D, ng/mL	7.3	7.0	7.0
i-PTH, pg/mL	49	49	49
sCa, mmol/L	2.17	2.19	2.18
sUA, µmol/L	285	280	284
Creatinine, µmol/L	61	64	62
uCa, mmol/24 h	2.47	2.35	2.42
uUA, mmol/24 h	2.1	1.7	1.8
CrCl, mL/min	65.9	61.1	62.1

25(OH)D = 25-hydroxy vitamin D; i-PTH = intact parathyroid hormone; sCa = serum calcium; sUA = serum uric acid; uCa = urinary calcium; uUA = urinary uric acid; CrCl = creatinine clearance.
*Numbers of patients in the respective treatment groups were 78 and 78 for this parameter.
†Numbers of patients in the respective treatment groups were 92 and 85 for these parameters.

gone gastrectomy for gastric neoplasia and had been hospitalized for severe psychiatric and gastric problems probably resulting from cerebral metastasis. In the placebo group, a 91-year-old woman with angina pectoris presented with fatal acute pulmonary edema. All of these events were considered unrelated to treatment. In both groups, adverse events possibly related to study treatment were mainly metabolic and nutritional disorders (notably, hypercalcemia) or gastrointestinal disorders of mild or moderate intensity.

No clinically significant changes in weight, blood pressure, heart rate, or grip strength were observed during the study. No major complications directly related to calcium + vitamin D supplementation occurred during the course of treatment.

Laboratory Safety

Laboratory values at the end of treatment are presented in **Table III**. With regard to calcium homeostasis, after 1 year of treatment, >90% of women in the calcium + vitamin D group had 25(OH)D levels above the threshold for hypovitaminosis D. Approximately 20% had high rates of uCa excretion, with a 24-hour uCa:uCr above the threshold value. The 24-hour uCa:uCr ratio was significantly higher in the calcium + vitamin D group compared with the placebo group (3.97 vs 2.35, respectively; $P < 0.001$) and serum i-PTH was significantly lower (31.0 vs 38.5 pg/mL; $P < 0.001$). Moreover, the median i-PTH value was within the normal range (31 pg/mL) in the calcium + vitamin D group. These changes in calcium homeostasis had no effect on cal-

Table II. Number (%) of women with ≥1 adverse event during the study.

Category	Calcium + Vitamin D (n = 95)	Placebo (n = 96*)	P
No. of women with ≥1 adverse event	69 (72.6)	70 (72.9)	1.00
Specific adverse events, by body system			
Osteomuscular	32 (33.7)	24 (25.0)	0.21
Gastrointestinal	22 (23.2)	21 (21.9)	0.86
Metabolic and nutritional	16 (16.8)	18 (18.8)	0.85
Hypercalcemia	7 (7.4)	11 (11.5)	-
Serious adverse events, by body system	14 (14.7)	12 (12.5)	0.68
Cardiovascular	6 (6.3)	5 (5.2)	0.62–1.00†
Osteomuscular	5 (5.3)	2 (2.1)	0.27
Nervous	1 (1.1)	2 (2.1)	1.00
Gastrointestinal	1 (1.1)	2 (2.1)	1.00
Body as a whole	1 (1.1)	1 (1.1)	1.00
Other‡	2 (2.1)	3 (3.2)	0.50–1.00†
Adverse events judged possibly treatment related	21 (22.1)	23 (24.0)	0.86
Metabolic and nutritional	9 (9.5)	10 (10.4)	1.00
Hypercalcemia	6 (6.3)	8 (8.3)	-
Gastrointestinal	9 (9.5)	8 (8.3)	0.81

*One subject was withdrawn from the study before receiving the first dose of study medication and was excluded from analysis.
†Statistical analyses (χ^2 test) were performed separately for general cardiovascular, cardiac, and vascular disorders. For the "other" category, statistical analyses were performed by body system.
‡The other serious adverse events were malaria, infection, uterovaginal prolapse, and hemorrhage.

cemia, which did not differ between the 2 groups (2.29 and 2.19 mmol/L).

With regard to renal function, there was no significant difference in uUA between the calcium + vitamin D group and the placebo group (1.9 mmol/24 hours in both groups). A significantly greater number of patients in the calcium + vitamin D group had sUA levels above the normal threshold (52.3% calcium + vitamin D vs 37.2% placebo; $P = 0.046$), but without any changes in UA Cl. There were no significant changes in creatinine metabolism.

