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Controlled Trial of Long-term Oral Calcium Supplementation in Essential Hypertension

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SUMMARY **A randomized, double-blind, placebo-controlled crossover trial of oral calcium supplementation was carried out in 18 patients with uncomplicated essential hypertension. After 15 weeks of oral calcium supplementation, 1 g/day, of the patients' habitual diet, the only blood pressure change (compared with the results of placebo treatment) was in the average standing systolic blood pressure, which was significantly reduced (−8.6 mm Hg; $p<0.01$). The 24-hour urinary calcium excretion and the total serum calcium concentration increased significantly during calcium supplementation ($p<0.05$), indicating good compliance with the treatment. The individual blood pressure changes with high calcium intake were found to be inversely related to basal 24-hour urinary calcium excretion ($r=-0.69$, $p<0.001$ for standing systolic pressure; $r=-0.55$, $p<0.002$ for standing diastolic pressure). This correlation was independent of age, basal blood pressure, serum calcium concentration, basal 24-hour urinary sodium excretion, and body weight changes during the trial. In particular, a subgroup of six patients, who had a basal 24-hour urinary calcium excretion higher than the mean + 2 SD of a reference healthy population previously described, showed a substantial average blood pressure fall at variance with the other patients in the study. These results do not support the usefulness of an oral calcium supplement in the majority of subjects with mild essential hypertension; however, they suggest that a group of patients with a previously reported abnormality of calcium metabolism may be responsive to this therapeutic measure. (Hypertension 8: 1084–1088, 1986)**

KEY WORDS • **calcium intake** • **essential hypertension** • **urinary calcium excretion** • **controlled trial**

EPIDEMIOLOGICAL,[1–9] clinical,[10–15] and experimental[16–22] data have been presented recently in support of a possible influence of habitual Ca intake on blood pressure (BP). Because of methodological inadequacies or questionable interpretation of the data, this evidence should be considered inconclusive. In fact, there is as yet only one satisfactorily controlled clinical trial of the effects of increased oral Ca intake in hypertensive patients,[14] and its results are debated. This issue is of great interest with regard to prevention and to nonpharmacological control of arterial hypertension; in addition, it is potentially relevant to a better understanding of the pathogenesis of this disease.

The present report describes the results of a long-term, double-blind, randomized crossover trial comparing the effects of oral Ca supplementation with those of placebo in patients with mild essential hypertension.

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Subjects and Methods

Eighteen patients with mild essential hypertension (World Health Organization Stage I–II), who had been referred to the Hypertension Clinic, participated in the study. The mean age (± SEM) of the 11 men and 7 women was 43 ± 9 years and their mean body weight was 68.7 ± 2.9 kg. All of them gave their informed consent to the study procedures, which were in accordance with the institutional guidelines of the University of Naples.

The diagnosis of uncomplicated essential hypertension was made by standard clinical investigation, including routine biochemistry evaluations, measurement of glomerular filtration rate, 24-hour urinary aldosterone and catecholamine excretion, electrocardiogram, radioisotope renogram, and rapid-sequence intravenous pyelography.

All patients were on an unrestricted diet and were instructed to remain on their customary diet throughout the study. Based on a 3-day dietary recall obtained before entry into the trial, the average Ca and phosphorus intakes of the whole group were (mean ± SEM) 602 ± 62 mg/day (range, 361–1074) and 1110 ± 74 mg/day (range, 635–1796) respectively.

Nine patients had been receiving no pharmacological treatment; nine were regularly treated with a β-blocker (metoprolol or atenolol), and their therapy had not been changed during the previous 3 months. No one had recently taken diuretics or other drugs known to affect Ca metabolism.

All patients had a diastolic blood pressure (DBP) between 90 and 105 mm Hg on repeated clinic visits during a run-in period of 2 months before admission to the study. The mean (± SEM) supine BP of treated patients was 150.9 ± 5.4/94.3 ± 3.5 mm Hg and that of untreated patients was 154.7 ± 5.0/98.0 ± 2.4 mm Hg.

