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Original Article

Combined Calcium and Vitamin D_3 Supplementation in Elderly Women: Confirmation of Reversal of Secondary Hyperparathyroidism and Hip Fracture Risk: The Decalyos II Study

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Abstract. Vitamin D insufficiency and low calcium intake contribute to increase parathyroid function and bone fragility in elderly people. Calcium and vitamin D supplements can reverse secondary hyperparathyroidism thus preventing hip fractures, as proved by Decalyos I. Decalyos II is a 2-year, multicenter, randomized, double-masked, placebo-controlled confirmatory study. The intention-to-treat population consisted of 583 ambulatory institutionalized women (mean age 85.2 years, SD = 7.1) randomized to the calcium–vitamin D_3 fixed combination group (n = 199); the calcium plus vitamin D_3 separate combination group (n = 190) and the placebo group (n = 194). Fixed and separate combination groups received the same daily amount of calcium (1200 mg) and vitamin D_3 (800 IU), which had similar pharmacodynamic effects. Both types of calcium-vitamin D_3 regimens increased serum 25-hydroxyvitamin D and decreased serum intact parathyroid hormone to a similar extent, with levels returning within the normal range after 6 months. In a subgroup of 114 patients, femoral neck bone mineral density (BMD) decreased in the placebo group (mean = –2.36% per year, SD = 4.92), while remaining unchanged in women treated with calcium-vitamin D_3 (mean = 0.29% per year, SD = 8.63). The difference between the two groups was 2.65% (95% CI = –0.44, 5.75%) with a trend in favor of the active treatment group. No significant difference between groups was found for changes in distal radius BMD and quantitative ultrasonic parameters at the os calcis. The relative risk (RR) of HF in the placebo group compared with the active treatment group was 1.69 (95% CI = 0.96, 3.0), which is similar to that found in Decalyos I (RR = 1.7; 95% CI = 1.0, 2.8). Thus, these data are in agreement with those of Decalyos I and indicate that calcium and vitamin D_3 in combination reverse senile secondary hyperparathyroidism and reduce both hip bone loss and the risk of hip fracture in elderly institutionalized women.

Keywords: Bone mineral density (BMD); Calcium; Elderly; Hip fracture risk; Secondary hyperparathyroidism; Supplementation; Vitamin D_3 (cholecalciferol)

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Introduction

Several studies have shown that low dietary calcium intake associated with reduced intestinal calcium absorption is common in elderly people [1–3]. This results in part from vitamin D insufficiency – vitamin D being a key modulator of intestinal calcium and phosphate absorption [4] – due to a lack of exposure to sunlight combined with reduced vitamin D dietary intake and decreased vitamin D cutaneous synthesis [5–12].

Low calcium intake and vitamin D insufficiency – usually defined as a serum 25-hydroxyvitamin D (25(OH)D) concentration below 12 ng/ml [13] – are responsible for secondary hyperparathyroidism which is associated with increased bone turnover and indirectly an increased risk of fracture [3]. In addition, recent data

suggest that vitamin D insufficiency is actually more common than previously believed because of the upward reappraisal of the classical 25(OH)D threshold level below which parathyroid hormone secretion (PTH) begins to increase [14–16].

Two controlled studies, Decalyos I performed in French institutionalized elderly women [17,18] and another in elderly American men and women [19], have demonstrated a significant protective effect of a combined supplement of calcium and vitamin D on hip and/or other nonvertebral fractures. This reduction in fracture risk is associated with an increase in bone mineral density (BMD) and serum 25(OH)D concentration and a decrease in serum PTH.

The aim of this 2-year randomized, placebo-controlled study entitled Decalyos II (vitamin D, Calcium Lyon Study II) was to confirm the effects of combined calcium and vitamin D supplementation on biochemical variables of calcium homeostasis, femoral neck BMD and hip fracture risk.

