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Original Contributions

Reduction of Blood Pressure With Calcium Supplementation in Young Adults

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• **Epidemiologic and animal studies have suggested an inverse relationship between calcium intake and BP. Furthermore, calcium intake seems to be inversely correlated with the incidence of eclampsia in pregnancy. In a randomized clinical trial, young adults were allocated to a calcium-supplemented group receiving 1 g/day of elemental calcium (15 men and 15 women) or a placebo group (14 women and 13 men) for a period of 22 weeks. The calcium-supplemented group showed a significant decrease in diastolic BP; this effect was stabilized after nine weeks in women and six weeks in men. The reduction in diastolic BP was 5.6% and 9% from the initial values for women and men, respectively. This study supports epidemiologic and animal evidence of the effect of calcium intake on BP and suggests the need for more research exploring the mechanisms involved in the observed effect.**

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INTEREST in the effect of calcium intake on BP levels rose after the observation that persons drinking "hard water" (with high calcium content) had a low incidence of cardiovascular disease.[1] This reduction has been suggested to be due to lower BP figures in those populations.[2] Subsequent studies of the hard-water effect have not been as supportive of an association as the initial work.[3] It is possible that the weak association found could be related to the low amount of calcium in drinking water compared with dietary calcium. Indeed, calcium in drinking water represents only about 10% to 15% of total calcium intake in a population with high calcium intake.

An inverse relationship between the level of calcium intake and the incidence of eclampsia of pregnancy has been described in other populations. On the basis of these and other observations, we recently postulated that low calcium intake could be a factor predisposing to the development of pregnancy-induced hypertension.[4]

A significantly higher BP value has been described in calcium-deprived rats.[5] Furthermore, spontaneously hypertensive rats showed a diminished increase in BP values when fed an increased calcium diet.[6]

This article describes a controlled double-blind clinical trial of calcium supplementation in healthy young adults. A significant reduction in diastolic BP values was observed in those receiving a supplemental 1-g tablet of calcium daily.

SUBJECTS AND METHODS

A total of 57 subjects (28 men and 29 women) was recruited for this study. They were volunteers, either students or employees of the Institute of Nutrition of Central America and Panama or San Carlos University, Guatemala City. All subjects were between 18 and 35 years old, were not receiving any medical treatment at the time of recruitment (none of the women was using hormonal contraceptives), and were free of diseases as assessed by a comprehensive clinical examination and blood and urine tests performed before candidates were accepted into the study. Eligibility also included written consent from each volunteer after the nature of the study was fully explained. After completion of the examination, baseline data were collected for periods of eight weeks for men and two

Table 1.—Average (±SD) Baseline Measurements for All Subjects, by Sex and Treatment Group

	Women		Men	
	Placebo (n=14)	Calcium (n=15)	Placebo (n=13)	Calcium (n=15)
Age, yr	23.6±4.4	24.0±4.9	25.8±4.7	25.7±4.0
Initial weight, kg	47.4±6.7	53.5±7.6	63.0±9.8	65.6±8.2
Systolic BP in dorsal position, mm Hg	100.2±6.0	104.1±6.7	109.0±7.0	117.8±8.5*
Diastolic BP in dorsal position, mm Hg	67.5±3.9	69.0±5.3	68.1±8.8	74.1±7.7
Serum total calcium, mg/dL	9.58±0.35	9.51±0.43	9.53±0.20	9.74±0.29
Serum magnesium, mg/dL	1.53±0.16	1.54±0.09	1.47±0.09	1.52±0.10
Inorganic phosphate, mg/dL	4.31±0.61	4.20±0.50	4.49±0.64	4.67±0.41
Albumin, g/dL	4.53±0.38	4.40±0.32	4.81±0.53	4.67±1.12
Serum calcium-magnesium ratio	6.30±0.54	6.20±0.32	6.49±0.44	6.42±0.37
Total protein, g/dL	7.38±0.42	7.45±0.50	7.50±0.38	7.66±0.37

*$P<.05$.

