Preliminary evidence of the effect of calcium supplementation on blood pressure in normal pregnant women

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In this study the hypothesis that calcium supplementation during pregnancy can modify blood pressure patterns in a population of normal pregnant women was tested. Thirty-six women with normal single pregnancies, between 20 and 35 years of age, in the second trimester of gestation (15 weeks), were randomly assigned to receive 1 gm of calcium per day (n = 11), 2 gm per day (n = 11), or a placebo (n = 14). No differences were observed at the times of admission into the study (baseline) in demographic and clinical variables or in the calcium intake of each group. Baseline blood pressure measures in several positions also were not different. After the initial blood pressure measures (fifteenth week), five follow-up blood pressure measures were obtained. The supplemented groups had significantly lower diastolic blood pressure than the control subjects between the twentieth and twenty-fourth weeks of gestation. Thereafter, an increase in the control group and the group receiving 1 gm of calcium was observed, but levels were similar at term. On the contrary, patients receiving 2 gm of calcium had blood pressure values that remained significantly lower throughout the third trimester. No differences or clear patterns were observed in the blood levels of calcium, magnesium, phosphorus, and proteins between and within groups during gestation. A possible explanation involving parathyroid hormone is attempted. (AM. J. OBSTET. GYNECOL. 146:175, 1983.)

Recently we have suggested that there is an association between calcium intake and pregnancy-induced hypertension (PIH) or preeclampsia.[1] Women with low calcium intake have an increase in mean blood pressure that predisposes them to the development of PIH during the last part of gestation.

Data from animal studies tend to support this hypothesis. For example, calcium-deprived rats evidence a significant increase in blood pressure values.[2-4] Further, it has been demonstrated that rats which spontaneously developed hypertension after birth (SHR) showed a significant reduction in rates of blood pressure increase when fed a double-calcium diet.[5] In our study[4] calcium-deprived rats showed a significant increase in systolic blood pressure before pregnancy which continued through gestation. The rise in blood pressure was negatively significantly correlated with the serum calcium-magnesium ratio. Therefore, in rats at least, the more the calcium metabolism is affected, the higher are the blood pressure values obtained.

We have recently found a reduction in diastolic blood pressure of 6% from the pretreatment values in nonpregnant women in their childbearing years who received 1 gm of calcium supplement per day.[6] Further, McCarron and associates[7] have shown a significant reduction in calcium intake among hypertensive subjects when compared with normotensive control subjects.

The present paper offers data on the effect of calcium supplementation on the blood pressure of normal pregnant women.

Material and methods

A total of 36 pregnant women with a single fetus, attending the outpatient clinic of the Guatemalan Social Security Hospital (IGSS), between 20 and 35 years of age, without evidence of a previous pathology, and with certain dates of their last menstrual periods were enrolled in this study. The patients were volunteers and were not receiving any medical treatment at the time of recruitment (15 weeks of gestation). After patients had agreed to participate and had completed their initial examination (15 weeks), they were randomly (simple randomization method) assigned to one of three treatment groups: a 1 gm/day of elemental calcium supplement group (n = 11), a 2 gm/day of elemental calcium supplement group (n = 11), and a

