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Long term effect of calcium supplementation during pregnancy on the blood pressure of offspring: follow up of a randomised controlled trial

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Abstract

Objective: To explore the long term effect of calcium supplementation during pregnancy on the offspring's blood pressure during childhood.

Design: Follow up of a population enrolled in a double blind, randomised, placebo controlled trial.

Setting: Perinatal research unit, World Health Organisation's collaborative research centre.

Subjects: 591 children at a mean age of 7 years whose mothers were randomly assigned during pregnancy to receive 2 g/day of elemental calcium (n = 298) or placebo (n = 293).

Main outcome measures: Mean blood pressure and rate of high blood pressure of children.

Results: Overall, systolic blood pressure was lower in the calcium group (mean difference − 1.4 mm Hg; 95% confidence interval − 3.2 to 0.5) than in the placebo group. The effect was found predominantly among children whose body mass index at assessment was above the median for this population (mean difference in systolic blood pressure − 5.8 mm Hg (− 9.8 mm Hg to − 1.7 mm Hg) for children with an index > 17.5 and − 3.2 mm Hg (− 6.3 mm Hg to − 0.1 mm Hg) for those with an index of > 15.7 to 17.5). The risk of high systolic blood pressure was also lower in the calcium group than in the placebo group (relative risk 0.59; 0.39 to 0.90) and particularly among children in the highest fourth of body mass index (0.43; 0.26 to 0.71).

Conclusion: Calcium supplementation during pregnancy is associated with lower systolic blood pressure in the offspring, particularly among overweight children.

Introduction

Impaired maternal nutritional state,[1] mother's diet,[2] and lower birth weight of the offspring[3] have been implicated in the development of hypertension later in life, suggesting that fetal life is a period for programming blood pressure. More specifically, the dietary calcium intake of pregnant women may be associated with the blood pressure of their infants,[4] and calcium intake is inversely correlated with systolic blood pressure in young children.[5]

Using the population of a large, multicentre, randomised, placebo controlled trial of the effect of calcium supplementation during pregnancy,[6] we explored the effect of calcium supplementation during pregnancy on the blood pressure of the women's children.

Materials and methods

The trial

A detailed description of the methodology of the original trial has been published.[6] In short, the trial examined the effectiveness of 2 g of elemental calcium supplementation a day (four tablets of calcium carbonate 500 mg) for the prevention of hypertensive disorders of pregnancy. Women were eligible for the study if they were nulliparous, had singleton pregnancies, and had blood pressure values below 140/90 mm Hg at the time of randomisation. Supplementation was started at 20 weeks' gestation and continued until delivery.

In all, 1194 pregnant women were enrolled in three public hospitals (580 women) and one private hospital

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Table 1 Study population available for follow up

Population	Calcium group	Placebo group	Total
Women randomised in original study	593	601	1194
Women randomised at selected hospital	309	305	614
Women eligible for pregnancy study:	301	299	600
Death of infant between birth and age 1 year	2	6	8
Death of mother	1	0	1
Children eligible to participate in current study	298	293	591
Women contacted:	289	285	574
Refused to participate	10	5	15
Living outside the city or country	22	19	41
Women assessed (with their children) in current study (% of those eligible)	257 (86.2)	261 (89.1)	518 (87.6)

(614) affiliated with the Centro Rosarino de Estudios Perinatales. The joint human voluntary committee of the Centro Rosarino and its collaborating hospitals approved the study, and all women gave informed written consent for the study examining supplementation during pregnancy and oral consent for the examination of their children.

Study subjects

The follow up study was restricted to the 614 children born between August 1987 and November 1990 at the private hospital, and their mothers. Fourteen pregnant women had been lost to follow up (six in the placebo group and eight in the calcium group) after randomisation but before treatment, so they were not included in the analysis of the original study or in the current follow up.

From January 1995 to March 1996 we located mothers and their children from the index pregnancy by using the original addresses recorded in the medical records; the log book of the obstetricians and paediatricians; the health insurance lists; data from the city census; and personal contacts. We telephoned the mothers or visited them at home, and invited them to participate with their child. If they agreed, we conducted blood pressure measures, an anthropometric evaluation, and a short health questionnaire. We performed no other clinical examination and referred the mothers and children to their private doctor if necessary. The mothers continued to be blinded to whether they had received placebo or calcium in the main study. Blood pressure values of the children were matched with the mothers' treatment group only at the time of the current analyses. In all, 236 women did not attend the study clinic (118 in each group), for whom home visits were conducted by the same staff responsible for the clinical examination and blood pressure measures.