Subjects and Methods

Subjects

We enrolled 639 patients (mean age 85 years, range 64–99 years) living in 55 apartment houses for elderly people, 610 of whom were randomized in the study. To be eligible for the study the women had to be ambulatory (able to walk indoors with a cane or a walker) and to have a life expectancy of at least 24 months. We excluded women who had intestinal malabsorption, hypercalcemia (serum calcium >2.63 mmol/l) or chronic renal failure (serum creatinine >150 μmol/l). Women who had received drugs known to alter bone metabolism, such as corticosteroids, anticonvulsants or a high dose of thyroxine, within the past year were excluded. Treatments with fluoride salts (>3 months), bisphosphonates, calcitonin (>1 month), calcium (>500 mg/day) and vitamin D (>100 IU/day) during the last 12 months were also exclusion criteria.

The study was approved by the Lyon Hospital Ethics Committee and written consent was obtained from all study subjects or from their family representative.

Study Design and Supplements

In this 2-year, double-masked, placebo-controlled and comparative trial, the 610 subjects were randomly assigned either to one of the two active groups (calcium–vitamin D_3 fixed combination group or separate calcium and vitamin D_3 supplements group) or to the placebo group.

The sachet of the calcium–vitamin D_3 fixed combination (Ostram–vitamin D_3, Merck KGaA) contains a fixed combination of 1200 mg elemental calcium in the form of tricalcium phosphate and 800 IU (20 μg) of vitamin D_3. The calcium (Ostram, Merck KGaA) contains 1200 mg of elemental calcium in the form of tricalcium phosphate. Vitamin D_3 (Devaron, i.e., cholecalciferol, Duphar Solvay) was given in two pills of 400 IU each.

The study was conducted using the double dummy method, i.e., each day women in the treated groups received 1200 mg of elemental calcium and 800 IU of vitamin D3 given either by a sachet of calcium–vitamin D_3 fixed combination (Ca–D_3 group) or as a sachet of calcium and two tablets of vitamin D_3 (Ca+D_3 group). The other women received a placebo of calcium and vitamin D_3 (one sachet containing lactose, microcrystalline cellulose and the same excipient as the active treatment and two tablets of vitamin D_3 placebo). The supplements were taken in an aqueous suspension at lunchtime during a meal in the presence of a nurse to ensure compliance.

At baseline, the women's relevant medical history was recorded for a history of falls and fractures, basic diet and mobility (level of daily life activities). Dietary data were collected by a questionnaire for gathering information on calcium and vitamin D intake. All treatments prescribed during the previous year were documented. A general physical examination including all major body systems was performed. Heart rate and supine blood pressure were measured at each visit.

Every 3 months women were assessed and the investigators recorded their medical status. They were asked whether they had experienced any adverse event or fracture since their last visit. For each new peripheral fracture, the date, site and cause of the trauma were recorded on a specific form in the Case Report Form. Vertebral fractures had to be confirmed by systematic radiographs of the spine.

Biochemical Measurements

Serum intact parathyroid hormone (PTHi) was measured by immunochemoluminometric assay (Ciba-Corning Diagnostic). The normal range for adults from 40 to 70 years of age is 11–55 pg/ml (1.2–5.8 pmol/l). Serum 25(OH)D was assessed by competitive-binding protein assay after extraction and purification. The normal range for adults given by the manufacturer of the kit (Incstar) is 15–50 ng/ml (37–125 nmol/l). Serum bone alkaline phosphatase was measured by a two-site radioimmunoassay (Tandem-R-Ostase kit, Beckman-Coulter, CA). Serum calcium, phosphate, creatinine, sodium, potassium, ALT, AST, γGT, albumin and total proteins were measured by standard laboratory methods. Twenty-four hour urinary excretion of calcium and creatinine was also assessed. Blood and urine samples were taken after an overnight fast at each investigation site and sent to a centralized laboratory for measurement. All samples were kept frozen at –70 °C until analysis.