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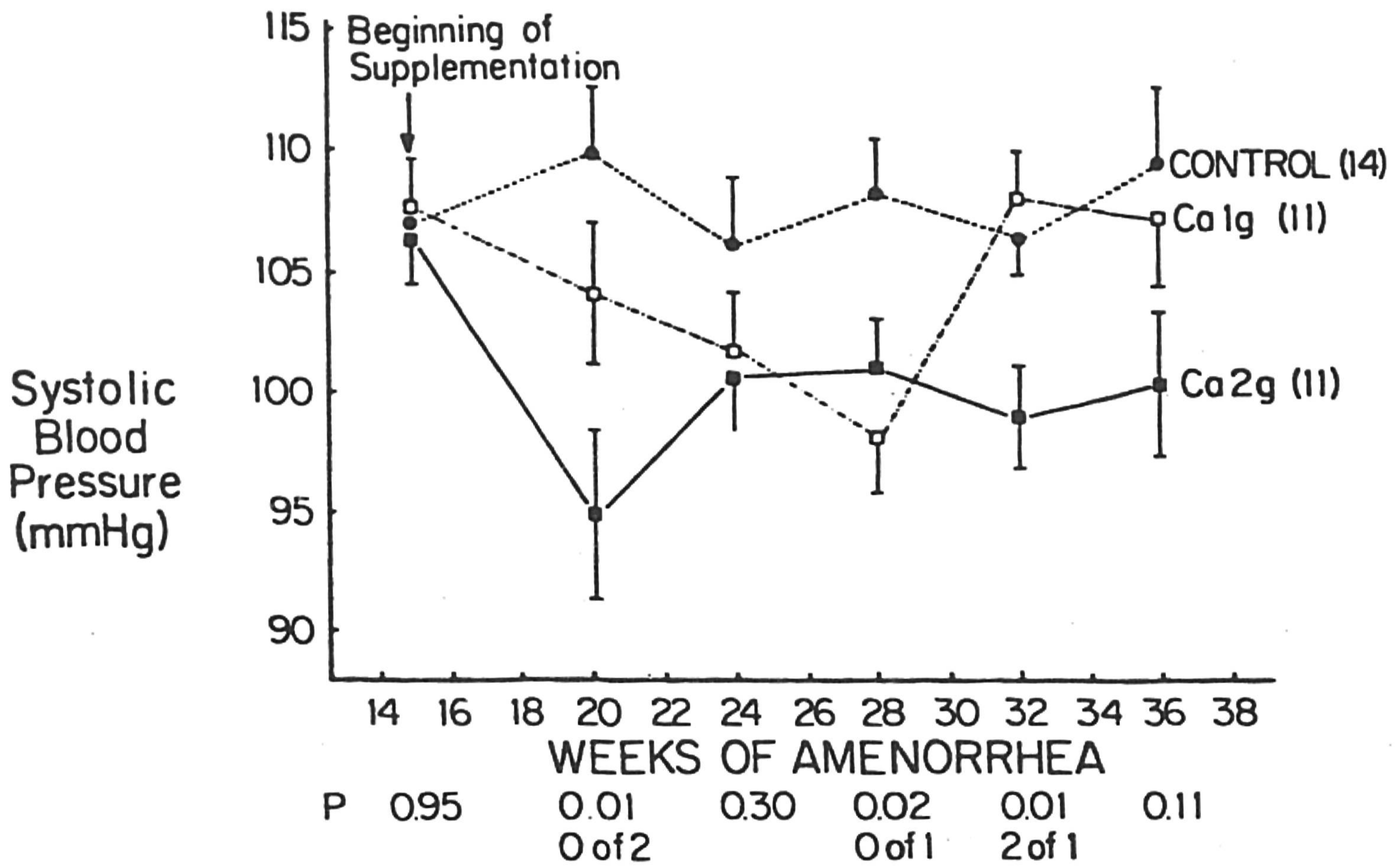

Fig. 1. Means and SEs for systolic blood pressure measured in the lateral position at different points during pregnancy are presented. The control group showed fluctuations in its values throughout pregnancy. The two supplemented groups had a significant reduction by the second trimester (lowest points at 20 weeks for the 2 gm of calcium group and at 28 weeks for the 1 gm of calcium group). By the thirty-second week the 1 gm of calcium group had reached the control group's values. The 2 gm of calcium group continued to have lower mean values throughout the third trimester.