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Table 2.—Estimated Mean (±SD) Daily Dietary Intake at Baseline and During Two Study Periods, by Sex and Treatment Group

		Women			Men		
			Week of Supplementation			Week of Supplementation	
Nutrient	Group	Basal Value	2-9	10-20	Basal Value	2-9	10-23
Calories, kcal	Placebo	1,595±310	1,594±291	1,627±305	2,226±459	2,231±440	2,193±448
	Calcium	1,701±438	1,710±579	1,663±591	2,109±515	1,867±590	1,836±416
Protein, g	Placebo	63.3±19.1	57.1±9.9	56.1±13.7	80.7±27.7	76.2±19.0	83.0±20.1
	Calcium	60.9±16.2	61.6±25.4	59.1±25.8	77.1±27.3	62.6±22.5	68.6±24.0
Fat, g	Placebo	43.8±14.2	46.6±11.0	45.1±14.6	45.8±19.4	57.0±9.6	50.7±14.4
	Calcium	48.3±13.3	51.4±16.8	50.4±16.9	55.2±17.5	46.1±20.7	47.9±15 4
Calcium, mg†	Placebo	616±287	581±215	518±205	779±327	749±381	762±328
	Calcium	615±177	683±311	626±294	803±353	629±248	528±209‡
Iron, g	Placebo	13.9±4.2	12.3±2.2	13.1±3.5	19.1±7.1	17.8±6.0	18.9±6.0
	Calcium	14.5±5.2	12.8±4.5	11.8±4.8	19.5±6.5	16.5±4.9	15.9±5.5

*There were 14 women in the placebo and 15 women in the calcium-supplemented group; 13 men in the placebo and 15 men in the calcium-supplemented group.

†The supplemented calcium is not included.

‡Significant differences from basal values and from placebo group ($P<.05$).

Table 3.—Regression Coefficients of Effect of Supplementation on Percent BP Changes, Adjusted by Initial BP, by Sex and Treatment Group

	Women		Men	
	Placebo (117)*	Calcium (127)	Placebo (96)	Calcium (144)
Lateral position				
Systolic BP	−.101	−.240†	−.071	−.11
Diastolic BP	−.088	−.405†	−.074	−.380†
Dorsal position				
Systolic BP	−.020	−.259†	−.022	.022
Diastolic BP	.117	−.333†	−.066	−.302†
Seated position				
Systolic BP	.179	−.236†	.167	.114
Diastolic BP	−.010	−.271†	−.0132	−.109

*Number of BP values is given in parentheses.

†$P<.01$

menstrual cycles for women. Then, the subjects were randomly assigned to two treatment groups. Separate randomization schedules were used for sex and age groups (18 to 23 years and 24 to 35 years). The treatment assignment was made in a double-blind fashion, ie, the composition of the tablet was not known to the person under study or to the professional in charge of the examinations.

The calcium-supplemented group received a daily oral tablet containing 0.8 g of calcium carbonate and 5.23 g of calcium lactate gluconate (Calcium-Sandoz, 1,000 mg), representing 1 g of elemental calcium. The placebo group received a daily tablet of the same weight, size, and organoleptic characteristics as the calcium tablet. The containers were similar for both types of tablets, and a key number indicated the composition.

Data were gathered for men every two weeks. During the fifth examination (eighth week), a blood sample was drawn and supplementation began. Supplementation continued for 22 weeks. Blood samples were also taken at the eighth week of supplementation and at the termination of the study. Women's samples were scheduled to be taken according to their menstrual cycles because of the known effect of menstrual hormonal changes on calcium metabolism. The phase of menstrual cycle, however, did not show any significant effect ($P>.05$) on systolic and diastolic BP; the subsequent analysis of women's data considers only the time elapsed from the beginning of supplementation in weeks, as is presented for men.

During each session, information about diseases, drug intake, BP, weight, and compliance with supplementation was recorded. A percentage of scheduled but unattended sessions by group and sex was calculated as an indicator of adherence to the study calendar.

One trained professional, who was unaware of the group status of the subject, was in charge of all BP measurements. Twenty percent of the measurements were validated by simultaneous measurement with a double-auricular stethoscope. A mercury column sphygmomanometer was used. The readings were taken from the left arm. First, five readings were taken with the patient in the left lateral position, then five in the dorsal position, and finally five readings in a seated position with the subject's left arm held at heart level.

Systolic BP was read when the appearance of the first Korotkoff's sound occurred; the diastolic reading was taken at the disappearance of the fifth Korotkoff's sound.

The five readings in each position were averaged for analysis. The blood samples were used for determination of levels of total calcium and magnesium by atomic absorption spectrophotometry, inorganic phosphate by spectrophotometry, and albumin by dye-binding bromocresol purpose.