Bone Mineral Density (BMD) and Quantitative Ultrasound assessments

BMD of the distal radius was measured by single X-ray absorptiometry (SXA) at the investigator's site using a mobile Hologic DTX100 Osteometer (Hologic, Waltham, MA) operated by two nurses specifically recruited and trained for this study. The SXA scanners were calibrated each day, using their own standard phantom. A cross-calibration of the two densitometers was performed twice weekly using the same phantom. In addition, a monthly quality control of the densitometers was performed by the central laboratory (Synarc, Lyon, France). Longitudinal variability was expressed as a coefficient of variation (CV) using phantom data and estimated at 0.66% and 0.76%. Short-term in vivo precision was estimated at 1.39% (CV) for repeated baseline distal forearm BMD measurements.

Femoral neck BMD was measured in a subgroup of 114 patients living near the Lyon study co-ordination center by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR 1000 Plus device. Positioning of the patients was controlled by using the Osteodyne device [20]. Longitudinal in vitro coefficient of variation (CV%) using a phantom was estimated at 0.29%. In the same subgroup of 114 patients, quantitative ultrasound parameters (speed of sound (SOS), broadband ultrasound attenuation (BUA) and Stiffness) were measured at the os calcis. The ultrasound measurements were performed with a Lunar Achilles Plus device (Lunar, Madison, WI). A daily quality control was performed using the phantom provided by Lunar. Longitudinal in vitro CV% was of 0.14% and 0.81% for SOS and BUA, respectively.

Statistical Analysis

Efficacy data are presented for the intention-to-treat (ITT) population consisting of all randomized patients who had taken at least one dose of treatment and who provided at least one follow-up measurement for one or more efficacy variables (biochemical markers, BMD).

Changes from baseline of biochemical parameters were analyzed by ANCOVA using treatment group as main factor and baseline value as covariate. Given the very similar pharmacodynamic profile of the $Ca–D_3$ group and the $Ca+D_3$ group, these two groups were combined to evaluate the global impact of calcium and vitamin D_3 treatment. For each patient the yearly changes in BMD were estimated by linear regression analysis [21]. The annual percentage rate of change was calculated as 100 times the slope divided by the intercept of the regression line at study entry. The mean rate of change in BMD over time was analyzed using a fixed model analysis of variance with the treatment group (active treatment or placebo) as main factor parameter. Changes in quantitative ultrasound parameters from baseline were analyzed using ANCOVA.

Times to onset of new fractures (nonvertebral and hip) were estimated using the Kaplan–Meier method [22]. The log-rank test was used to compare the placebo and active treatment groups. Risk ratios according to the Cox proportional hazard model and their 95% confidence intervals were calculated.

Incidences of adverse events, changes in standard hematologic and biochemical parameters and changes in vital signs were analyzed in all randomized subjects treated at least once with the study medication. Statistical tests were performed two-sided at a significance level of 5%.

Results

Six hundred and ten patients were randomized in the study. Among them, 608 were actually given the study treatment and 583 were assessed at least once while on study treatment (i.e. are eligible for the ITT population): 199 were given the $Ca–D_3$ fixed combination, 190 the $Ca+D_3$ separate combination and 194 the placebo.

Baseline data were similar in the three treatment groups (Table 1). In the whole population the mean dietary calcium (557.7 mg/day) and vitamin D (40.8 IU/day) intakes were very low. Table 2 shows that 66.0 % of the patients were suffering from both low vitamin D status (25(OH)D < 12 ng/ml) and calcium intake (< 800 mg/day). This percentage increases to 78.9% when the cut-off limit for 25(OH)D was set to 20 ng/ml. Among the 610 women randomized in the study, 422 (69.2%) subjects completed the 24 months of follow-up. The drop-out rates during the study were similar in the three groups (27.2% in the $Ca–D_3$ group, 29.1% in $Ca+D_3$ group and 36.1% in the placebo group). The main reason for drop-out was death (15.0% in the $Ca–D_3$ group, 19.1% in the $Ca+D_3$ group and 22.4% in the placebo group).

The mean compliance was more than 95% for both sachets and tablets in each treatment group for the ITT population.

Changes in Biochemical Parameters of Bone Metabolism

Mean values for serum calcium, phosphate and bone alkaline phosphatase at baseline and at each subsequent control visit are shown in Table 3. In the placebo group no significant change was observed for any parameters. Serum calcium and phosphate levels increased slightly in the two active treatment groups ($p < 0.05$ vs placebo for calcium) but remained within normal limits. Bone alkaline phosphatase concentration decreased in the two active treatment groups ($p < 0.03$ vs placebo at all time points) (Table 3).