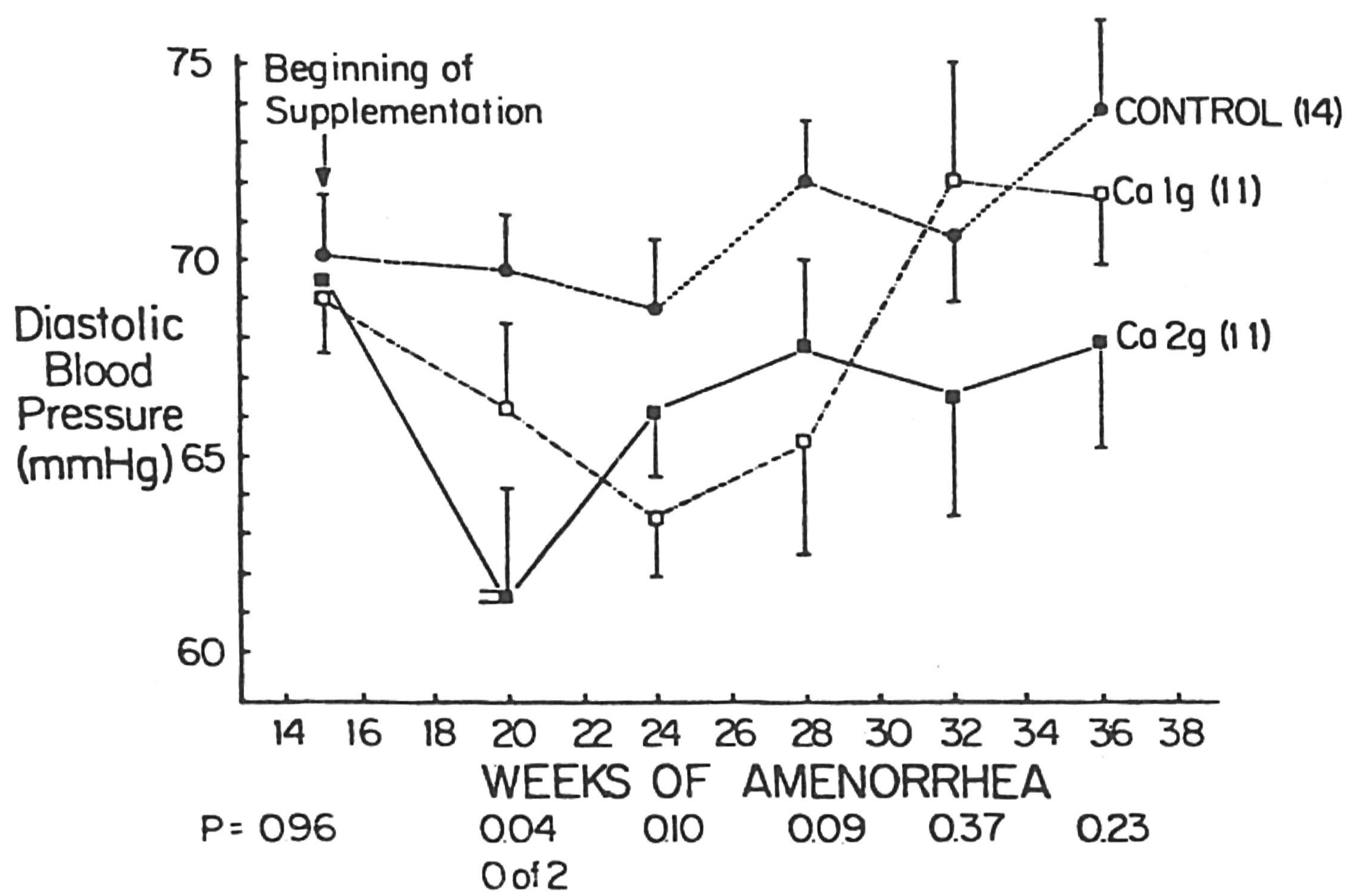

Fig. 2. Means and SEs for diastolic blood pressure measured in the lateral position at different points during pregnancy are presented. The control group showed a decline during the second trimester (lowest point at the twenty-fourth week). The two supplemented groups had a significant reduction (lowest point at 20 weeks for the 2 gm of calcium group and at 24 weeks for the 1 gm of calcium group). By the thirty-second week, the 1 gm of calcium group had reached the control group's values. The 2 gm of calcium group continued to have lower mean values throughout the third trimester.