The study had a randomized, double-blind, crossover design that included a 1-week baseline period, two 15-week periods of either Ca or placebo treatment, and an intermediate washout period of 12 weeks of placebo treatment. Two separate randomization lists were used for drug-treated and untreated patients.

The oral Ca supplementation (1 g/day) was given twice daily in the form of one Calcium (Sandoz) tablet. Each tablet contained Ca lactogluconate plus Ca carbonate and delivered 500 mg of elemental Ca. During placebo treatment the subjects received placebo tablets identical in appearance to the Ca tablets. The two treatments were prepackaged in identical containers so that both the patients and the medical staff were unaware of the type of medication being administered. Compliance with treatment was checked by questioning and by pill counting at each visit.

The BP and pulse rate (PR) were measured twice at 1-week intervals during baseline and every 3 weeks during each treatment period, always by the same observer, who was blind to the patient's treatment. All measurements were made with the same Hawksley random zero sphygmomanometer (Lancing, Sussex, England)[23] in a quiet and comfortable room kept at constant temperature. After the patient had been resting quietly for 30 minutes in the supine position, three BP and PR measurements were taken 2 minutes apart; then, two upright values were obtained after 2 minutes of standing. The DBP was taken as the disappearance of the fifth Korotkoff sound. The average of all measurements in each position was used in the analysis.

All patients provided two 24-hour urine collections at the start and at the end of each treatment period (a total of 8 collections) for determination of 24-hour sodium, potassium, Ca, phosphate, and creatinine excretion. On the same occasions a venous blood sample was obtained in the morning after a 12-hour fast for measurement of serum total and ionized Ca, phosphorus, creatinine, aldosterone, and plasma renin activity (PRA).

Serum total Ca and urinary Ca were measured by atomic absorption spectrophotometry; sodium and potassium were measured by flame photometry (300 atomic absorption spectrophotometer, Perkin-Elmer, Norwalk, CT, USA). Serum ionized Ca concentration was determined in samples collected in anaerobiosis with a Ca-specific electrode (Orion SS-20, Orion Research, Cambridge, MA, USA). Serum creatinine and urinary creatinine were measured by the picric acid colorimetric method; serum and urinary phosphate by the Seragen Inorganic Phosphorus colorimetric method (Seragen Diagnostics, Indianapolis, IN, USA); serum aldosterone and PRA by radioimmunoassay, using commercially available kits by Sorin Biomedica (Saluggia, Vercelli, Italy).

Statistical analysis was done by standard methods[24] using a Hewlett-Packard HP-85 computer system (Cupertino, CA, USA). An analysis of variance randomized block design was used to assess the comparability of the four initial average blood pressure values (Ca treatment, Phase 1 and 2; placebo treatment, Phase 1 and 2). The effect of Ca supplementation on BP, PR, and biochemical parameters was evaluated by a two-sided paired *t* test comparing the values obtained at the various time points during the Ca treatment period with the corresponding values obtained during placebo treatment. Comparisons of means for subgroup analysis were made using two-sided *t* tests for unpaired observations. Tests of simple and multiple correlation were used to examine the relationship of BP changes during Ca supplementation with different variables. All values are given as the mean ± SEM.

Based on the BP variance during Ca and placebo treatment, the study had a 90% chance of detecting a blood pressure fall of 8/6 mm Hg, a probability level of 0.05 being considered statistically significant.

Results

Seventeen patients completed the trial: one subject had to be withdrawn from the study because of a marked BP increase during placebo treatment. No untoward effects were associated with Ca supplementation; compliance with treatment throughout the study was satisfactory in all subjects.

Average BP was similar at the onset of the Ca and of the placebo treatment period (Figure 1); similarly, there were no differences in the average PR, body weight, and all biochemical variables under investigation. In addition, the initial BP values for Ca treatment, Phase 1 and 2, or placebo treatment, Phase 1 and 2, were not significantly different when tested by analysis of variance with multiple comparison, which permits the exclusion of any carryover effect. Therefore, the effect of Ca supplementation on BP could be evaluated by direct comparison of the respective BP values at the various time points during the two treatment periods.