At baseline serum 25(OH)D levels were very low. Compared with the placebo group the mean serum 25(OH)D concentrations increased markedly in each treated group ($p = 0.0001$ vs placebo at each time point) (Fig. 1). At baseline serum PTHi concentrations were about 30% higher than the upper limit of the normal

Table 1. Baseline characteristics of the study subjects (intention-to-treat population)

	$Ca–D_3$ fixed combination (n=199)	$Ca+D_3$ separate combination (n=194)	Placebo (n=190)
Age (years)[a]	84.9 ± 6.6	84.9 ± 7.0	85.7 ± 7.6
Weight (kg)[a]	58.7 ± 11.8	59.0 ± 12.6	59.9 ± 11.9
Height (cm)[a]	155 ± 6.9	155 ± 7.3	155 ± 7.3
Calcium intake (mg/day)[a]	565 ± 230.1	551 ± 238.0	556 ± 246.1
Vitamin D intake (IU/day)[a]	42 ± 28.3	40 ± 27.3	41 ± 28.8
Fallers (%)[b]	14.1%	18.6%	15.8%
Ability to walk			
Without help	55.8%	61.9%	60.5%
With one or two crutch(es)	24.6%	19.5%	26.3%
With a walker	19.6%	18.6%	13.2%
Walking capacities			
<10 m	6.0%	05.7%	06.3%
[10, 100 m[	40.7%	37.1%	35.8%
[100, 1000 m[	32.7%	37.6%	39.5%
$\geqslant$ 1000 m	20.6%	19.6%	18.4%
Serum calcium (mg/dl)[a]	9.24 ± 0.44	9.16 ± 0.48	9.2 ± 0.44
Serum 25(OH)D (ng/ml)[a]	8.5 ± 5.3	9.0 ± 6.6	9.1 ± 6.9
Serum PTHi (pg/ml)[a]	71.2 ± 76.2	70.8 ± 51.3	71.7 ± 48.5
Bone mineral density (g/cm^2)[c]			
Total femoral[a]	0.677 ± 0.147	0.682 ± 0.146	0.708 ± 0.125
Femoral neck[a]	0.598 ± 0.141	0.589 ± 0.113	0.615 ± 0.176
Distal forearm[a]	0.323 ± 0.080	0.305 ± 0.069	0.313 ± 0.069
Quantitative ultrasound[c]			
BUA (dB/MHz)	91.6 ± 16.7	91.3 ± 11.7	91.5 ± 14.9
SOS (m/s)	1488 ± 30.2	1487.0 ± 24.0	1491.8 ± 24.0

[a]Mean ± SD
[b]Percentage of subjects who fell in the 3 months prior to randomization
[c]Neck and total femoral BMD, SOS and BUA were assessed in a subgroup of patients living close to the Lyon Study Coordination and Quality Control Center (n = 114) whereas forearm BMD was assessed in the whole population (n = 583).

Table 2. Breakdown of the study population at baseline according to vitamin D status and calcium intake (intention-to-treat population)

Serum 25-hydroxyvitamin D	Calcium intake	
	C $<$ 800 mg/day	$\geqslant$ 800 mg/day
$<$ 12 ng/ml	66.0%	10.8%
$\geqslant$ 12 ng/ml	19.9%	3.3%

range. In the placebo group the mean PTHi serum level increased progressively throughout the study, whereas a significant decrease in both active treatment groups ($p = 0.0001$ vs placebo at all time points) was observed as early as 6 months and levels returned within the normal range (Fig. 2). No significant difference in any biochemical parameter was observed between the two active treatment groups. Consequently, these two groups