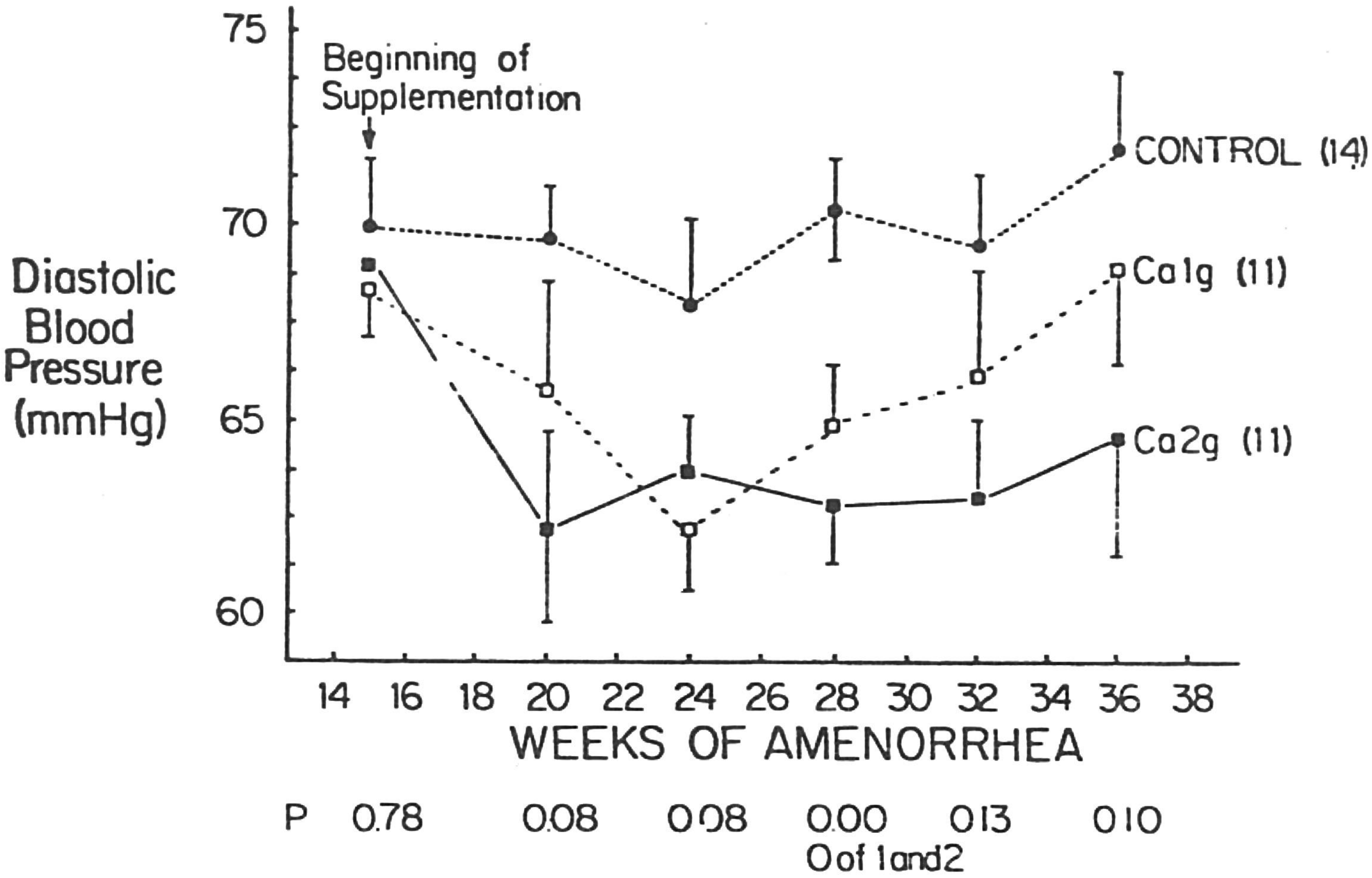

Fig. 3. Means and SEs for diastolic blood pressure measured in the seated position at different points during pregnancy are presented. The control group showed a decline during the second trimester (lowest point at the twenty-fourth week). The two supplemented groups had a significant reduction (lowest point at 20 weeks for the 2 gm of calcium group and at 24 weeks for the 1 gm of calcium group). After that time, the 1 gm of calcium group's mean diastolic blood pressure values increased, although they did not reach the control group's values. The 2 gm of calcium group continued to have lower mean values throughout the third trimester.

placebo group (n = 14). Patients were unaware of their group status. Tablets each contained 1 gm of elemental calcium, composed of 0.8 gm of calcium carbonate and 5.23 gm of calcium lactate gluconate (calcium, 1,000 mg, Sandoz Pharmaceuticals). The placebo group received tablets of the same weight, size, and organoleptic characteristics as the calcium tablets.