Figure 1 shows the BP trend during each period: a significant difference was found only in the final (15th week) standing systolic blood pressure (SBP) value,

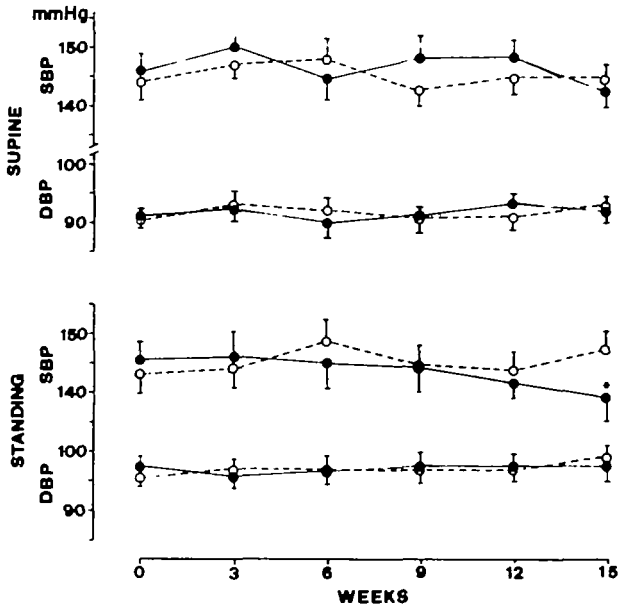

FIGURE 1. *Supine and standing blood pressures during oral Ca supplementation (●) or placebo treatment (○) in 17 patients with essential hypertension. The asterisk indicates a statistically significant difference of calcium versus placebo treatment (p<0.01). DBP = diastolic blood pressure; SBP = systolic blood pressure.*

which was significantly lower during Ca supplementation compared with either placebo treatment (138.9 ± 3.9 vs 147.5 ± 3.1 mm Hg; $p<0.01$) or baseline (138.9 ± 3.9 vs 145.9 ± 3.3 mm Hg; $p<0.01$).

The PR was unchanged by Ca supplementation, as was body weight (70.0 ± 2.1 kg during Ca treatment; 71.2 ± 2.2 kg during placebo treatment).

The BP response to Ca supplementation was also analyzed separately in medically treated and untreated participants. No significant difference was detectable, although SBP in untreated patients was reduced to a slightly greater extent.

Serum total Ca was modestly increased at the end of the Ca supplementation period (2.55 ± 0.05 vs 2.39 ± 0.04 mmol/L; $p<0.05$), whereas a 10% decrease occurred in mean serum phosphorus concentration (1.15 ± 0.06 vs 1.27 ± 0.05 mmol/L; $p = 0.01$).

No statistically significant differences were found in serum ionized Ca (1.16 ± 0.01 vs 1.12 ± 0.01 mmol/L during Ca and placebo treatment, respectively), PRA (1.60 ± 0.35 vs 1.46 ± 0.25 ng angiotensin I/ml/hr), and serum aldosterone (113.9 ± 9.8 vs 124.9 ± 6.6 pg/ml).

The 24-hour urinary Ca excretion during Ca supplementation was significantly enhanced (6.40 ± 0.47 vs 5.57 ± 0.53 mmol/24 hr; $p<0.05$), while no differences were found in sodium (211 ± 18 vs 207 ± 14 mmol/24 hr), potassium (62 ± 5 vs 58 ± 4 mmol/24 hr), or phosphate excretion (660 ± 60 vs 661 ± 59 mg/24 hr).

Pearson correlation analysis indicated that the individual BP changes during Ca supplementation were inversely related to basal 24-hour urinary Ca excretion ($r = -0.69$ for standing SBP, $p<0.001$; $r = -0.55$ for standing DBP, $p<0.02$). Figure 2 is a scattergram of the individual changes in standing SBP as compared with urinary Ca excretion.

