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Effects of a Short-Term Vitamin D_3 and Calcium Supplementation on Blood Pressure and Parathyroid Hormone Levels in Elderly Women*

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ABSTRACT

Calcium supplementation is effective in reducing blood pressure in various states of hypertension, including pregnancy-induced hypertension and preeclampsia. In addition, calcitropic hormones are associated with blood pressure. The hypothesis is that short-term therapy with calcium and vitamin D_3 may improve blood pressure as well as secondary hyperparathyroidism more effectively than calcium monotherapy.

The effects of 8 weeks of supplementation with vitamin D_3 (cholecalciferol) and calcium on blood pressure and biochemical measures of bone metabolism were studied. The sample consisted of 148 women (mean ± SD age, 74 ± 1 yr) with a 25-hydroxycholecalciferol ($25OHD_3$) level below 50 nmol/L. They received either 1200 mg calcium plus 800 IU vitamin D_3 or 1200 mg calcium/day. We measured intact PTH, $25OHD_3$, 1,25-dihydroxyvitamin D_3, blood pressure, and heart rate before and after treatment.

Compared with calcium, supplementation with vitamin D_3 and calcium resulted in an increase in serum $25OHD_3$ of 72% ($P < 0.01$), a decrease in serum PTH of 17% ($P = 0.04$), a decrease in systolic blood pressure (SBP) of 9.3% ($P = 0.02$), and a decrease in heart rate of 5.4% ($P = 0.02$). Sixty subjects (81%) in the vitamin D_3 and calcium group compared with 35 (47%) subjects in the calcium group showed a decrease in SBP of 5 mm Hg or more ($P = 0.04$). No statistically significant difference was observed in the diastolic blood pressures of the calcium-treated and calcium- plus vitamin D_3-treated groups ($P = 0.10$). Pearson coefficients of correlation between the change in PTH and the change in SBP were 0.49 ($P < 0.01$) for the vitamin D_3 plus calcium group and 0.23 ($P < 0.01$) for the calcium group.

A short-term supplementation with vitamin D_3 and calcium is more effective in reducing SBP than calcium alone. Inadequate vitamin D_3 and calcium intake could play a contributory role in the pathogenesis and progression of hypertension and cardiovascular disease in elderly women. (*J Clin Endocrinol Metab* **86:** 1633–1637, 2001)

CALCIUM AND VITAMIN D_3 are essential regulating factors in biological systems. The pivotal role of calcium and vitamin D deficiency in the pathogenesis of osteoporosis is generally accepted (1–3). In addition, other reports suggest that calcium intake may have effects in a variety of unrelated diseases such as arterial hypertension (4–7), cancer of the colon (8, 9), and prevention of nephrolithiasis (10). Furthermore, an association of 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$] and blood pressure has been shown in normotensive men (11), myocardial infarction was inversely associated with plasma 25-hydroxyvitamin D_3 ($25OHD_3$) levels in a community-based study (12), and higher blood pressure in elderly women correlated to increased bone loss in a recently published prospective study (13). On the other hand, dietary calcium intake fails to meet recommended levels in virtually all categories of Americans (14, 15), and hypovitaminosis D affects both Americans (16) and Europeans (17).

We have previously shown that short-term supplementation with vitamin D_3 and calcium improves body sway and secondary hyperparathyroidism and therefore prevents falls and subsequent nonvertebral fractures in elderly women (18, 19). We have now extended our studies to the effects of short-term supplementation with vitamin D_3 and calcium on blood pressure, as vascular smooth muscle is a target organ for vitamin D (20). The role of calcitropic hormones in the regulation of blood pressure is unclear (21–23). To our knowledge this is the first randomized, placebo-controlled, and double-blind clinical trial investigating the effects of calcium and vitamin D_3 compared with calcium therapy on blood pressure in elderly women.