All patients had prenatal visits at 15, 20, 24, 28, 32, and 36 to 38 weeks of gestation. At each visit, standard prenatal care information was collected. Blood samples were drawn at 15, 24, and 36 to 38 weeks of gestation. Information about intake of other drugs, if any, and compliance with supplementation since the previous interview was recorded. Several blood pressure measures were obtained at each visit. After the patient had been in the supine position for 10 minutes, five blood pressure measures were taken in that position; five more were taken in the left lateral position, and, finally, five more in a seated position with the left arm at the level of the heart. Systolic blood pressure was read when the appearance of the first Korotkoff sound occurred, while diastolic blood pressure was taken when the appearance of the fifth Korotkoff sound occurred. Only three obstetrics and gynecology residents were in charge of the measures, after standardization with a double auricular stethoscope.

Parathyroid hormone (PTH) was measured by radioimmunoassay with the use of human serum standard and CH/9 antiserum (by G. Bryce at Hoffmann-La Roche Inc.). One microliter equivalent equals 10 pg of bovine PTH. Calcium and magnesium were measured by atomic absorption, while phosphorus was measured by a colorimetric technique.

Nutrient intake (with special emphasis on calcium and dairy products) was obtained with the use of a 24-hour recall method. The conversions from foodstuffs to actual nutrients were done with the use of a food composition table developed by the Institute of Nutrition of Central America and Panama (INCAP).

Group means were compared by one-way analysis of variance at different points during pregnancy. When significant differences were obtained at the $p < 0.05$ level, multiple comparisons between groups were performed with the use of Duncan's procedure[8] (see Figs. 1, 2, and 3). Partial correlation coefficients were calculated between blood pressure values and PTH values, with adjustment for their initial (15 weeks) values. These partial correlation coefficients were obtained with the use of the program presented in the Statistical Package for the Social Sciences (SPSS).[9]

Results

Baseline data. Table I presents information on several baseline and neonatal variables. As can be seen, no

Table I. Baseline data: Maternal and neonatal characteristics

Characteristic	Control group (n = 14) Mean	SD	1 gm of calcium group (n = 11) Mean	SD	2 gm of calcium group (n = 11) Mean	SD	Significance
Age	23.5	5.1	26.5	5.6	25.0	5.8	NS
No. of gestations	3.6	2.6	3.2	1.7	2.4	1.7	NS
Initial weight (kg)	53.8	9.6	53.1	6.2	58.1	8.0	NS
Weight gain (kg)	7.0	2.7	9.1	4.4	7.7	3.0	NS
Gestational age at birth (wk)*	39.2	1.1	38.9†	1.1	39.2†	1.2	NS
Gestational age at birth (wk)‡	39.0	0.7	38.9†	0.9	39.4†	0.5	NS
Birth weight (gm)	3,106	397	2,752†	409	3,148†	154	$p = 0.03$
Birth length (cm)	48.6	2.1	48.4†	1.7	49.8†	1.8	NS
Head circumference (cm)	33.8	16.4	33.5†	15.3	34.0†	16.8	NS

*Determined by last menstrual period.
†Only nine cases.
‡By physical examination.

Table II. Baseline data: Blood pressure* (millimeters of mercury) by studied group

Blood pressure	Control group (n = 14) Mean	SD	1 gm of calcium group (n = 11) Mean	SD	2 gm of calcium group (n = 11) Mean	SD	Significance
Systolic lateral	107.3	10.1	107.5	6.3	106.4	7.2	NS
Diastolic lateral	70.0	6.6	69.4	5.9	69.5	6.3	NS
Systolic dorsal	108.4	10.6	106.2	7.4	106.5	5.8	NS
Diastolic dorsal	68.8	7.9	69.6	5.8	69.0	6.2	NS
Systolic seated	107.4	8.4	105.0	6.7	103.6	8.6	NS
Diastolic seated	70.0	6.4	68.3	4.2	68.9	6.8	NS

*Mean of five consecutive measurements at fifteenth week of gestation.

differences were observed in the age of the mother, parity, initial weight, and weight gain during pregnancy. With regard to the newborn infants, birth weight in the group receiving 1 gm of calcium was significantly different from birth weights in the other two groups (2,752 versus 3,106 and 3,149 gm). Calcium intake at the time of admission into the study (15 weeks of gestation) was not significantly different among groups (815 ± 509 mg for the placebo group, 733 ± 421 mg for the 1 gm and calcium group, and 549 ± 344 mg for the 2 gm of calcium group). Overall, the calcium intake for the studied population was 739 ± 448 mg at 15 weeks, 788 ± 360 mg at 24 weeks, and 666 ± 221 mg at term.