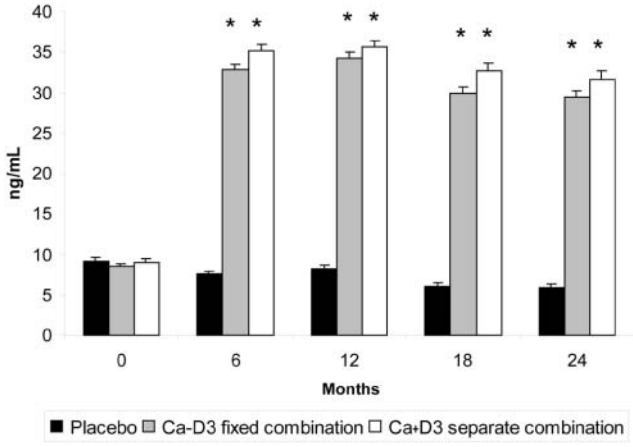

Fig. 1. Effect of the study medication on 25(OH)D serum concentrations (intention-to-treat population). *p = 0.0001 for the comparison of changes from baseline of treated groups with the placebo group.

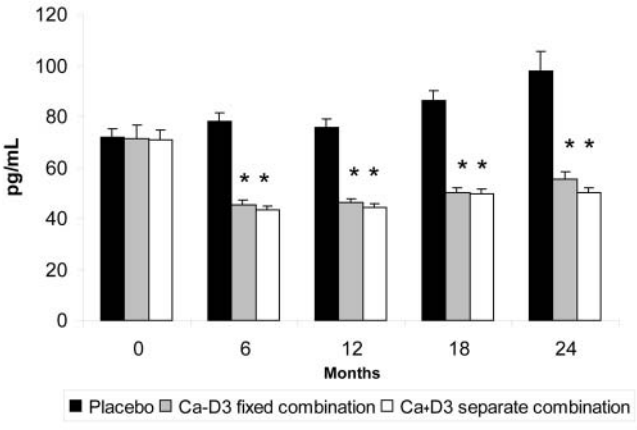

Fig. 2. Effect of the study medication on PTH serum concentrations (intention-to-treat population). *p = 0.0001 for the comparison of changes from baseline of treated groups with the placebo group.

Table 3. Mean biochemical parameters of bone metabolism in the treatment and placebo groups at baseline and after 6, 12, 18 and 24 months of follow-up (intention-to-treat population)

	Baseline	6 months	12 months	18 months	24 months
Calcium (mg/dl)					
Treated group					
$Ca–D_3$	9.24 ± 0.44	9.28 ± 0.52*	9.32 ± 0.48*	9.24 ± 0.48*	9.24 ± 0.48*
$Ca+D_3$	9.16 ± 0.48	9.28 ± 0.48*	9.32 ± .052*	9.32 ± 0.68*	9.28 ± 0.52*
Placebo	9.20 ± 0.44	9.00 ± 0.44	9.00 ± 0.44	8.96 ± 0.44	9.08 ± 0.52
n ($Ca–D_3$, $Ca+D_3$, Placebo)	(*199,194,190*)	(*185,185,175*)	(*175,170,163*)	(*162,152,144*)	(*142,137,127*)
Phosphate (mg/dl)					
Treated group					
$Ca–D_3$	3.22 ± 0.50	3.41 ± 0.43	3.32 ± 0.37	3.35 ± 0.46*	3.35 ± 0.46
$Ca+D_3$	3.25 ± 0.46	3.44 ± 0.43	3.38 ± 0.40	3.32 ± 0.40*	3.35 ± 0.43
Placebo	3.22 ± 0.50	3.35 ± 0.43	3.32 ± 0.46	3.22 ± 0.43	3.32 ± 0.50
n ($Ca–D_3$, $Ca+D_3$, Placebo)	(*199,194,190*)	(*185,185,175*)	(*175,170,163*)	(*162,152,144*)	(*142,137,127*)
Bone alkaline phosphatase (ng/ml)					
Treated group					
$Ca–D_3$	14.71 ± 7.71	11.97 ± 5.86*	11.79 ± 6.24*	12.03 ± 5.70*	13.53 ± 7.14*
$Ca+D_3$	15.26 ± 11.22	12.31 ± 7.45*	11.49 ± 6.65*	11.77 ± 4.43*	13.59 ± 8.92*
Placebo	17.14 ± 20.44	17.40 ± 19.31	18.74 ± 20.29	19.16 ± 21.95	19.84 ± 22.62
n ($Ca–D_3$, $Ca+D_3$, Placebo)	(*161,155,147*)	(*148,134,140*)	(*159,157,155*)	(*139,133,173*)	(*147,140,132*)