The total amounts of calcium received by the subjects were evaluated using information from two sources: (1) basal dietary intake, using nutrition intake information collected the day before each visit to the clinic, and (2) compliance with the prescribed daily tablet treatment, assessed by questioning the subject during each follow-up visit. With regard to the first, this method was relatively simple and reliable for this study population, as most of the subjects were either students of nutrition and/or field workers with training in dietary surveys. Each subject registered his or her intake in a special form immediately after each major meal and snack. For the second assessment, the percentage of numbers of tablets taken of the total number of tablets required during the study period was calculated for each group and sex.

Subjects who enrolled in the study between April 22 and July 15, 1980, were randomized in accordance with the prepared schedule. A total of 28 men were divided among the calcium-supplemented (n=15) and placebo (n=13) groups and 29 women among the calcium-supplemented (n=15) and placebo (n=14) groups. All of them were included in the treatment group to which they were originally randomly assigned, irrespective of any follow-

up experience.

For statistical analysis, BP was considered the major end point. The BP measurements obtained during the baseline period for each subject (five examinations) were averaged, and the mean was considered as the initial basal value. Given the possibility that differences in this initial value could be present between groups, two methods were used to control for it: (1) correlation and regression coefficients adjusted for the initial value, using multiple regression analysis, and (2) percent changes from these basal values for each measurement after the beginning of supplementation. These percent changes were used to calculate regression and correlation coefficients in a simple linear regression model. The figures in this report show the mean values at different periods of supplementation obtained using the percentual changes. This allows for a more clinical interpretation of results. Nevertheless, all of the analyses were performed using multiple regression as well, and these are presented in the corresponding tables. All values obtained were included in the models; dropouts contributed to the analysis all of the data collected during the period they were in the study.

RESULTS

Baseline Comparability

The basal information by treatment group and sex is given in Table 1. No differences between groups were found in the variables collected during the baseline period except for systolic BP in the dorsal position among the men. Therefore, the randomization achieved satisfactory comparability between the calcium-supplemented and placebo groups in both sex categories. Weight changes during the study were specially analyzed. In women, weight change at the end of the study in relation to basal values showed average figures of -0.026 ± 1.4 (SD) kg and 0.06 ± 0.9 kg for the placebo and calcium-supplemented groups, respectively, with no statistical differences. For men, weight changes after 28 weeks of study were 0.04 ± 1.2 kg and 1.45 ± 1.6 kg for the placebo and calcium-supplemented groups, respectively. The increase in the calcium-supplemented group was significantly different from that of the placebo group ($P<.05$).