Blood pressure measurements

Four examiners blinded to the randomisation group measured systolic and diastolic blood pressures in the children (mean age 7.1 (SD 0.7) years (range 5 years to 9 years and 10 months)). The measurements were taken in the right arm, after 15 minutes' rest, with the child seated in a quiet room at the study centre. The same methodology was used at the home visits. No measurements were taken if the child was reported sick or was taking drug treatment. The measurements were validated by the field supervisor, who took repeated measurements in randomly selected children.

Three consecutive measurements of the children's systolic and diastolic blood pressure (Korotkoff V sound) were taken at one minute intervals with a standard mercury sphygmomanometer. All measures in children were taken with a cuff bladder 17.0 cm × 9.0 cm, with its centre placed directly over the brachial artery.

The examiners also took three consecutive measurements in the mothers, seated, using a random-zero sphygmomanometer following standard methodology.[6]

Other measurements

With the children undressed and without shoes, the examiners measured their height to the last complete millimetre and weight to the last complete 0.1 kg. At the end of the whole examination they administered a general health questionnaire to the mother about any major illnesses, hospital admissions, or episodes of urinary stones or gall stones. When a mother reported that she or her child had a diagnosis or symptoms of one of these diseases, a detailed history was taken, including information on the diagnostic method.

Statistical analysis

Children remained in the group to which their mothers were originally randomised, regardless of the women's compliance with the treatment and any postnatal experience (intention to treat analysis). The mean of the three blood pressure recordings was used as the blood pressure for the analyses. Cut off points specific for sex, age, and height for systolic and diastolic pressure corresponding to the 95th centile were used to classify children as having high or normal blood pressure.[7] For children's height by age we used centiles according to the World Health Organisation.[8] We compared children in the calcium and placebo groups at ages 5 to 9 years. Relative risk for high blood pressure was calculated for both groups. Crude mean and standard deviations of blood pressure in the two groups were compared. Analysis of covariance was used to obtain mean adjusted blood pressure during childhood, with sex, age, birth weight, and maternal blood pressure during pregnancy and at follow up included in the model. These values were expressed as crude and adjusted mean differences in blood pressure between the groups. Similar analyses were stratified by current body mass index of the children. We used the software package SAS (Cary, NC, United States).

Results

Table 1 shows the study population available for follow up (87.6% of the original population (86.2%, calcium group; 89.1%, placebo group)).

Generally, the women were older and taller and had higher mean systolic and diastolic blood pressures than the population in the original study.[6] The mothers of all the children eligible for the current study and the mothers of the children who were finally assessed had had closely similar characteristics at randomisation. Within these two populations the mothers in the calcium group had also had similar characteristics to those in the placebo group at randomisation.[6] Calcium

supplementation started at a mean gestational age of 21.3 (SD 1.6) weeks in the calcium group and 21.0 (SD 1.4) weeks in the placebo group. On average, the women in the placebo group took 87% of their tablets and the women in the calcium group 85%. These figures are closely similar to those in the original study.

Complications and outcomes in pregnancy

The proportion of women with anaemia, premature rupture of membranes, diabetes mellitus, third trimester haemorrhage, and receiving medical treatment, and the numbers of hospital admissions, inductions of labour, and caesarean sections were closely similar in the calcium and placebo groups. The rate of urinary tract infection was higher in the calcium group (12/257) than in the control group (7/261) (P = 0.23). The incidence of gestational hypertension was lower in the calcium group (15/257) than in the placebo group (22/261). One woman in the calcium group and two in the placebo group had pre-eclampsia. At birth, the weight, length, gestational age, and the rate of preterm delivery were closely similar between the two groups. A higher proportion of newborn infants in the calcium group had an Apgar score <7 at the first minute (20/248 *v* 10/251), and more newborn infants were admitted to the neonatal intensive care unit (38/248 *v* 29/251) (not significant).

Mothers' and children's characteristics 5 to 9 years after delivery

At assessment the mean maternal systolic blood pressure was similar in both groups, but the mean diastolic blood pressure was lower in the calcium group (table 2). Women in the calcium group had a lower risk of high diastolic blood pressure (≥90 mm Hg) than those in the placebo group (table 2). These blood pressure patterns did not change after adjustment for age and body mass index (weight (kg)/height (m)^2).

The mean systolic blood pressure in children was lower in the calcium group than in the placebo group (table 2).

Stratified analysis of the mean systolic blood pressure according to body mass index of the child at the time of assessment showed that most of the calcium effect was concentrated among children with body mass index in the upper two fourths of this population (table 3). Adjusting these analyses by age, sex, and birth weight did not modify these results. Including maternal blood pressure during the third trimester of pregnancy did not modify the overall effect observed. Including the mother's blood pressure at follow up reduced the difference between groups, although it did not change the overall pattern (table 3).