A subgroup of six patients with a basal 24-hour urinary Ca output higher than the mean + 2 SD of a healthy population sample previously examined by our laboratory,[25] experienced a substantial average SBP fall on Ca supplementation that was at variance with the other patients in the study (standing SBP: −16.6 ± 6.5 vs −1.7 ± 2.0 mm Hg; $p<0.02$; supine SBP: −10.7 ± 3.9 vs +1.9 ± 2.9 mm Hg; $p = 0.02$). They also had some appreciable decrease in standing DBP (−8.0 ± 5.5 vs +2.2 ± 3.0 mm Hg) and supine DBP (−5.5 ± 4.6 vs +2.3 ± 3.0 mm Hg) compared with normocalciuric patients. The baseline BP of this subgroup was similar to that of the remaining study population. The hypercalciuric subgroup had an equal number of patients on ($n = 3$) or off ($n = 3$) drug treatment; similarly, the normocalciuric subgroup had five untreated and six treated patients.

No other significant correlations were found between BP changes during treatment with orally administered Ca and the variables tested, including habitual dietary Ca and phosphorus intake. In multivariate analysis, when the effects of age, baseline BP, body weight changes, basal urinary sodium and Ca excretion, and serum ionized Ca were tested simultaneously, urinary Ca was confirmed to be the only variable associated with the BP response to treatment (Table 1).

Discussion

The two main findings of the present study were 1) that long-term Ca supplementation had minor effects on the BP levels of our study population overall, as a significant decrease was only detected in standing SBP at the end of the 15-week treatment period, and 2) a

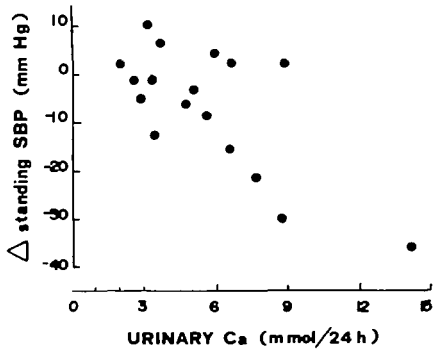

FIGURE 2. *Inverse correlation between 24-hour urinary Ca excretion (average value from two urine collections) and change in standing systolic blood pressure (SBP) after oral Ca supplementation (compared with placebo values):* $y = 9.48 - 2.92x$, $r = -0.69$, $p<0.001$.

TABLE 1. *Multiple Linear Regression, Standing Systolic Pressure Changes,* and Specified Variables*

Variable	Regression coefficient (b)	Variance	*F*
Basal 24-hour U_{Ca} (mmol)	−3.73	0.71	19.6†
Age (yr)	0.59	0.09	6.4‡
Basal 24-hour U_{Na} (mmol)	0.11	0.01	4.9
Basal SBP (mm Hg)	−0.07	0.71	4.1
Serum Ca^{2+} (mmol/L)	0.04	3.21	0.4
Body weight (kg)	0.21	2.07	0.1

U_{Ca} = urinary Ca excretion; U_{Na} = urinary Na excretion; SBP = systolic blood pressure.
*Ca supplementation versus placebo treatment.
†$p < 0.01$, ‡$p < 0.05$.

subgroup of patients characterized by an elevated 24-hour urinary Ca excretion experienced a much larger BP fall, which accounted for most of the standing SBP reduction observed overall. With regard to the first observation, our data are in line with the findings of two recently published studies. Johnson et al.,[11] reporting on the effect of an oral Ca supplement in subjects who received concomitant drug treatment for high BP and were followed up for 4 years, found a significant decrease only in SBP. In their 8-week crossover trial, McCarron and Morris[14] also demonstrated a clinically meaningful response only in standing SBP, with very small, albeit significant, falls in supine SBP and standing DBP.

The BP lowering effect, if any, of an increased Ca intake clearly requires a long interval before becoming apparent (8 weeks in the report by McCarron and Morris,[14] even more in our experience). In fact, as one looks at the standing SBP trend on Ca supplementation in Figure 1, a very slow but continuous decline in the average standing SBP values can be observed over time. Indeed, at present the possibility that more impressive BP changes might occur with more prolonged treatment and follow-up cannot be excluded.