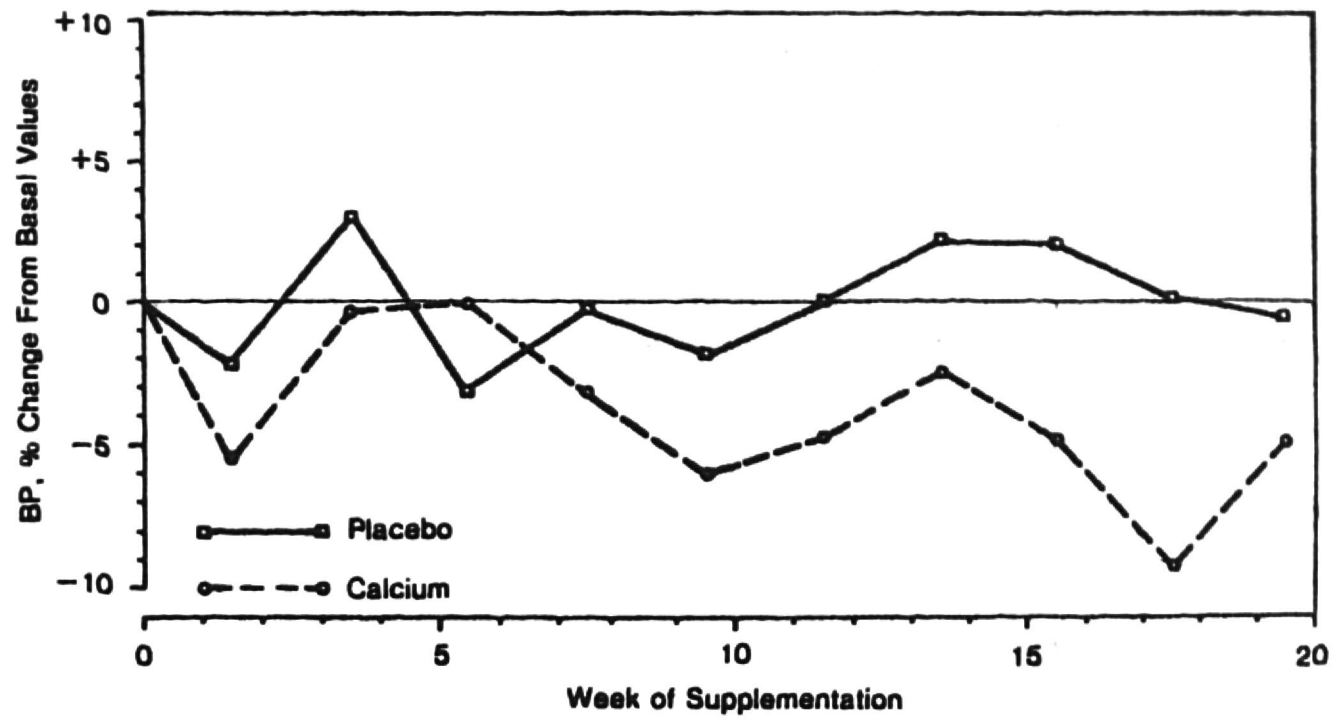

Fig 1.—Women's diastolic BP in dorsal position. Mean percent changes in relation to basal values, by week of supplementation. Placebo group: $b=.117$ (NS); calcium-supplemented group: $b=.333$ ($P<.01$). In latter group, effect stabilized in ninth week of supplementation.

Table 4.—Women's Mean (±SD) BP Percent Changes Between Basal Values and Stable Period (Weeks 9 Through 23)

	Placebo (n=54)	Calcium (n=77)	P
Lateral position			
Systolic BP	0.23±4.96	−1.55±5.21	.04
Diastolic BP	0.42±10.7	−4.19±9.73	.01
Dorsal position			
Systolic BP	1.12±4.72	−1.21±5.14	.009
Diastolic BP	0.91±6.98	−5.64±8.41	.0001
Seated position			
Systolic BP	3.51±7.43	0.24±6.43	.006
Diastolic BP	1.38±8.83	−2.85±7.71	.004