Values are the mean ± SD.
$Ca–D_3$, calcium and vitamin D_3 fixed combination; $Ca+D_3$, calcium and vitamin D_3 separate combination.
*$p < 0.05$ for the comparison with placebo based on ANCOVA for changes from baseline.

were combined in a single active treatment groups for the subsequent analyses.

Bone Mineral Density and Quantitative Ultrasonic Parameters

After 12 months of treatment, femoral neck BMD decreased on average by –3.6% (SD = 6.0) in the placebo group but remained unchanged in the active treatment group (mean = 0%, SD = 5.6). After 24 months, a slight decrease in femoral neck BMD was observed in the active treatment group compared with baseline (mean = −1.2%, SD = 7.4), whereas BMD decreased even more in the placebo group (mean = −4.5%, SD = 7.1). The annual mean rate of change was estimated at 0.29% (SD = 8.63) for the active treatment group and at –2.36% (SD = 4.92) for the placebo group (Table 4), resulting in a difference between active and placebo groups of 2.65% (95% confidence interval: −0.44 to 5.75%). No significant effect of treatment on distal radius BMD (Table 4) and BUA or SOS of the os calcis was observed.

Hip Fracture Incidence

During the study 27 of 393 women (6.9%) treated with calcium and vitamin D_3 and 21 of 190 (11.1%) in the placebo group suffered from a hip fracture. The ITT analysis performed with 583 patients showed that cumulative probability of hip fracture was higher in

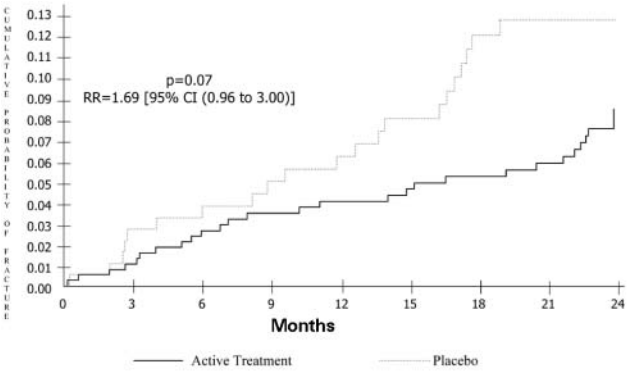

Fig. 3. Cumulative probability of hip fracture (intention-to-treat population).

Table 4. Mean rate of change in BMD (intention-to-treat population)

	Active treatment			Placebo			*p* value[a]
	n	Annualized mean rate of change	95% confidence interval	*n*	Annualized mean rate of change	95% confidence interval	
Femoral neck	79	0.29%	–1.43, 2.01	35	–2.36%	–4.94, 0.22	0.09
Distal radius	392	–1.65%	–2.13, –1.18	190	–1.95%	–2.63, –1.27	0.48

[a]Based on comparison between groups by ANCOVA.

the placebo group compared with the active treatment group, although the difference did not reach significance ($p = 0.07$) (Fig. 3). Cumulative probability curves for hip fracture incidence started to deviate about 9 months after initiation of the trial.

The risk ratio for hip fracture among women in the placebo group compared with those in the active treatment group was 1.69 (95 % confidence interval, 0.96–3).

Other Nonvertebral Fractures

In the active and placebo groups, 17.8% and 17.9% of subjects respectively, experienced at least one non-vertebral fracture (NS). There was no significant difference in the percentage of fallers between groups (63.9% vs 62.1% in the active and placebo groups, respectively).

