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ORIGINAL ARTICLE

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The effect of a single dose versus a daily dose of cholecalciferol on the serum 25-hydroxycholecalciferol and parathyroid hormone levels in the elderly with secondary hyperparathyroidism living in a low-income housing unit

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Abstract We designed a randomized, double-blind, controlled clinical trial to compare the effect of two regimens for administering cholecalciferol on the serum 25-hydroxycholecalciferol [25(OH)D] levels and in the reversion of secondary hyperparathyroidism in the elderly living in a low-income housing unit in the city of Porto Alegre, southern Brazil. We studied 28 individuals ranging in age from 65 to 102 years with serum parathyroid hormone (PTH) levels greater than 48 pg/ml and normal or reduced serum calcium levels. Subjects were randomized to receive oral cholecalciferol, as a single dose of 300 000 IU (group 1) or 800 IU (group 2) daily for 9 months. Both groups received 1250 mg calcium carbonate per day. Serum 25(OH)D and PTH levels were measured at baseline and after 1, 2, 3, 6, and 9 months. Serum 25(OH)D levels in group 1 were significantly higher than in group 2 during the study ($P < 0.001$). After 1 ($P < 0.001$) and 2 ($P < 0.04$) months of treatment, mean serum 25(OH)D levels were higher in group 1. The number of subjects who reached serum 25(OH)D levels ≥20 ng/dl was higher in group 1, after the first ($P < 0.001$) and third ($P = 0.008$) months. In the short term, a single 300 000 IU oral dose of vitamin D_3 was more effective than 800 IU per day to increase serum 25(OH)D levels in elderly persons, living in a low-income housing unit, who were taking 500 mg elementary calcium supplement per day.

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Introduction

Vitamin D deficiency is a common disorder, especially in the elderly. It is diagnosed by assessing serum 25-hydroxyvitamin D [25(OH)D] levels [1,2]. It causes a decrease in intestinal calcium absorption and a rise in parathyroid hormone (PTH) levels, which may increase bone resorption and cortical bone loss [3,4].

The elevated risk of fractures that occurs with hypovitaminosis D is mainly the result of reduced bone mass [5] and increased number of falls [6,7]. The bone mass loss has been attributed to secondary hyperparathyroidism [8–11], although the increase in the number of falls probably results from muscle weakness caused by hypovitaminosis D and, possibly, secondary hyperparathyroidism [11–13].

In studies demonstrating a decrease in fracture risk with the administration of vitamin D supplements, serum 25(OH)D levels were always higher than 20 ng/ml [5,14–17]. In the meta-analysis conducted by Bischoff-Ferrari et al., there was a reduction in the number of fractures in individuals whose mean serum of 25(OH)D level was 29.6 ng/ml [18]. In these studies, there was a reduction in serum PTH levels parallel to the increase in serum of 25(OH)D levels [8].

One of the major problems in vitamin D supplementation is the adherence to daily use, because even in large clinical trials compliance was around 40% to 60% [11,19]. Intermittent administration of high doses of this vitamin could improve adherence without loss of effectiveness. Trivedi et al. administered orally 100 000 UI vitamin D_3 to individuals over 65 years of age, every 4 months. After 5 years, the relative risk for all nonvertebrae fractures was 0.67 (0.46–0.99) in vitamin D_3-treated subjects, when compared to the group receiving placebo [15]. Other studies suggest that high doses of vitamin D_3, taken as single or multiple doses, could be effective for at least 6 months,

without major adverse effects [20–23]. Knowing how long a single high dose of cholecalciferol is able to provide optimal serum 25(OH)D levels is important for clinical practice. Also, the time required to attain recommended serum 25(OH)D levels is important, especially in individuals aged 75 to 80 years who have a low life expectancy [24]. The objective of this study was to compare the effect of a single oral dose of 300 000 IU cholecalciferol with the daily use of 800 IU for 9 months on serum 25(OH)D and PTH levels, in elderly subjects with secondary hyperparathyroidism, living in a low-income housing unit, and taking 500 mg elementary calcium supplement per day.