Table II shows baseline blood pressure measurements for the three groups in several different positions. None of the measurements was significantly different. Therefore, it can be said that the randomization was effective in producing relatively comparable groups.

Blood pressure changes. Fig. 1 shows changes in systolic blood pressure for the three groups during the follow-up period. The control group's mean systolic blood pressure oscillated throughout gestation, while both supplemented groups tended to have reductions in systolic blood pressure during the second trimester. After the twenty-sixth week for the 1 gm of calcium group and after the thirty-second week for the control group, systolic blood pressure demonstrated an increase, to levels close to those shown during the first trimester. On the contrary, the group that received 2 gm of calcium did not have an increase in systolic blood pressure; systolic blood pressure remained significantly lower than in the other two groups during the third trimester of pregnancy.

Figs. 2 and 3 present changes in diastolic blood pressure in lateral and seated positions. All three groups had a decline in diastolic blood pressure in both positions during the second trimester of gestation (lowest point, between 20 and 24 weeks). Thereafter, an almost parallel increase was noticed in the control and 1 gm of calcium groups in the seated position, while the 2 gm of calcium group had diastolic blood pressures that remained significantly lower throughout the third trimester. The pattern was similar in the lateral position; however, the 2 gm of calcium group also experienced an increase in diastolic blood pressure. Despite this increase it remained lower than that of the other two groups by the end of gestation.

Diastolic and systolic blood pressures in positions other than the ones presented in this report showed patterns similar to those described here.

Table III. Biochemical data by treatment group and trimester of pregnancy

Trimester	Treatment group	Total calcium (mg/dl)			Magnesium (mEq/ml)			Phosphorus (mg/dl)			Protein (gm/100 ml)		
		Mean	SD	Sample size	Mean	SD	Sample size	Mean	SD	Sample size	Mean	SD	Sample size
First	Placebo	10.01	0.87	10	1.99	0.27	12	4.81	1.02	12	6.98	0.31	14
	1 gm of calcium	10.03	1.42	10	1.73	0.10	6	4.77	0.82	9	7.05	0.54	10
	2 gm of calcium	10.85	1.28	10	1.84	0.14	9	4.35	0.71	11	6.97	0.47	11
p Value			NS			0.05			NS			NS	
Second	Placebo	10.03	1.24	13	1.89	0.26	13	4.72	1.26	11	6.83	0.29	12
	1 gm of calcium	9.94	1.79	11	1.78	0.16	9	4.60	0.80	10	7.09	0.32	8
	2 gm of calcium	9.37	1.45	10	1.76	0.21	10	4.45	0.64	11	6.89	0.54	10
p Value			NS			NS			NS			0.001	
Third	Placebo	9.09	1.60	10	1.80	0.19	14	4.38	0.42	14	7.14	0.38	14
	1 gm of calcium	9.51	1.36	7	1.90	0.38	9	4.62	1.34	9	7.01	0.56	9
	2 gm of calcium	10.03	1.87	7	1.72	0.18	9	4.55	0.92	9	7.22	0.40	9
p Value			NS			NS			NS			0.03	

Biochemical values. No statistically significant differences in the total calcium and phosphorus levels were observed between groups. Magnesium values were lower in the 1 gm of calcium group than in the other two groups at 15 weeks ($p = 0.05$). Protein values were also different at 24 and 36 to 38 weeks. The placebo group had the lowest values in the second trimester, while the 1 gm of calcium group had the lowest values at term (Table III).

Serum levels of PTH were determined. The placebo group had an increase in mean values of serum PTH from 1.76 μl Eq/ml at 15 weeks to 2.29 μl Eq/ml at 36 to 38 weeks. The 2 gm of calcium group had mean values of 2.25 μl Eq/ml at 15 weeks that were reduced to 1.47 μl Eq/ml at term (about 65% lower). No changes were observed in the 1 gm of calcium group. None of these figures were statistically significant.

In an attempt to evaluate the association between PTH levels and diastolic blood pressure, partial correlation coefficients (correlation coefficients controlling for the initial PTH and diastolic blood pressure values) were calculated. A significant association obtained between both variables, with values between $r = 0.30$ and $r = 0.34$ ($p < 0.05$) in the three positions studied.