Subjects and Methods

Subjects

We studied ambulatory women 70 yr of age or older who were recruited through newspaper advertisements in our community. The inclusion criterion was a $25OHD_3$ serum level below 50 nmol/L, and the exclusion criteria included hypercalcemia or primary hyperparathyroidism; fractures of the extremities due to osteoporosis; therapy with thiazide, bisphosphonate, calcitonin, vitamin D_3 and other vitamin D metabolites, estrogen, antiestrogen in the past 6 months, or fluoride in the past 2 yr; known intolerance to study medication; chronic renal failure (serum creatinine >20% of the upper limit of the reference range); history of drug or alcohol abuse; nicotine abuse (>20 cigarettes/day); more than seven cups of coffee daily; scheduled holiday along the geographic longitude during the study period, diabetes mellitus; and severe cardiovascular disease (*e.g.* myocardial infarction, stroke, and known hypertension with a systolic blood pressure of >180 mm Hg and a diastolic blood pressure of >95 mm Hg after 5 min of resting).

Two hundred and eight subjects were prescreened by a standardized telephone interview. One hundred and sixty-five (79%) were invited for screening, of whom 148 (71%) were finally enrolled. The protocol was

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TABLE 1. Baseline clinical characteristics of the 148 subjects

Characteristic	Value	
	Calcium (n = 74)	Calcium-vitamin D_3 (n = 74)
Age (yr)	74.7 ± 4.2	74.8 ± 4.1
Range (yr)	70–86	70–86
Height (cm)	162.8 ± 5.1	162.0 ± 6.0
Weight (kg)	65.1 ± 9.1	65.2 ± 9.7
Physical activity		
Daily/weekly/monthly/sporadic (%)	19/31/0/50	16/27/1/55
Concomitant diseases–no. (%)		
Cardiovascular (mild hypertension)	27 (18)	31 (21)
Central nervous, neurological	8 (5)	11 (7)
Psychiatric	1 (<1)	0
Musculoskeletal system	17 (11)	16 (11)
Concomitant medication–no. (%)		
Benzodiazepine use	2 (1.4)	2 (1.4)
Thyroidotherapy	10 (6.8)	10 (6.8)
Cardiovascular drugs	32 (47)	36 (53)

Values for age, height, and weight are the mean ± SD.

approved by the responsible ethics committee, and written informed consent was obtained from each subject.

Study design and supplements

During an 8-week, double-blind, controlled trial, subjects were randomly assigned to either the calcium or the vitamin D_3-calcium group. At study entry, a complete physical examination and assessment of each subject's medical history, diet, and physical activity were performed. In addition, blood and urine were analyzed. The subjects were advised to maintain their usual diets and to avoid taking supplemental calcium and vitamin D on their own. The subjects took either one tablet containing 600 mg elemental calcium in the form of calcium carbonate or one tablet with 600 mg elemental calcium and 400 IU vitamin D_3 at breakfast and dinner together with meals. The tablets of calcium or calcium plus vitamin D_3 were identical.

The study took place in Bad Pyrmont and Hameln, two neighborhood cities in Lower Saxony, Germany (latitude, 52°N). It commenced in March (when vitamin D levels are known to be at their lowest level) 1997 and terminated in May 1997.

Status of subjects and compliance

During the trial one subject in the calcium group was excluded from the study due to noncompliance. She refused to undergo the measurements. One subject in the vitamin D_3-calcium group and another in the calcium group discontinued for personal reasons (loss of interest and decision to go on holiday). One hundred and forty-five subjects were examined at their final visit and included in the intention to treat analyses. The mean ± SD rate of compliance with treatment, assessed on the basis of pill counts, was 95 ± 12% for the calcium tablets and 96 ± 10% for the vitamin D_3-calcium tablets.

Measurements

The calcium, vitamin D, and salt intakes of the subjects were assessed semiquantitatively by a food frequency questionnaire. Physical activity as well as consumption of alcohol and nicotine were also determined by questionnaires. Height was measured with a stadiometer, and weight was determined with a digital scale. Concomitant medication was classified according to Anatomical Therapeutic Chemical groups and anatomical regions depending on the active compound and the indication (Anatomical Therapeutic Chemical classification index 1994) (24). Blood pressure and pulse rate were measured after at least 5 min of supine rest in a quiet room using a sphygmomanometer with an appropriate cuff. Systolic and diastolic blood pressures were taken at Korotkov sounds I and V.