Materials and methods

Population and recruitment

The study was performed in a low-income housing unit in the city of Porto Alegre, parallel 30°, southern Brazil. The elderly living in this facility had been screened for vitamin D deficiency. Individuals age 65 or above who had serum PTH levels higher than 48 pg/ml, and normal or low serum calcium levels, were invited to participate. Subjects who had taken calcium and/or vitamin D supplements or glucocorticoids in the previous month were excluded. Those subjects who had hypercalcemia, primary hyperparathyroidism, or renal failure, defined as an endogenous creatinine clearance rate of less than 20 ml/min as calculated by the Cockroft–Gauld equation [25], were also excluded. All individuals or their relative in charge provided an informed consent term. The study was approved by the Ethics Committee of the Hospital de Clínicas in Porto Alegre (HCPA). All subjects were recruited in December 2005.

Study design and interventions

A randomized, double-blind, controlled clinical study was performed. The calculated number of subjects to detect a 15 pg/ml difference in serum PTH levels, with a power of 80%, was 15 per group. They were randomized 1:1, all at the same time, by randomization tables, stratified for PTH levels, in groups of 10.

According to randomization, cholecalciferol was administered, at breakfast, as a single oral dose of 300 000 IU on the first day, for group 1 subjects, or as a daily oral dose of 800 IU for 9 months, for group 2 subjects. Calcium carbonate at 1250 mg was administered to both groups daily at breakfast during the study. Capsules containing calcium or vitamin D_3 plus calcium had the same flavor and appearance and were prepared by the same pharmacist (Deg, Sao Paulo/SP – Brazil). The quality control was made through high performance liquid chromatography. The nursing staff of the institution administered the medications. The individuals participating in the study, as well as the nursing and research team, did not know to which groups they belonged, except for one team member who managed the medications and did not participate in the assessments.

Measurements

The following data were obtained during recruitment using a standardized questionnaire: age, exposure to sun, medications, and tobacco and alcohol use. Weight, height, and skin phototype were determined the same day by two authors (M.O, Premaor and R. Scalco). A nutritionist estimated calcium ingestion, based on the diet offered by the institution.

Blood samples were collected between 10 AM and noon, after a fasting at least 4 h. All the samples were frozen at –20°C and analyzed at the same time. Serum 25(OH)D and PTH levels were measured, respectively, by chemiluminescence (LIAISON; DiaSorin, Stillwater, MN, USA: CV intraassay, 6%) and electrochemiluminescence (Elecsys; Roche Diagnostics, Indianapolis, IN, USA, CV intraassay, 2%), before the allocated treatment and after 1, 2, 3, 6, and 9 months. Serum albumin, total calcium, phosphorus, magnesium, creatinine, and alkaline phosphatase levels were measured at the month of recruitment, and serum albumin, total calcium, phosphorus, and alkaline phosphatase levels were measured after 1, 2, 3, 6, and 9 months of treatment, by routine methods at HCPA.

Normal range for serum PTH levels were calculated in a prior study, by the mean ± 2 SD, in inpatients with serum 25(OH)D levels ≥20 ng/ml [26,27]. Secondary hyperparathyroidism was defined as serum PTH level >48 pg/ml, with normal or low serum total calcium levels, and vitamin D deficiency was defined as serum 25(OH)D levels <20 ng/ml.

The following adverse effects were assessed: hypercalcemia and gastrointestinal intolerance. The nursing staff of the institution evaluated adherence to treatment by direct supervision of its ingestion.