The most intriguing finding of our study was the statistically significant, relatively strong inverse correlation between individual BP changes and basal 24-hour urinary Ca excretion. When a subgroup was identified based on a particularly high value of this parameter at baseline, using a cut-off point given by the mean + 2 SD of a healthy population sample previously studied by our laboratory,[25] it was found that the six subjects so characterized had an average BP response to Ca supplementation that was remarkably better than that of the other patients in the study. This finding may be of interest given the previous demonstration that 24-hour urinary Ca output is increased in a significant proportion of patients with uncomplicated arterial hypertension and otherwise normal renal function.[22, 25-27] This relative hypercalciuria, also described in some models of rat genetic hypertension,[16, 28] may be due to a defect in renal Ca handling, as previously discussed.[25] An obvious explanation for the better response of this subgroup to increased oral Ca intake is not at hand. Subjects with higher urinary Ca loss might have had a higher compensatory increase in parathyroid activity and thus higher levels of circulating 1,25-dihydroxyvitamin D, which in turn could increase the intestinal absorption of the calcium supplement. This hypothesis would have been supported by a higher increase of 24-hour Ca excretion during Ca supplementation in the responders, a finding not observed in this study.

The average dietary Ca intake of the patients in this trial was relatively low; this can be traced to a very low consumption of milk, often observed in adult population samples in southern Italy. Nevertheless, no significant association was found between habitual Ca intake and BP changes on Ca supplementation.

One of the mechanisms proposed for the possible antihypertensive effect of increased Ca intake is that it might promote sodium excretion and thus a decrease in extracellular fluid volume[14]; however, a short-term study of the water and sodium balance during high or low Ca intake did not detect any significant effect of oral Ca administration in this respect.[13] An alternative hypothesis, proposed by Lau et al.,[20] is that high Ca intake could be associated with phosphate depletion, which in turn would reduce myocardial contractility and thereby induce a fall in BP. Among the results of this trial was a significant reduction in serum phosphorus concentration after 15 weeks of oral Ca supplementation (an average 10% decrease). It is hard to say whether such a small reduction could produce a clinically meaningful decrease in heart contractility. Nevertheless, the fact that SBP was preferably reduced (as compared to DBP) should argue against excluding this possibility.

In conclusion, oral Ca supplementation for 15 weeks was well tolerated; overall, it was not associated with a clinically impressive effect on BP. In a subgroup of patients characterized by an elevated urinary Ca output, however, it did have a clinically meaningful BP lowering effect. These results do not support the therapeutic usefulness of a substantial increase in oral Ca intake, at least in the majority of patients with arterial hypertension. Nevertheless, they do suggest the possibility that a group of patients with an abnormality of Ca metabolism, previously described in several studies, may be responsive to this therapeutic measure. More studies are necessary to further characterize these subjects and to better understand the relevance of their metabolic abnormality to the pathogenesis of arterial hypertension.

References

1. McCarron DA, Morris CD, Cole C. Dietary calcium in human hypertension. Science 1982;217:267–269
2. Ackley S, Barrett-Connor E, Suarze L. Dairy products, calcium and blood pressure. Am J Clin Nutr 1983;38:457–461
3. McCarron DA, Morris CD, Henry HJ, Stanton JL. Blood pressure and nutrient intake in the United States. Science 1984;224: 1392–1398
4. Garcia-Palmieri MR, Costas R Jr, Cruz-Vidal M, Sorlie PD, Tillotson J, Havlik RJ. Milk consumption, calcium intake, and de-