TABLE 2. Initial and final routine laboratory parameters at 8 weeks in 145 study subjects, according to study group (intention-to-treat)

Index and Study Group	Initial value	Final value
Hemoglobin (g/dL), [11.0–16.5]		
Calcium	13.65 ± 0.91	13.34 ± 1.02
Vitamin D_3-calcium	13.42 ± 0.95	13.24 ± 0.90
Hematocrit (%), [36.0–48.0]		
Calcium	41.04 ± 2.79	40.30 ± 2.66
Vitamin D_3-calcium	40.33 ± 3.10	40.04 ± 2.80
MCV (fL), [82–96]		
Calcium	91.69 ± 4.26	92.43 ± 4.46
Vitamin D_3-calcium	90.39 ± 3.65	91.26 ± 4.80
Erythrocyte count (1/pl), [4.1–5.4]		
Calcium	4.48 ± 0.32	4.37 ± 0.28
Vitamin D_3-calcium	4.47 ± 0.33	4.39 ± 0.32
Leukocyte count (L/nL), [4.0–9.0]		
Calcium	6.56 ± 1.58	6.38 ± 1.94
Vitamin D_3-calcium	7.46 ± 2.24	6.82 ± 2.67
Platelet count (L/nL), [150–400]		
Calcium	227.1 ± 51.6	194.9 ± 57.8
Vitamin D_3-calcium	224.8 ± 59.1	192.0 ± 61.6
Total bilirubin (mg/dL), [<1.0]		
Calcium	0.37 ± 0.23	0.34 ± 0.14
Vitamin D_3-calcium	0.36 ± 0.20	0.36 ± 0.17
γ-GT (U/L), [<25]		
Calcium	16.34 ± 19.84	15.59 ± 9.63
Vitamin D_3-calcium	20.04 ± 17.29	21.61 ± 20.37
Total cholesterol (mg/dL), [200–260]		
Calcium	248.7 ± 45.0	239.5 ± 37.5
Vitamin D_3-calcium	246.8 ± 42.1	245.2 ± 43.0
Albumin (g/L), [35.0–55.0]		
Calcium	45.23 ± 3.29	39.19 ± 2.38
Vitamin D_3-calcium	45.30 ± 3.99	39.54 ± 2.26
Serum creatinine (mg/dL), [<1.1]		
Calcium	0.84 ± 0.11	0.88 ± 0.11
Vitamin D_3-calcium	0.86 ± 0.14	0.93 ± 0.19
Potassium (mmol/L), [3.6–5.4]		
Calcium	4.53 ± 0.39	4.37 ± 0.33
Vitamin D_3-calcium	4.57 ± 0.53	4.36 ± 0.37
Sodium (mmol/L), [135–150]		
Calcium	144.1 ± 4.0	142.9 ± 3.1
Vitamin D_3-calcium	143.9 ± 4.4	142.6 ± 3.2

Values are the mean ± SD; [reference range]. γ-GT, γ Glutamyltransferase.

Laboratory analyses

Blood was drawn between 0800–0900 h after the subjects had fasted for at least 8 h. Urine measurements were made in overnight collections, taken between 0000–0700 h. Serum $25OHD_3$, and $1,25\text{-}(OH)_2D_3$ were measured by RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA), serum PTH by immunometric assay (Nichols Institute Diagnostics), serum ionized calcium and urinary calcium by the kresolphtalein method, serum creatinine and urinary creatinine by the Jaffé method, total bilirubin by the dichlorphenyldiazo method, γ-glutamyl-transferase by the Szasz method, and albumin by the bromkresolgreen method. Erythrocytes, leukocytes, and platelets were counted by an electronic counter; hemoglobin was determined by the cyanhemoglobin method; and hematocrit and mean corpuscular volume were calculated. The coefficients of variation for the assays ranged from 5.5–7.9%. All samples, except for the screening samples and the hematological samples, were frozen at −80 C and analyzed at the same time.