Statistical analysis

Population baseline characteristics were compared using Student *t* tests, Fisher's exact test, and χ^2 with Yates correction. The serum 25(OH)D and PTH levels were transformed logarithmically. The differences between the means observed in the two groups were evaluated by analysis of variance (ANOVA) for repeated measures. One-way ANOVA was used to study the differences between the means in the same group. The Bonferroni test was used to adjust multiple comparisons. The Fisher's exact and χ^2 with Yates correction tests were used for categorical variables. Only the data from individuals completing the allocated treatment were analyzed. Differences were considered significant when the two-tailed *P* value was less than 0.05. Data were calculated using the SPSS statistics package for Windows version 13.0.

Results

Twenty-eight individuals were followed from April 2006 to January 2007. Thirteen individuals concluded the study in

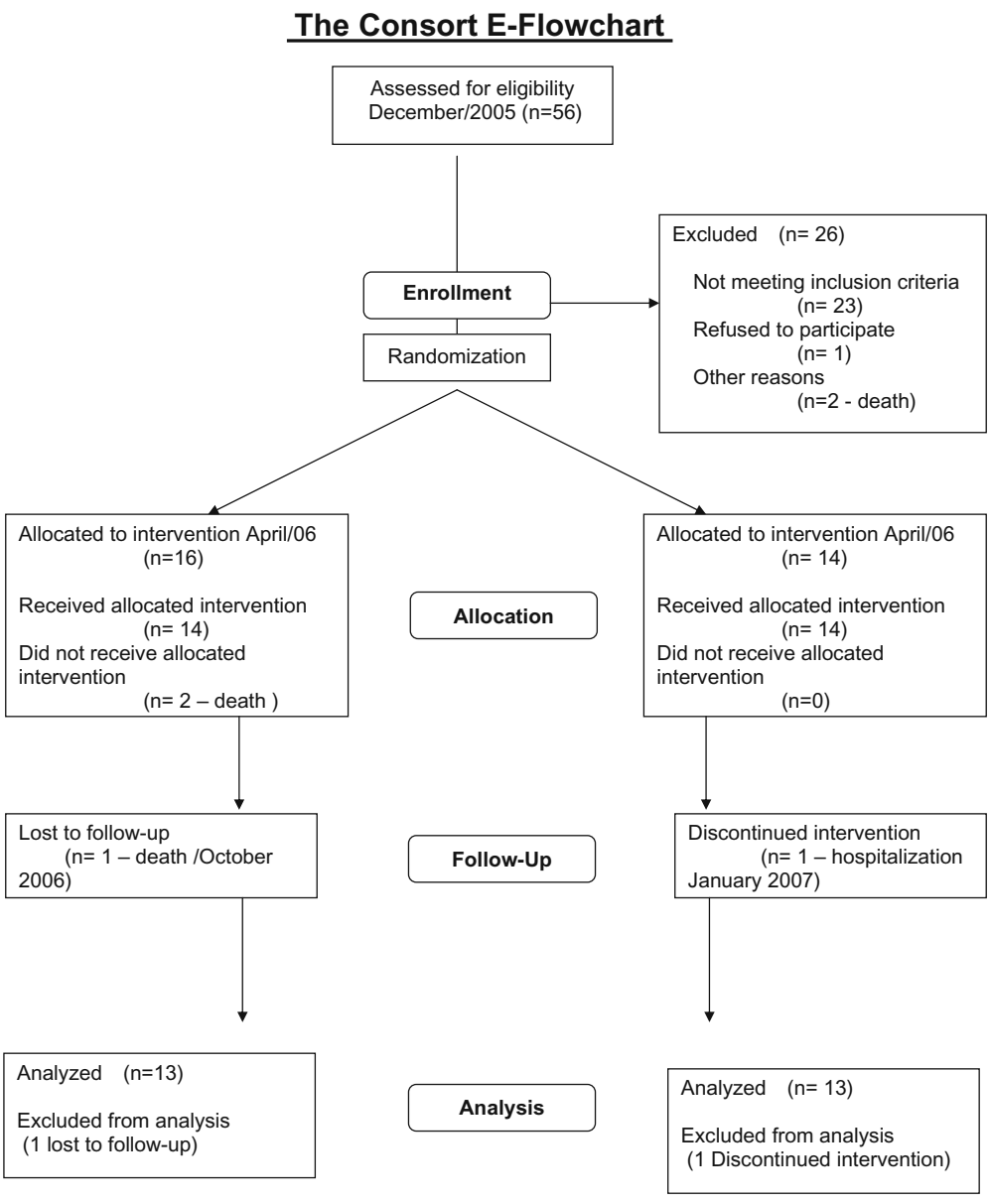

Fig. 1. Flowchart of elderly adults who participated in the study

each group (Fig. 1). Adherence to treatment in both groups was similar and greater than 95%.

The baseline characteristics for this population are described in Table 1. The mean calculated calcium intake in their regular diet was diet was 720 mg per day.

After treatment with a single oral dose of 300 000 IU vitamin D_3, mean serum 25(OH)D levels were significantly higher than after a daily oral dose of 800 IU ($P < 0.001$), during the 9 months using the ANOVA for repeated-measures test. Mean serum 25(OH)D levels were higher in group 1, at the end of the first ($P = 0.001$), second ($P = 0.039$), and third months, although not significant in the latter. At the end of the sixth month, mean serum 25(OH)D levels were similar in both groups, and, at the end of the ninth month, they were similar in group 2 ($P = 0.038$). Mean serum