Safety Results

The percentages of deaths were similar in the active treatment (18.1%) and placebo (23.9%) groups. Only 40 patients (24 in the active treatment group and 16 in the placebo) reported gastrointestinal disorders (nausea, diarrhea, epigastric pains). These gastrointestinal symptoms led to discontinuation of the study only in 3 cases. Three patients developed hypercalcemia in the active treatment group: one resulting from recent myeloma, the two others from hyperparathyroidism which was masked at baseline by the very low serum vitamin D level and was revealed under therapy.

At baseline mean values of urinary calcium were in the same range for the two treatment groups (Table 5). Compared with baseline levels, the ratio of 24 h urinary calcium/creatinine concentrations increased significantly in the active treatment groups ($p < 0.003$ vs placebo at each time point). There was no difference between the groups in the percentage of patients with a urinary calcium level higher than 350 mg/24 h at any time (Table 5). Treatment had no significant effect on serum creatinine levels. No renal calculus was reported.

Discussion

This 2-year, randomized, placebo-controlled study (Decalyos II) showed that an appropriate daily supplement of calcium (1200 mg) in the form of tricalcium phosphate and vitamin D_3 (800 IU) in ambulatory elderly women living in apartment homes normalized serum PTHi and 25(OH)D levels. These biochemical effects were associated with a reduced bone loss at the femoral neck and decreased risk of hip fracture. Treatment was very well tolerated.

In this study we found that calcium–vitamin D treatment reduced bone loss at the femoral neck – although not significantly, probably because of the limited number of subjects – but not at the distal radius. This suggests that the forearm site is not sensitive to changes induced by calcium–vitamin treatment, as has been previously reported for other antiresorptive therapy [23]. The decrease in femoral neck bone loss under treatment is likely to be mediated by a reduction in the rate of bone turnover as indicated by the sustained 8–20% decreased levels of serum bone alkaline phosphatase, in agreement with previous studies using similar treatments [17,19].

Although this study was not powered to detect a reduction in hip fracture rate, the ITT analysis performed on 583 patients showed that the cumulative probability of hip fracture was higher in the placebo group compared with the active treatment group. The risk ratio for hip fracture among women in the placebo group compared with the active treatment group was 1.69 (95% confidence interval, 0.96 to 3), which is very close to that found in the Decalyos I study (1.7; 95% confidence interval, 1.0 to 2.8) [17].

Three randomized controlled studies using a similar total amount of calcium and vitamin D namely Decalyos

Table 5. Effect of treatments on 24 h urinary calcium/creatinine ratio, percentage of patients with urinary calcium >350 mg per 24 h and serum creatinine and (intention-to-treat population)

	Baseline	12 months	24 months
24 h urinary calcium/creatinine ratio (mg/g creatinine per 24 h)			
Active treatment	119.13 ± 78.40	149.51 ± 89.36*	167.86 ± 123.10*
Placebo	124.74 ± 82.78	117.28 ± 73.53	113.15 ± 97.28
n (Active treatment, Placebo)	(*276, 128*)	(*166, 77*)	(*89, 35*)
Percentage of patients with urinary calcium >350 mg per 24 h			
Active treatment	1.4%	3.0%	3.4%
Placebo	2.3%	1.3%	2.9%
n (Active treatment, Placebo)	(*276, 128*)	(*166, 77*)	(*89, 35*)
Serum creatinine (mml/l)			
Active treatment	88.1 ± 19.1	92.3 ± 19.5	94.1 ± 20.5
Placebo	88.6 ± 21.3	90.3 ± 23.9	89.5 ± 23.8
n (Active treatment, Placebo)	(*403, 205*)	(*345, 163*)	(*279, 127*)

Values are mean ± SD or percentage.
*$p < 0.03$ for the comparison with placebo based on Fisher's exact test.

I [17,18], the Dawson-Hughes et al. study [19] and Decalyos II, have established the beneficial effects of combined calcium and vitamin D_3 supplement on the prevention of fracture risk. The Dawson-Hughes et al. study comprised both men and women living independently and participants were younger (mean age 71 years) than those involved in the Decalyos I and II studies. The authors reported a reduction in femoral neck, spine and total body BMD loss, and in the incidence of nonvertebral fractures. This trial is of particular interest because it suggests that the concept that calcium and vitamin D insufficiencies inducing hyperparathyroidism, previously established in institutionalized elderly population [17,18] and now confirmed by the Decalyos II study, can be extended to younger people living at home.