Statistical analyses

The biostatistical evaluation was carried out using the statistical software package SAS for Windows (version 6.10) and NCSS (version 6.0.21, CCDRD, Berlin, Germany). For determination of sample size, the software package NCSS-PASS 1.0 was used. The expected difference between both therapy groups was estimated at 40–60% of the SD. To detect

TABLE 3. Initial and final laboratory values at 8 weeks in 145 study subjects, according to study group (intention-to-treat)

Index and study group	Initial value	Final value[a]	P^b
Serum ionized calcium (mmol/mL), [2.1–2.7]			
Calcium	2.40 ± 0.11	2.49 ± 0.14	
Vitamin D_3-calcium	2.43 ± 0.11	2.52 ± 0.15	
Serum 25(OH)D_3 (nmol/mL), [25–75]			
Calcium	24.63 ± 12.14	44.36 ± 27.38	
Vitamin D_3-calcium	25.65 ± 13.63	64.84 ± 25.84	<0.01
Serum 1,25$(OH)_2D_3$ (ng/L), [16–43]			
Calcium	36.78 ± 15.69	48.43 ± 25.67	
Vitamin D_3-calcium	36.35 ± 16.52	51.20 ± 24.35	
Serum PTH (pmol/L), [1.1–6.9]			
Calcium	6.14 ± 2.60	5.26 ± 3.79	
Vitamin D_3-calcium	6.11 ± 2.34	4.55 ± 2.26	0.04
Urinary calcium:creatinine ratio (nmol/L)			
Calcium	1.84 ± 1.52	3.42 ± 2.45	
Vitamin D_3-calcium	1.60 ± 1.15	3.43 ± 2.46	

Values are the mean ± SD; [reference range].
[a] $P < 0.01$ (probability for a population mean of 0 by the Wilcoxon test by chance alone).
[b] P values represent the probability of the difference between the two treatments.

a difference of 50% of the SD with a power of 80%, 74 subjects/group were needed. A normal distribution could be assumed for the pre-post differences. A 2-sided t test for independent samples could be applied. If a significant deviation from normality was found, the Mann-Whitney U test was used. In addition, Pearson coefficients of correlation were calculated between the changes in PTH and the changes in blood pressure.

Results

Of the 165 subjects who underwent screening, 151 (91%) had a 25OHD_3 level below 50 nmol/L. The baseline characteristics of the 148 subjects enrolled in this trial are shown in Table 1. Both treatment groups were comparable concerning age, height, weight, physical activity, concomitant diseases, and concomitant medication. Forty-seven percent in the calcium group and 53% in the vitamin D_3-calcium group used cardiovascular drugs (according to the Anatomical Therapeutic Chemical classification index) for the treatment of hypertension. There were no changes in these medications during the study. In addition, there were no group differences with regard to dietary calcium, vitamin D, and salt intake (data not shown).

Initial and final routine laboratory parameters of the subjects are presented in Table 2. All parameters were within the normal reference range and did not change significantly during the course of the study. However, we observed a tendency for a lower platelet count and a lower serum albumin in both treatment groups.

Compared with baseline, significant increases in serum ionized calcium, urinary calcium, serum 25OHD_3, and serum 1,25-$(OH)_2D_3$ were found in both treatment groups. Significant decreases were found in serum PTH (Table 3).

Compared with calcium, a significant increase in serum 25OHD_3 ($P < 0.01$) and a significant decrease in serum PTH ($P = 0.04$) were observed in the vitamin D_3-calcium group.

The changes in blood pressure and heart rate are documented in Tables 4 and 5. Compared with baseline, significant decreases were found in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in both treatment groups. Concerning heart rate, a significant decrease was found only in the vitamin D_3-calcium group.

Compared with calcium, treatment with vitamin D_3 and calcium led to a significant reduction in SBP ($P = 0.02$) and heart rate ($P = 0.02$). The reduction in DBP was more pronounced in the vitamin D_3-calcium group, but this difference did not reach the level of statistical significance ($P = 0.10$).