PTH levels were similar in both groups during the 9 months of the study ($P = 0.053$), although there was a trend for them to be lower in group 1, with mean serum levels significantly lower after the second month ($P = 0.027$) (Fig. 2). Mean serum albumin, total calcium, phosphorus, and alkaline phosphatase levels were similar in both groups (data not shown).

The number of individuals who reached serum 25(OH)D levels ≥20 ng/dl was higher in group 1 after 1 ($P < 0.001$), and 3 ($P = 0.008$) months (Fig. 3).

In both treatment groups, mean serum 25(OH)D levels increased ($P < 0.001$) (data not shown).

Two individuals in Group 1 presented gastric intolerance ($P = 1.0$). No hypercalcemia was identified.

Discussion

Two-months after the oral administration of cholecalciferol in a single 300 000 IU dose or a daily 800 IU dose, the higher

Table 1. Baseline characteristics of elderly treated with single or daily dose of vitamin D_3

	$n = 28$	300 000 IU single dose + Ca ($n = 14$)	800 IU daily + Ca ($n = 14$)	P
Age (years)	80.8 ± 8.7	78.9 ± 7.6	81.4 ± 9.9	0.46
Phototype I and II	92.9	92.9	92.9	1.00
Female	67.9	57.1	71.4	0.42
Smokers	25	21.4	28.6	0.51
Alcohol use	3.6	0	7.1	1.00
Use of more than 5 medications	28.6	28.6	30.8	1.00
Exposure to sun[a]	25	35.7	14.3	0.38
Weight (kg)	63.9 ± 12.4	62.8 ± 10.3	64.9 ± 14.4	0.67
BWI (kg/m^2)	23.9 ± 3.8	23.4 ± 3.1	24.4 ± 4.6	0.60
PTH (pg/ml)[b]	74.5 ± 26.2	70.6 ± 25.0	78.3 ± 27.6	0.35
25(OH)D (ng/ml)[b]	10.8 ± 5.9	12.4 ± 6.7	9.2 ± 4.9	0.21
Albumin (g/dl)	4.0 ± 0.2	3.986	4.043	0.45
Total calcium (mg/dl)	9.5 ± 0.3	9.5 ± 0.3	9.5 ± 0.4	1.0
Phosphorus (mg/dl)	3.8 ± 0.7	3.4 ± 0.7	3.6 ± 0.7	0.58
Magnesium (mg/dl)	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	0.84
Alkaline phosphatase (U/L)[b]	84.3 ± 19.7	86.5 ± 22.8	82.1 ± 16.6	0.85
Creatinine (mg/dl)	1.2 ± 0.5	1.2 ± 0.4	1.2 ± 0.5	0.68
GFR[c] (ml/min)	44.3 ± 17.3	46.8 ± 17.9	41.8 ± 16.9	0.45