creased hypertension in Puerto Rico: Puerto Rico Heart Health Program Study. Hypertension 1984;6:322–328
5. Nichaman M, Shekelle R, Paul O. Diet, alcohol and blood pressure in the Western Electric study. Am J Epidemiol 1984;120:469–470
6. Harlan WR, Hull AL, Schmouder RL, Landis JR, Thompson FE, Larkin FA. Blood pressure and nutrition in adults. Am J Epidemiol 1984;120:17–28
7. Reed D, McGee D, Yano K, Hankin J. Diet, blood pressure, and multicollinearity. Hypertension 1985;7:405–410
8. Harlan WR, Landis JR, Schmouder RL, Goldstein NG, Harlan LC. Blood lead and blood pressure: relationship in adolescent and adult U.S. population. JAMA 1985;253:530–534
9. Belizan JM, Villar J, Pineda O, et al. Reduction of blood pressure with calcium supplementation in young adults. JAMA 1983; 249:1161–1165
10. Belizan JM, Villar J, Zalazar A, Rojas L, Chan D, Bryce GF. Preliminary evidence of the effect of calcium supplementation on blood pressure in normal pregnant women. Am J Obstet Gynecol 1983;146:175–180
11. Johnson NE, Smith LE, Freudenheim JL. Effects on blood pressure of calcium supplementation of women. Am J Clin Nutr 1985; 42:12–17
12. Resnick LM, Laragh J. The hypotensive effect of short term oral calcium loading in essential hypertension [Abstract]. Clin Res 1983;31:334a
13. Markandu ND, Cappuccio FP, Beynon GW, Shore AC, MacGregor GA. Effect of increasing calcium intake on sodium balance and blood pressure in normotensive subjects [Abstract]. Presented at the International Symposium on Nutritional and Metabolic Aspects of Arterial Hypertension, Satellite Symposium of the 2nd European Meeting on Hypertension, Anacapri, June 3–4, 1985:21. J Clin Hypertens (in press)
14. McCarron DA, Morris CD. Blood pressure response to oral calcium in persons with mild to moderate hypertension. Ann Intern Med 1985;103:825–831
15. Ayachi S. Increased dietary calcium lowers blood pressure in the spontaneously hypertensive rat. Metabolism 1979;28:1234–1238
16. McCarron DA, Yung NN, Ugoretz BA, Krutzik S. Disturbances of calcium metabolism in the spontaneously hypertensive rat. Hypertension 1981;3(suppl I):I-162–I-167
17. Belizan JM, Pineda O, Sainz E, Menendez LA, Villar J. Rise of blood pressure in calcium deprived pregnant rats. Am J Obstet Gynecol 1981;141:163–169
18. McCarron DA. Calcium, magnesium, and phosphorus balance in human and experimental hypertension. Hypertension 1982;4(suppl III):III-27–III-33
19. McCarron DA. Blood pressure and calcium balance in the Wistar-Kyoto rat. Life Sci 1982;30:683–689
20. Lau K, Chen S, Eby B. Evidence for the role of PO_4 deficiency in antihypertensive actions of high-Ca diet. Am J Physiol 1984; 246:H324–H329
21. Schleiffer R, Pernot F, Berthelot A, Gairard A. Low calcium diet enhances the development of hypertension in the spontaneously hypertensive rat. Clin Exp Hypertens [A] 1984;6:783–793
22. McCarron DA, Pingree PA, Rubin RJ, Gaucher SM, Molitch M, Krutzik S. Enhanced parathyroid function in essential hypertension: a homeostatic response to a urinary calcium leak. Hypertension 1980;2:162–168
23. Wright BM, Dore CF. A random zero sphygmomanometer. Lancet 1970;1:337–339
24. Snedecor GW, Cochran WG, eds. Statistical methods. 6th ed. Ames, IA: Iowa University Press, 1979. 593 pp
25. Strazzullo P, Nunziata V, Cirillo M, et al. Abnormalities of calcium metabolism in essential hypertension. Clin Sci 1983;65: 137–141
26. Kesteloot H, Geboers J. Calcium and blood pressure. Lancet 1982;1:813–815
27. Strazzullo P, Galletti F, Siani A, Cirillo M, Nunziata V, Mancini M. Altered kinetics of an intravenous calcium load in hypertensive patients. J Hypertension 1984;2(suppl 3):499–501
28. Cirillo M, Galletti F, Mariano FC, Strazzullo P. Disturbance of renal and erythrocyte calcium handling in the Milan hypertensive strain of rat. J Hypertension 1986;4 (in press)