TABLE 4. Initial and final blood pressure and heart rate at 8 weeks in 145 study subjects, according to study group (intention-to-treat)

Index and study group	Initial value	Final value	P
SBP (mm Hg)			
Calcium	140.6 ± 14.7	134.9 ± 19.9[a]	
Vitamin D_3-calcium	144.1 ± 20.4	131.0 ± 16.9[a]	0.02[b]
DBP (mm Hg)			
Calcium	82.6 ± 6.4	75.7 ± 12.5[a]	
Vitamin D_3-calcium	84.7 ± 7.6	77.5 ± 12.4[a]	0.10
Mean heart rate (beats/min)			
Calcium	74.1 ± 8.4	73.9 ± 11.8	
Vitamin D_3-calcium	75.4 ± 11.4	71.3 ± 13.6[a]	0.02[b]

Values are the mean ± SD; measurements were done after 5 min of rest.
[a] $P < 0.01$ significantly different *vs.* baseline.
[b] P values represent the probability of the difference between the two treatments.

Sixty subjects (81%) in the vitamin D_3-calcium group compared with 35 (47%) subjects in the calcium group showed a decrease in SBP of 5 mm Hg or more ($P = 0.04$). In contrast, only 8 subjects (11%) in the vitamin D_3-calcium group compared with 29 subjects (39%) in the calcium group showed an increase in SBP of 5 mm Hg or more ($P = 0.04$).

A decrease in heart rate of 5 beats/min or more was observed in 38 subjects (51%) during treatment with vitamin D_3-calcium compared with 13 subjects (18%) treated with calcium alone ($P = 0.02$). On the other hand, we observed an increase in heart rate of 5 beats/min or more in only 7 subjects (9%) in the vitamin D_3-calcium group compared with 23 subjects (31%) in the calcium group ($P < 0.01$).

Pearson coefficients of correlation between the change in PTH and the change in SBP were 0.49 ($P < 0.01$) for the vitamin D_3 plus calcium group and 0.23 ($P < 0.01$) for the calcium group (Table 6).

TABLE 5. Changes in systolic blood pressure, diastolic blood pressure, and mean heart rate after 8 weeks of treatment in 145 study subjects, according to study group (intention-to-treat)

Index and study group		P^a
SBP (mm Hg)		
Subjects with a decrease in SBP >5 mm Hg–no. (%)		
Calcium	35 (47)	
Vitamin D_3-calcium	60 (81)	0.04
Subjects with an increase in SBP >5 mm Hg–no. (%)		
Calcium	29 (39)	
Vitamin D_3-calcium	8 (11)	0.05
DBP (mm Hg)		
Subjects with a decrease in DBP >5 mm Hg–no. (%)		
Calcium	36 (49)	
Vitamin D_3-calcium	58 (78)	0.10
Subjects with an increase in DBP >5 mm Hg–no. (%)		
Calcium	21 (28)	
Vitamin D_3-calcium	10 (13)	0.02
Mean HR (beats/min)		
Subjects with a decrease in HR >5 beats/min–no. (%)		
Calcium	13 (18)	
Vitamin D_3-calcium	38 (51)	0.02
Subjects with an increase in HR >5 beats/min–no. (%)		
Calcium	23 (31)	
Vitamin D_3-calcium	7 (9)	<0.01

HR, Heart rate.
[a] *P* values represent the probability of the difference between the two treatments.

TABLE 6. Pearson coefficients of correlation between the change in PTH and the change in blood pressure after 8 weeks of treatment in 145 subjects, according to study group (intention-to-treat)

	SBP	DBP
Calcium	+0.23[a]	+0.08[b]
Vitamin D_3-calcium	+0.49[a]	+0.44[a]

[a] $P < 0.01$.
[b] Not significant.

Discussion

In this study short-term supplementation with vitamin D_3 and calcium reduced SBP, heart rate, and PTH levels in women 70 yr of age or older who were living in our community. Although this study was started at the end of winter, there was a significant advantage for the vitamin D_3-calcium group compared with the calcium group. This indicates that even in spring naturally synthesized vitamin D in the skin is not able to compensate for the loss in winter.