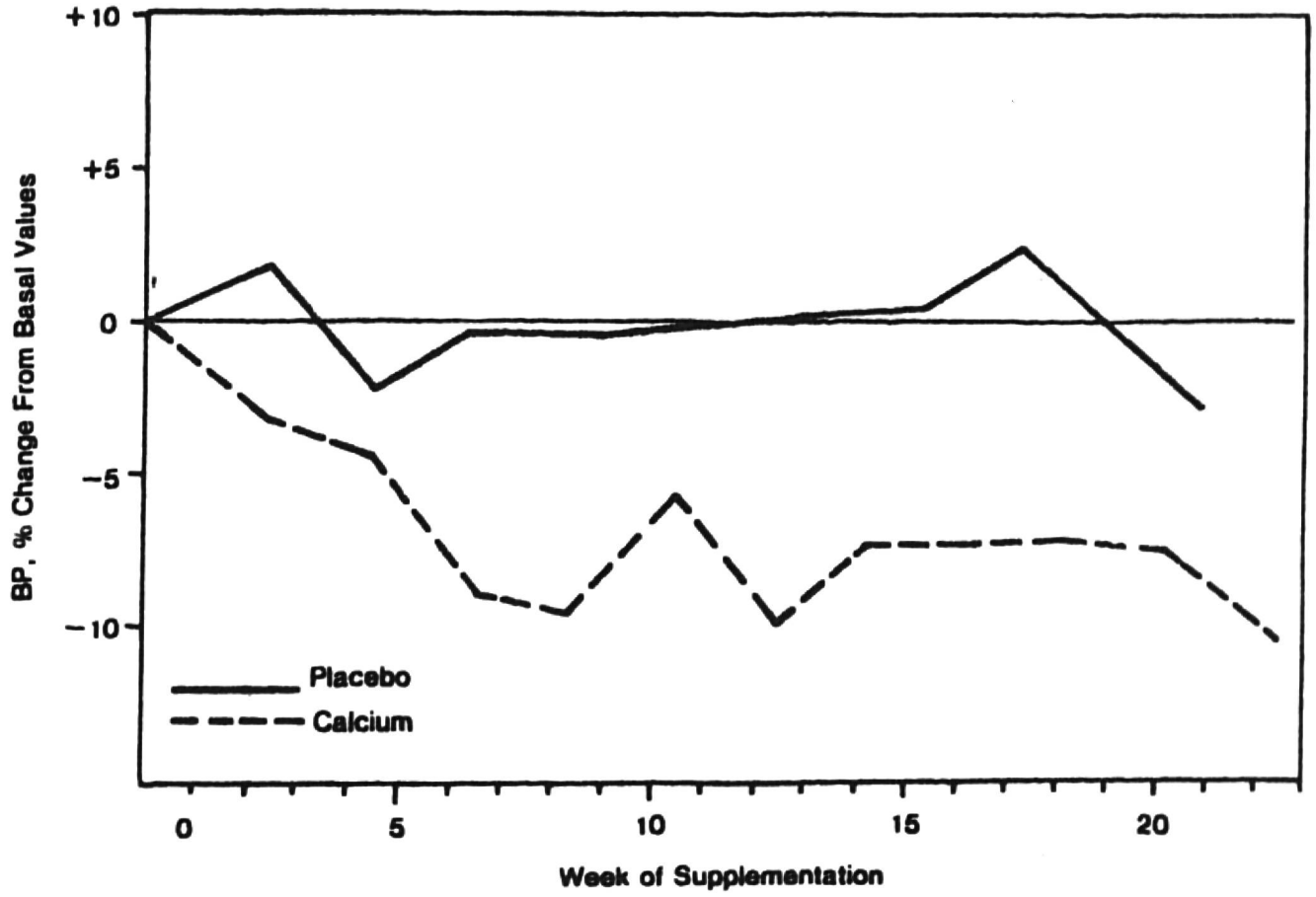

Fig 2.—Men's diastolic BP in dorsal position. Mean percent changes in relation to basal values, by week of supplementation. Placebo group: $b=.066$ (NS); calcium-supplemented group: $b=.302$ ($P<.01$). In latter group, effect stabilized after sixth week of supplementation.

Dietary Intake During Study

With only one exception, no changes or differences were observed in calories, protein, fat, iron, and calcium intake within and between groups during the three periods studied. There was a significant reduction ($P<.05$) in calcium intake among calcium-supplemented men by the 13th to 23rd weeks, when compared with their baseline intake as well as with that of the placebo group (Table 2).