The relationships between baseline laboratory values for the overall study population and on-treatment values for the calcium + vitamin D group (all study data pooled) were analyzed. The baseline values illustrated the known positive correlation between 25(OH)D and 24-hour uCa:uCr ($r = 0.19$; $P < 0.001$) and the negative correlation between i-PTH and both the 24-hour uCa:uCr ($r = -0.13$; $P = 0.016$) and 25(OH)D ($r = -0.24$; $P < 0.001$). Moreover, sUA was strongly correlated with the calcium homeostasis parameters 25[OH]D, i-PTH, and 24-hour uCa:uCr (25[OH]D: $r = 0.2$, $P = 0.005$; i-PTH: $r = 0.2$, $P = 0.004$; 24-hour uCa:uCr: $r = -0.25$, $P < 0.001$), particularly with the latter. Similar results were reported for UA Cl (25[OH]D: $r = 0.24$, $P < 0.004$; i-PTH: $r = -0.02$, $P = 0.006$; 24-hour uCa:uCr: $r = 0.5$, $P < 0.001$), whereas uUA was correlated only with 25(OH)D ($r = 0.3$, $P = 0.007$) and 24-hour uCa:uCr ($r = 0.49$, $P < 0.001$). CrCl was correlated only with 24-hour uCa:uCr ($r = 0.55$, $P < 0.001$). After 1 year of treatment with calcium + vitamin D, only 24-hour uCa:uCr was correlated with uric acid parameters (sUA: $r = -0.16$, $P = 0.007$; uUA: $r = 0.54$, $P < 0.001$; UA Cl: $r = 0.56$, $P < 0.001$).

DISCUSSION

In this 1-year, double-blind, prospective study in a large population of ambulatory elderly women with vitamin D insufficiency and normal renal function, combined calcium and vitamin D treatment was well tolerated. It is well known that long-term oral administration of appropriate doses of this combination can simultaneously produce marked increases in 25(OH)D and uCa levels and a decrease in i-PTH levels, reflect-

Table III. Laboratory values after 12 months of treatment with a combination calcium and vitamin D tablet or placebo.

	Calcium + Vitamin D (n = 95)				Placebo (n = 96*)				*P*	
Parameter	Median	Q1	Q3	Values Outside Normal Range,† no. (%)‡	Median	Q1	Q3	Values Outside Normal Range,† no. (%)‡	*t* Test	χ^2 Test
25(OH)D, ng/mL	28.75	23.25	35.75	8 (9.4)	10.75	8.00	14.0	58 (69.9)	<0.001	<0.001
i-PTH, pg/mL	31.0	23.0	40.0	20 (22.7)	38.5	26.0	61.0	40 (46.5)	<0.001	<0.001
sCa, mmol/L	2.29	2.19	2.39	7 (7.9)	2.27	2.19	2.42	12 (13.9)	0.805	0.205
sUA, µmol/L	316.5	237.5	362.0	46 (52.3)	291.0	229.0	364.0	32 (37.2)	0.603	0.046
Creatinine, µmol/L	64.0	57.0	59.5	17 (19.3)	64.5	55.0	72.0	20 (23.3)	0.851	0.526
24-Hour uCa:uCr	3.97	2.23	5.67	32 (37.2)	2.35	1.36	3.52	8 (9.4)	<0.001	<0.001
uUA, mmol/24 h	1.9	1.4	2.3	10 (11.6)	1.9	1.5	2.4	3 (3.5)	0.870	0.080
CrCl, mL/min	68.3	49.2	85.7	42 (48.8)	60.4	45.4	81.9	48 (56.5)	0.305	0.317
UA Cl, mL/min	4.3	3.2	6.0	82 (95.3)	4.6	3.0	6.7	84 (98.8)	0.157	0.367

Q1 = lower quartile; Q3 = higher quartile; 25(OH)D = 25-hydroxy vitamin D; i-PTH = intact parathyroid hormone; sCa = serum calcium; sUA = serum uric acid; uCa:uCr = urinary calcium:urinary creatinine ratio; uUA = urinary uric acid; CrCl = creatinine clearance; UA Cl = uric acid clearance.

*One subject was withdrawn from the study before receiving the first dose of study medication and was excluded from analysis.

†Threshold values were as follows: 25(OH)D ≤12 ng/mL; i-PTH >54 pg/mL; sCa >2.62 mmol/L; sUA >340 µmol/L; creatinine >130 µmol/L; 24-hour uCa:uCr >6.25 mmol/24h; uUA >3.5 mmol/L; CrCl <80 mL/min; UA Cl <6 mL/min or >9 mL/min. Percentages were calculated based on available data.