Data are shown as mean ± SD or %
[a] Exposure to sun more than 3 h/week
[b] For statistical analysis, these variables were transformed into their natural logarithms
[c] GFR, glomerular filtration rate, calculated by the Cockcroft–Gault equation

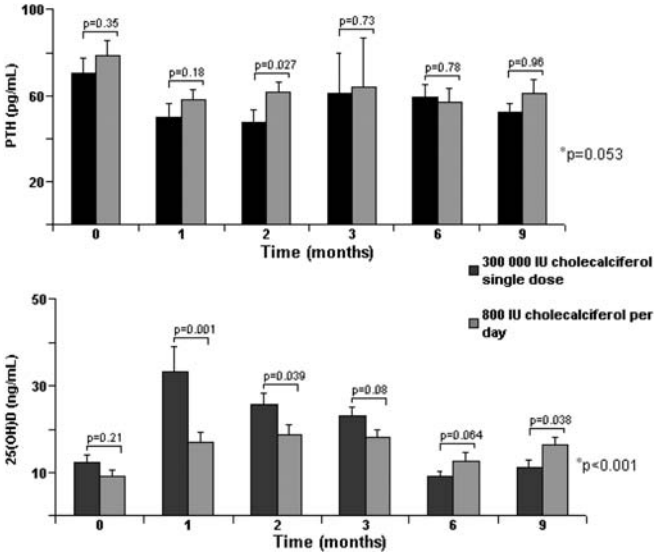

Fig. 2. Comparison of the effect of two cholecalciferol doses, 300 000 IU single dose and 800 IU per day, on serum parathyroid hormone (*PTH*) and *25(OH)D* levels. Data are shown as mean ± SD. *, comparison between groups from 0 to 9 months

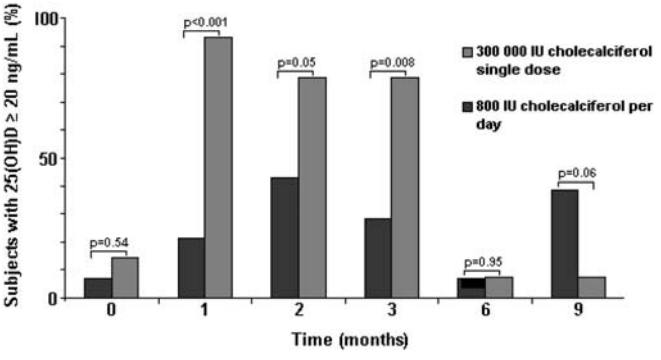

Fig. 3. Individuals with serum 25(OH)D levels higher than or equal to 20 ng/ml, after treatment with a single 300 000 IU cholecalciferol dose or 800 IU per day. The data are shown as percentages of the total

dose was more effective for increasing serum 25(OH)D levels and for decreasing secondary hyperparathyroidism in elderly living in a low-income housing unit. The number of individuals with serum 25(OH)D levels ≥20 ng/dl higher in group 1, only in the first 3 months. Unfortunately, serum 25(OH)D levels were not measured after 4 and 5 months, so it is not precisely known when this dose ceased to be more effective.

In our country, the winter months are July, August, and September, which correspond to months 3, 4, and 5, and this may have contributed to the reduction in serum vitamin D levels. After 6 months, both treatments were no longer effective in maintaining appropriate serum 25(OH)D levels. The influence of reduced sunlight during this period of the year cannot be disregarded. In some regions of Brazil the serum vitamin D levels could vary according to the seasons of the year. In a cohort study in the city of São Paulo, located on parallel 23° S, Brazil, 250 elderly living in the community had mean serum 25(OH)D levels varying from 33.6 ng/ml, in the high summer, to 11.6 ng/ml in September [28]. Other studies in locations with similar latitudes also revealed seasonal variations in serum 25(OH)D levels, similar to Buenos Aires, Argentina, 34° S [29–31] and Auckland, New Zealand, 36°51′ S [32]. As Porto Alegre, Brazil, is located on parallel 30° S, it is very likely that seasonal sunlight is also important to determine vitamin D production.