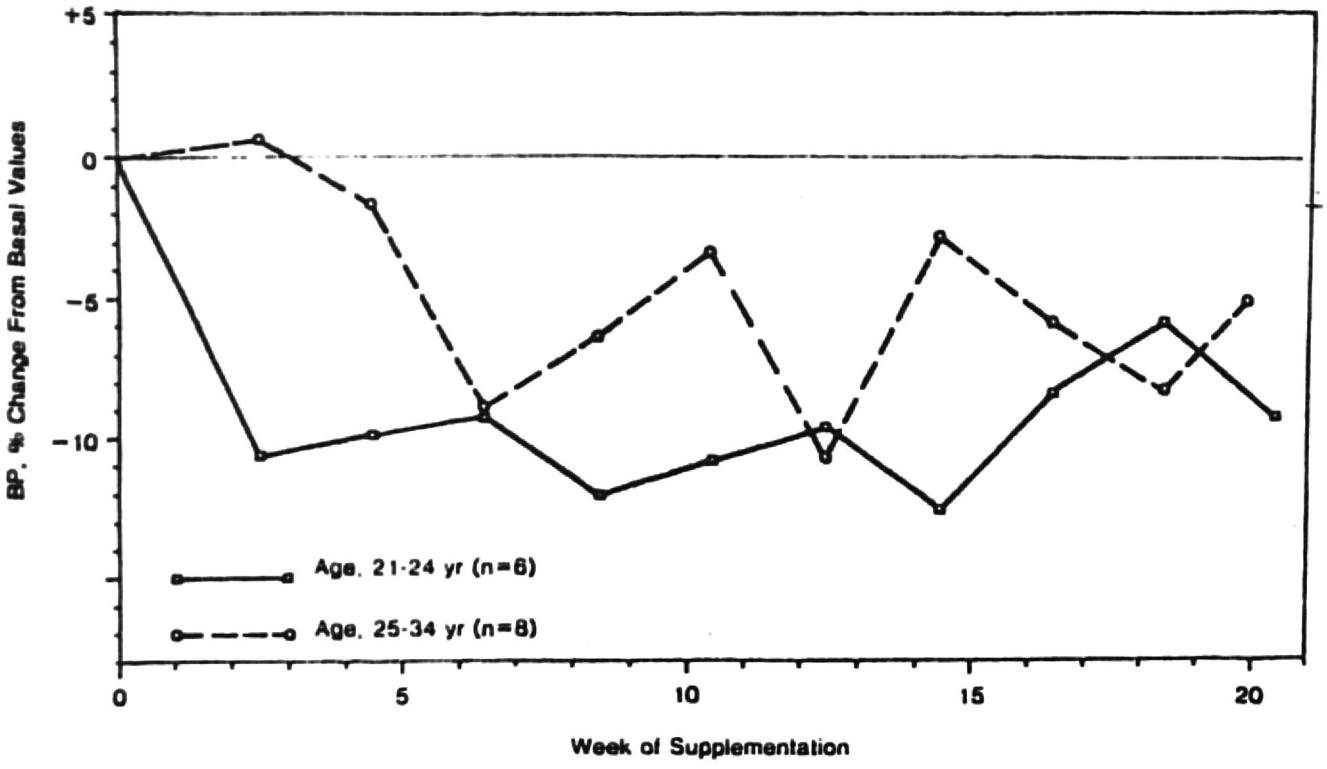

Fig 3.—Men's diastolic BP in dorsal position. Mean percent changes in relation to basal values, by week of supplementation and by two age groups. Younger persons showed earlier stabilization of effect and tendency toward greater reduction of diastolic BP with calcium supplementation.

Table 5.—Men's Mean (±SD) BP Percent Changes Between Basal Values and Stable Period (Weeks 7 Through 22)

	Placebo (n=57)	Calcium (n=97)	P
Lateral position			
Systolic BP	−0.10±5.4	−1.90±5.9	.08
Diastolic BP	0.10±14.0	−9.00±10.3	.0001
Dorsal position			
Systolic BP	0.59±4.5	−0.14±4.7	.35
Diastolic BP	−1.01±8.4	−9.05±8.3	.0001
Seated position			
Systolic BP	2.34±4.6	2.37±6.1	.98
Diastolic BP	1.95±7.3	−1.79±6.7	.002

Follow-up Compliance

Of the 28 men and 29 women randomized to the study groups, 23 men and 20 women completed the final examinations. Women took 96% and 97% of the total possible number of tablets in the calcium-supplemented and placebo groups, respectively, while the figures for men were 95.1% for the calcium-supplemented group and 98% for the placebo group.

Of all scheduled examinations, women did not complete 13% in the placebo group and 14% in the calcium-supplemented group, and men failed to attend 22% and 17% of sessions in the placebo and calcium-supplemented groups, respectively.

BP Effects

Women.—Multiple regression analysis disclosed that the calcium-supplemented group had negative regression coefficients of both systolic and diastolic BP changes from baseline when time of supplementation was used as an independent variable after adjusting for the initial BP values. All these regression coefficients were statistically different from zero ($P<.01$). In the placebo group, while four regression coefficients were negative, none was significantly different from zero ($P>.05$) (Table 3).

Figure 1 shows diastolic BP changes in the dorsal position during supplementation for women. A decrease in the calcium-supplemented group is evident and seems to have stabilized in the ninth week of supplementation. Similar changes in diastolic BP were observed in the lateral and seated positions but were less noticeable in the latter. (For easier interpretation, mean values at different times are graphed, but in the statistical analysis, all individual values were considered.)

The analysis of BP changes over time demonstrated that the effect was consistently present by nine weeks. Table 4 gives the percent change of BP in relation to basal values after nine weeks of supplementation (stable period). Significant decreases in the calcium-supplemented groups *v* the placebo groups were found in diastolic and systolic BPs in the three positions studied. In the calcium-supplemented group, diastolic BP showed a reduction of 2.85%, 4.19%, and 5.64% in the seated, lateral, and dorsal positions, respectively.

Men.—Results similar to those for women are given for men in Tables 3 and 5 and Fig 2.

Significant negative slopes ($P<.01$) were observed for changes in diastolic BP, allowing for basal values in the lateral and dorsal positions only in the calcium-supplemented group (Table 3).