There has been some debate about the relative contributions of calcium and vitamin D in the prevention of bone loss when these two products are combined. The rationale for combining vitamin D and calcium was pointed out by Chevalley et al. [24] several years ago in a small double-masked placebo-controlled study. The authors reported that addition of oral calcium supplements in vitamin D repleted elderly patients significantly prevented the decrease in femoral neck BMD. In addition, Lips et al. [25] reported in a study of 2578 elderly men and women that there was no reduction in the incidence of fractures among those given vitamin D alone compared with those given placebo, although the dose of vitamin D was half that used in the studies using combined treatment. Thus these data suggest that the combination of calcium and vitamin D is indeed more effective than vitamin D alone.

It has been suggested that both bone and extraskeletal effects are involved in the prevention of hip fracture risk by calcium–vitamin D. Indeed muscle cells contain vitamin D receptors and $1,25(OH)_2D_3$, the active metabolite of vitamin D, increases basal intercellular Ca^{2+}, as well as myosin light chain phosphorylation, in isolated vascular smooth muscle cells of rats [26]. In addition a recent study showed that vitamin D deficiency results in muscle weakness [27]. Thus it is likely that vitamin D deficiency or even insufficiency, which is very common in elderly people, could cause muscle weakness and disability of the lower extremities [28], which may result in increased risk of falls. In this study, however, there was no difference in the percentage of fallers between patients receiving calcium–vitamin D and placebo in agreement with the data reported by Dawson-Hughes et al. [19], but not in accordance with the recent results of Glerup et al. [29]. Thus a reduction in the incidence of falls does not clearly seem to account for the beneficial effects of treatment on the risk of hip fracture. More likely the beneficial effect of calcium–vitamin D results from increased bone strength mediated by stabilization of femoral neck BMD and/or reduction of bone turnover, high bone remodeling being a risk factor for hip fracture independent of BMD [30].

This study also revealed that elderly patients had very low calcium and vitamin D intakes which are respectively less than 50% and 7% of the recommended amount for the elderly over the age of 70 years [31]. This partly contributes to the high incidence of calcium and vitamin D insufficiencies reported in several previous publications, the proportion of elderly patients having low serum 25(OH)D levels (< 12 ng/ml) ranging from 36% to 57% [14,15,17–19,32–36]. Vitamin D insufficiency was also found in 14% of healthy younger men and women participating in the SU.VI.MAX. study which comprised of 465 men and 804 healthy women from France with a mean age of 50 years (SD = 6) [14]. The results of this study suggested also that the threshold of 25(OH)D concentration below which serum PTH begins to increase is actually much higher than the classical 12 ng/ml and was estimated to be around 28 ng/ml as confirmed in the Boston Medical Inpatient study [15]. In support of that concept, Malabanan et al. [37], in an intervention calcium–vitamin D trial performed in patients with serum 25(OH)D levels between 10 and 25 ng/ml, concluded that circulating levels of 25(OH)D have to reach at least 20 ng/ml in order to maintain normal PTH levels. Consequently, vitamin D insufficiency, defined to be a state of hypovitaminosis D influencing calcium and phosphate homeostasis and bone remodeling through the stimulation of PTH secretion, is probably more common than previously believed. Thus, as proposed by Utiger [36], widespread increase in vitamin D and calcium intakes are likely to have a beneficial effect on the management of osteoporosis and the prevention of other severe diseases. An association between vitamin D and/or calcium insufficiency and increased risk of dying of several cancers has been reported [38–40].

In conclusion, this placebo-controlled study showed that calcium and vitamin D supplementation is safe and induced a moderate reduction in femoral neck bone loss associated with a substantial reduction of the risk of hip fracture in elderly ambulatory women. These data together with previous double-masked placebo-controlled studies, support the treatment of all clinical situations associated with hypovitaminosis D and inadequate dietary calcium intake.

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