In individuals taking 800 IU vitamin D_3 per day, the percentage with serum 25(OH)D levels higher than

20 ng/ml varied from 21.4% to 42.9%, in the first 3 months, in different studies [33–36]. In the MORE study [17] approximately 77% of the subjects treated with vitamin D_3 (400–600 IU/day) and calcium (500 mg/day) for 6 months reached serum 25(OH)D >20 ng/ml. The administration of 800 IU vitamin D_3 plus calcium daily decreased serum PTH levels by 13% to 50% in different trials in a period between 3 and 24 months [33,37–39]. The magnitude of this reduction depended on the degree of vitamin D insufficiency [12]. In the Decayos I study, a group of institutionalized elderly women with initial mean serum 25(OH)D levels of 16 ± 11 ng/ml had a reduction of mean serum PTH levels of 29.6%, 6 months after the administration of 800 IU cholecalciferol plus 1200 mg elementary calcium. These results were confirmed in the Decayos II study [8,37]. In our study, there was no significant reduction in mean serum PTH levels after 800 IU cholecalciferol; however, the study may not have had sufficient statistical power to detect a difference of this magnitude.

Why were the serum 25(OH)D levels so low, in response to 800 IU vitamin D_3 daily, in the present study? Several factors may have contributed. Vitamin D_3 was ingested with a fat-poor meal, so its absorption may not have been complete. Another factor that may have contributed was the low initial serum 25(OH)D level. It is known that initial serum 25(OH)D levels are an important predictive factor for the serum levels of this vitamin to be reached after its replacement. In a study conducted with healthy adult men age 38.7 ± 12 years, Heaney et al [40]. observed that those who had initial serum 25(OH)D between 8 and 16 ng/ml needed doses as high as 2200 IU vitamin D daily, during 20 weeks, to reach serum 25(OH)D levels >30 ng/ml. Institutionalized elderly adults commonly have very low serum 25(OH)D levels in most industrialized countries [1,2] and are probably more vitamin D depleted than most individuals in large clinical trials [11], probably requiring daily doses of vitamin D higher than 800 IU to have appropriate 25(OH)D serum levels. Low daily calcium ingestion may have also interfered because the subjects received only 500 mg calcium supplement per day and the dietary calcium was not directly measured, so it may have been less than the estimated amount of 720 mg per day.

One to 3 months after a single oral dose of 300 000 IU vitamin D_3, 78.6% to 92.9% of the subjects had serum 25(OH)D levels higher than 20 ng/ml. After 6 months, mean serum 25(OH)D levels were similar to the baseline, indicating that the reserve obtained with the single dose of 300 000 IU vitamin D_3 was not enough to meet the demand for this period. Smaller doses divided into every 3 months, with the same total amount, may be more effective to maintain appropriate 25(OH)D levels, as was observed in a study conducted in Australia. In this study, elderly adults who were given 100 000 IU cholecalciferol per month for 3 months had an increase in mean serum 25(OH)D levels from 14.6 ± 4.2 ng/ml to 49.6 ± 11.2 ng/ml at the end of 6 months [41]; however, the influence of calcium ingestion was not evaluated.

To our knowledge, this is the first study comparing the effect of a single 300 000 IU oral dose of vitamin D_3 on serum 25(OH)D and PTH levels. In the short term, a single 300 000 IU oral dose of vitamin D_3 was more effective than 800 IU per day to increase serum 25(OH)D levels in elderly persons living in a low-income housing unit, who were taking 500 mg elementary calcium supplement per day.

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