These results are in accordance with a publication by Krause *et al.* (25), who demonstrated that ultraviolet B irradiation and increased circulating levels of 25OHD were related to a decrease in both SBP and DBP.

Two meta-analyses of controlled trials of blood pressure and calcium levels in 2412 adults and 2459 pregnant women provide compelling evidence that both normotensive and hypertensive individuals may experience reductions in blood pressure when calcium intake is increased (6, 7). However, the absolute change in SBP in the 2412 adults was only 1.3 mm Hg, and the change in DBP was 0.2 mm Hg. In the present study we observed substantially bigger changes in SBP, which may be due at least in part to the underlying hypovitaminosis D associated with elevated PTH levels. Calcium requirements vary across the life span (15). When calcium needs are increased, the relationship between calcium intake and biological responses may be amplified. Elderly people may require greater calcium intake (15) due to malabsorption and vitamin D deficiency (16, 17), and old age is also a period associated with an increased risk of elevated blood pressure (26).

In a cross-sectional study (11) an inverse association between serum 1,25-$(OH)_2D_3$ level and blood pressure was described in normotensive men. St. John *et al.* (27) investigated the relationship between calcitropic hormones and blood pressure in 583 elderly subjects who were untreated for hypertension, but who were not vitamin D deficient. Univariate analysis demonstrated that serum PTH and 1,25-$(OH)_2D_3$ were correlated significantly with mean blood pressure. The coefficients of correlation, however, were rather low (r = 0.15 and 0.10, respectively). Multivariate analysis in the same study demonstrated that PTH and 1,25-$(OH)_2D_3$ were both significant independent determinants of the mean blood pressure. In summary, the study by John *et al.* (27) showed a weak, but significant, relationship between blood pressure and calcitropic hormones in a group of elderly people. The researchers concluded that hypertension may be due in part to calcium deficiency. This conclusion could be supported by Hvarfer *et al.* (28), who showed a statistically significant inverse relationship between mean blood pressure and plasma ionized calcium in 97 healthy subjects, aged 16–82 yr (28).

Hyperparathyroidism has been associated with hypertension (29), and it increases calcium uptake in human cells (30). Parathyroidectomy after primary hyperparathyroidism improves blood pressure and arterial smooth muscle (31, 32). Chronic PTH infusion results in hypertension in normal subjects (33). Thus, if the beneficial effect of calcium supplementation is mediated by a reduction in PTH secretion, it is likely that it occurs by a restoration of parathyroid gland function to normal. In our study we found a positive significant correlation between the change in PTH and the change in SBP in the vitamin D_3 plus calcium group (r = 0.49)

and the calcium group ($r = 0.18$). These results are in accordance with the study by Brickman *et al.* (34), who demonstrated a similar positive correlation between intact PTH and SBP ($r = 0.41$; $P < 0.01$) in a group of 91 normotensive subjects. When multiple regression analysis was performed using mean arterial pressure as the dependent variable, PTH maintained a significant correlation with mean arterial pressure (34). Together, these results suggest that PTH is associated with blood pressure regulation in normotensive subjects.

High salt intake has been associated with reduced peak bone mass in young girls, aged 8–13 yr (35), and with a higher rate of bone mineral loss in postmenopausal women (36). High salt intake causes an increase in urinary calcium excretion (37), and a decrease in dietary intake should promote a positive calcium balance and lower blood pressure. Decreased salt intake should therefore lessen the risk of osteoporosis and hip fractures in elderly people and also have a blood pressure-lowering effect (38).

Our study demonstrates that short-term supplementation with vitamin D_3 and calcium is more effective in reducing SBP than calcium alone, and this effect is most likely to be due to the restoration of parathyroid gland function to normal. Inadequate vitamin D_3 and calcium intake are not only a risk for osteoporosis, but they could play a contributory role in the pathogenesis and progression of hypertension and cardiovascular disease, particularly in elderly people with vitamin D deficiency and secondary hyperparathyroidism. Consequently, our results are also consistent with the inverse association among bone mineral density (13), stroke incidence (39), and cardiovascular mortality (40).

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