Comment

We have presented here evidence that supports the hypothesis that calcium supplementation reduces blood pressure in humans and in animals.[5, 6]

Three groups of normal pregnant women with comparable baseline characteristics and calcium intakes were studied. Urban Guatemalan populations have a lower calcium intake than rural ones given that they do not always follow the traditional techniques for preparing tortillas and that the percentage of total intake derived from them is also lower in the cities. The population studied had intake values (about 700 mg/day) similar to those reported in the literature for urban Guatemala (787 mg/day).[1] Further, the intake amount is not considerably different from that of developed countries.

The lower birth weight in the 1 gm of calcium group appears not to be related to the treatment, given that the 2 gm of calcium group had birth weights similar to those of the control group. From similar baseline levels the groups showed different patterns of blood pressure.

Normally, systolic blood pressure shows relatively minor changes with some irregular fluctuations throughout pregnancy. A significant decline occurs, however, in diastolic blood pressure by the second trimester, with a return during the last trimester to levels close to those before pregnancy. Although actual values may be different, several reports agree with this general pattern.[10, 11]

Some disagreement still exists on the effect of posture during gestation.[12, 13] Our data tend to agree with those of MacGillivray and associates,[12] but they do not concur with those of other reports.[13] Therefore, blood pressure values taken in different positions were presented. In our study, the control group had a small reduction in systolic blood pressure and a decline in diastolic blood pressure by the twenty-fourth week; thereafter, diastolic blood pressure increased up to levels above the ones reported for the fifteenth week. The two tested groups also experienced a declining pattern until the twenty-fourth to twenty-sixth week (the 2 gm of calcium group had an earlier reduction in both systolic and diastolic blood pressure by the twentieth week). Therefore, during the second trimester, the data reproduce the normal patterns of blood pressure during pregnancy. However, the magnitude of the blood pressure reduction was far greater among those receiving calcium supplementation.

In those women who received calcium supplementation, after having this dramatic decline, two different patterns were followed. Blood pressure values increased in the 1 gm of calcium group as they did in the control group. In contrast, those who received 2 gm of calcium continued to have lower values all through the third trimester. A dose-response effect appeared to be present.

The fact that the accepted pattern of blood pressure during pregnancy was reproduced in all groups, the tendency to a dose-response effect, and the presence of the same results regardless of the position in which blood pressure was measured are strong arguments in favor of a treatment effect. This concurs with our previous report on the effect of calcium supplementation in women of childbearing age.[6]

The explanation of this process is, however, not clear. The third trimester of pregnancy is a stage of major calcium adjustments. There is an increase in fetal calcium demand[14] and the increase in estrogen production blocks maternal bone reabsorption. Further, high protein intake increases calcium excretion in urine, aggravating the situation.[15] As a compensatory mechanism PTH tends to increase progressively, reaching a maximum level at term.[16] PTH will increase intestinal absorption of calcium as the only compensatory process during pregnancy. Thus, the third trimester of pregnancy is a hyperparathyroid state that maintains Ca^{++} levels within their physiologically narrow limits. If calcium supplementation is provided, particularly late in pregnancy, this hyperparathyroid state may be reduced.

In our study, normal pregnant women (placebo group) had an increase in PTH levels similar to the increase reported for other normal pregnant populations.[16] In contrast, the group that received 2 gm of calcium had a tendency toward lower values at term when compared with the baseline data. However, these figures did not reach significant levels. Furthermore, a significant positive association between PTH and diastolic blood pressure values was observed. Whether this association has a biologic explanation remains to be seen.

A PTH effect on blood pressure has been supported by several reports in animals,[17, 18] although not yet confirmed during pregnancy. Further, as has been suggested, the PTH rise can be a consequence of rather than the mediator of the low calcium effect.[19]

Other physiologic mechanisms also can be involved, given that calcium is present in several metabolic processes related to the control of vascular tone, such as prostaglandin production.

Regardless of the pathophysiology, it is clear by now that low calcium is associated with an elevation in blood pressure[4, 7, 20] and that calcium supplementation is shown to be effective in reducing blood pressure in animals and in nonpregnant and pregnant women.[5, 6] More research is needed in this promising field.

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