‡The number of patients assessed for each parameter ranged from 83 to 89 in the calcium + vitamin D group and from 83 to 86 in the placebo group.

ing normalization of secondary hyperparathyroidism[22,23] and leading to a reduction in bone remodeling.[21,22] These changes are associated with an increase in bone mineral density, reducing the risk of peripheral fracture in the elderly,[9,10] particularly in women.[24]

Vitamin D insufficiency in the elderly has been reported in France and in countries at higher latitudes.[13,14] This insufficiency is common in elderly people living in institutions or at home, both due to less skin production of vitamin D during the winter months[25] and because dietary intake of vitamin D may be too low.[18] Dietary calcium intake also may be insufficient in the elderly.[21] This is the rationale for treatments combining calcium and vitamin D.[21] Although use of such supplementation is common, the safety of long-term oral administration of calcium and vitamin D in the elderly had not been fully examined.

At baseline, the study population had lower-than-normal vitamin D and calcium intake based on standard recommendations.[26] The study used the recommended daily dose of the combination calcium + vitamin D tablet for the elderly.[26] Doses of calcium 1 g/d and vitamin D 400 IU/d have been shown to prevent hip fracture,[27] and a calcium dose of 1.6 g/d has been shown to improve bone mineral density and bone biomarkers.[28] The main trials concerning the effects on bone of long-term supplementation with calcium + vitamin D in the elderly, which used identical doses to those in the present study, did not focus on safety.[9,10]

The incidence of withdrawals due to adverse events was high in both groups (21.1% and 29.9% in the calcium + vitamin D and placebo groups, respectively), although the number of adverse events was fairly low. Clinical adverse events were mainly gastrointestinal, osteomuscular, metabolic, or cardiovascular, oc-

curring with a similar incidence in both groups. Three deaths occurred in the calcium + vitamin D group and 1 in the placebo group, none of them considered possibly related to study treatment.

In terms of changes in laboratory parameters, no significant difference in sCa was observed between the 2 groups. There were several cases of hypercalcemia, with no statistical difference between groups. Two women in the calcium + vitamin D group were withdrawn from the study due to hypercalcemia. It has been reported that calcium therapy may cause hypercalcemia in those with conditions such as chronic renal disease[29]; women with chronic renal failure, however, were excluded from this study. Moreover, vitamin D is potentially toxic: hypercalciuria, hypercalcemia, and an increase in creatinine levels have been reported with vitamin D therapy at doses 20 to 30 times physiologic levels.[30] Vitamin D at a dosage of 2000 IU/d for 6 months produced hypercalcemia in an elderly population,[31] and dosages <2000 IU/d may also cause hypercalcemia in these patients, suggesting an increased susceptibility to the action of vitamin D.[30]

Given the potential renal toxicity of calcium + vitamin D therapy, this study focused on measures of renal function, particularly uric acid metabolism. At baseline, a significant correlation was found between uCa on the one hand and sUA, uUA, UA Cl, and CrCl on the other (all, $P < 0.001$). After 1 year of treatment, this relationship persisted only for parameters of uric acid metabolism. Such a relationship has been reported in patients with primary hyperparathyroidism, with a positive correlation between 24-hour uCa:uCr and 24-hour uUA:uCr, suggesting a possible relationship between the metabolism of calcium and uric acid.[32] Moreover, a positive correlation has been found between serum levels of 1.25(OH)2D, the active metabolite of vitamin D, and uUA and uCa in patients who form calcium stones.[33] Therefore, the fact that significantly more women in the calcium + vitamin D group than in the placebo group had elevations in sUA ($P = 0.046$) in the present study must be taken into consideration. However, long-term administration of calcium + vitamin D did not lead to any significant change in creatinine levels. It may be necessary to monitor levels of sUA during long-term supplementation with calcium + vitamin D.

CONCLUSIONS

In these ambulatory elderly women with vitamin D deficiency, supplementation with calcium + vitamin D appeared to be well tolerated over 1 year of treatment. No significant effects on CrCl were observed. However, the proportion of women with elevated sUA concentrations was significantly greater in those who received calcium + vitamin D compared with those who received placebo.

ACKNOWLEDGMENTS

This study was supported by Innothera Laboratories, Arcueil, France.

The authors thank Fabienne Peretz for assistance with the writing of this article and the PREDOS Association, Amiens, France, particularly Fabienne Hervy, for technical assistance.

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