The graph relating diastolic BP changes to time of supplementation shows a stabilization of effects in the calcium-supplemented group at around the sixth week after beginning supplementation (Fig 2). When individual values were considered, however, stabilization occurred earlier in younger than in older men (Fig 3).

In the stable period (seven to 22 weeks after beginning supplementation), the reduction of diastolic BP in the calcium-supplemented group was 1.79%, 9.00%, and 9.05% in the seated, lateral, and dorsal positions, respectively. These values are statistically different from those for the same position in the placebo group ($P<.002$) (Table 5). There were no significant reductions in systolic BP ($P\geq.08$).

Biochemical Effects

Changes in biochemical values of total calcium, magnesium, calcium-magnesium ratio, inorganic phosphate, proteins, and albumin were studied at baseline and by the eighth and 22nd week of supplementation. In both men and women, no differences were found in the values between groups and within groups.

COMMENT

Supplementation with 1 g of calcium produced a significant reduction in diastolic BP in young healthy persons of both sexes. The effects were stabilized in the ninth week of supplementation for women and in the sixth week for men. The reduction in diastolic BP in the decubitus position was approximately 5% in women and

9% in men.

These findings confirm the relationship between calcium intake and BP described for rats[5,6] and support the epidemiologic observations of the association between low calcium intake and hypertension during pregnancy[4] and among hypertensive human subjects.[7]

There is no clear explanation of the mechanisms involved in the observed relationship. The effect of calcium on smooth vascular muscle has been the subject of considerable study, and controversy still exists as to its mechanisms of action. What seems to be clear is that when the permeability of the membrane is increased and an increase in intracellular calcium concentration is produced, then the responsiveness of the muscle cells is increased.[8] The entrance of Ca^{++} into the cell seems to stimulate the release of Ca^{++} from the sarcoplasm, raising its concentration and initiating the mechanical response.[8]

Parathyroid hormone (PTH) level changes may be involved in this effect. A rise in the PTH level is observed with low calcium intake, and it has been shown that PTH increases the intracellular calcium concentration in several types of cells.[9,10]

This effect is due to the influence of PTH on the cell membrane, which enhances the entry of calcium into the cell, and to the PTH stimulus of adenyl cyclase activity for the formation of cyclic adenosine monophosphate (AMP). Cyclic AMP stimulates the efflux of calcium from mitochondrial stores, increasing cytoplasmic calcium levels. Given the known role of calcium in the mechanism of vascular tonus and smooth-muscle contraction, this mechanism could explain why persons with primary hyperparathyroidism, in absence of renal damage, show a higher incidence of hypertension with a 20% remittance after parathyroidectomy,[11] and why parathyroidectomized rats show a lower vascular sensitivity to mineralocorticoids.[12]

If the effect of low calcium intake on BP is mediated through a PTH effect on the intracellular concentration of Ca^{++}, drugs that can reduce the calcium influx into the cell should have an inverse effect. This may be true for the calcium entry blockers, which, by acting at the plasma membrane level, reduce Ca^{++} intracellular concentration, producing relaxation of smooth muscle. These drugs have been suggested for the treatment of hypertension.[13]

The observed effect could be attributed to the direct relationship reported between the renal clearances of calcium and sodium.[14] Micropuncture studies suggest common absorptive mechanisms of calcium and sodium in the nephron proximal tubule.[15] Popovtzer[16] proposes that the reabsorption of calcium and sodium in the distal tubule can be disassociated, since PTH reduces urinary excretion of calcium but augments a urinary excretion of sodium and thiazide diuretics, thus inducing natriuresis but causing urinary retention of calcium when administered on a long-term basis.[16,17] In our results, the fact that no weight changes were evident during the supplementation and the six to nine weeks needed for effect stabilization argues against the possible diuretic effect of the calcium supplementation.

Finally, calcium also plays a role in modulating prostaglandin synthesis, and in vitro studies have demonstrated an influence of prostaglandins on PTH release.[18]

It is generally admitted that humans can adapt to very low calcium intakes, yet the consequences of dietary calcium deficiencies have not been completely described. This report and calcium restriction studies in animals[5] seem to indicate that the adaptation to low calcium intakes could lead to increased BP. Inversely, high calcium intake, which is associated with lower BP,[4] may produce a protective effect against hypertension. Additional research is required, particularly on the adequacy of present calcium intake recommendations, using outcome measures other than bone structure.

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