The proportion of children with high systolic blood pressure was lower in the calcium group (11.4%) than in the placebo group (19.3%) (relative risk 0.59; confidence interval 0.39 to 0.90). The proportion of children with high diastolic blood pressure was also lower in the calcium group (10.2% *v* 12.7% (0.80; 0.49 to 1.30)).

Stratified analysis for the risk of high blood pressure according to current body mass index of the child showed that most of the effect on blood pressure was concentrated in the subgroup of children with high body mass index. Among the children with body mass index >17.5, those whose mothers had received calcium had a lower risk of high systolic (0.43; 0.26 to 0.71) and high diastolic (0.60; 0.33 to 1.12) blood pressure than those whose mothers had not. The protective effect is also extended to the children with body mass index 15.7-17.5 (relative risk for high systolic blood pressure 0.37 (0.12 to 1.10)). The risk of high blood pressure among children whose body mass index at assessment was in the two lower fourths was the same, regardless of whether their mother had received calcium.

Furthermore, there was a significant positive effect of children's age at assessment on systolic and diastolic blood pressure (P = 0.001), independent of the randomisation group, but the interaction between children's age and randomisation group was not significant (P = 0.88).

We explored the differential effect of calcium supplementation during pregnancy on children's blood pressure at two levels of birth weight (>2500 to

Table 2 Characteristics of mothers and children at assessment 5 to 9 years after delivery, according to randomisation group during pregnancy. Values are means (SD) unless indicated otherwise

Characteristic	Calcium group (n=257)	Placebo group (n=261)	Mean difference (95% CI)
Mothers			
Age (years)	34.6 (4.0)	34.4 (4.5)	0.18 (–0.56 to 0.91)
No of deliveries	2.0 (0.7)	2.0 (0.7)	0.04 (–0.08 to 0.16)
Weight (kg)	60.1 (10.3)	60.9 (11.2)	–0.61 (–2.51 to 1.30)
Body mass index (kg/m^2)	22.9 (2.5)	22.7 (2.7)	–0.24 (–0.89 to 0.42)
Systolic blood pressure (mm Hg)	112.1 (13.6)	112.4 (14.0)	–0.34 (–2.72 to 2.04)
Diastolic blood pressure (mm Hg)	69.6 (10.3)	71.4 (12.3)	–1.77 (–3.73 to 0.19)
Systolic blood pressure ≥140 mm Hg (%)	3.9	3.1	1.25 (0.50 to 3.13)*
Diastolic blood pressure ≥90 mm Hg (%)	3.5	7.3	0.48 (0.22 to 1.04)*
Children			
Sex (% boys)	51.0	54.8	0.93 (0.79 to 1.09)*
Age (years) at assessment	7.1 (0.7)	7.1 (0.7)	–0.004 (–0.12 to 0.11)
Weight (kg)	25.2 (5.8)	24.9 (5.5)	0.29 (–0.61 to 1.19)
Height (cm)	124.3 (6.8)	124.1 (7.1)	0.17 (–1.04 to 1.37)
Body mass index (kg/m^2)	16.1 (2.5)	16.2 (2.2)	0.17 (–0.23 to 0.58)
Systolic blood pressure:	103.9 (10.6)	105.3 (11.0)	–1.4 (–3.3 to 0.5)
Adjusted†			–1.4 (–3.2 to 0.5)
Diastolic blood pressure:	65.4 (9.3)	65.8 (9.3)	–0.4 (–2.0 to 1.2)
Adjusted†			–0.4 (–2.0 to 1.2)

Blood pressure could not be recorded adequately in three children in the calcium group and one child in the placebo group.
*Relative risk.
†Adjusted for age, sex, and birth weight.

Table 3 Mean difference in blood pressure in children aged 5 to 9 years whose mothers received calcium during pregnancy, compared with those in placebo group, according to children's body mass index at assessment

Fourths of body mass index (kg/m^2) at assessment	No of children		Mean difference (95% CI) in blood pressure (mm Hg)	
	Calcium group	Placebo group	Diastolic	Systolic
>17.5	68	60	–3.7 (–7.4 to 0.0)	–5.8 (–9.8 to –1.7)
>15.7 to 17.5	63	69	0.8 (–2.2 to 3.8)	–3.2 (–6.3 to –0.1)
>14.4 to 15.7	62	65	–1.7 (–4.5 to 1.1)	1.8 (–1.2 to 4.8)
≤14.4	61	65	2.4 (–0.3 to 5.1)	0.5 (–2.7 to 3.8)
Overall	254	260	–0.4 (–2.0 to 1.2)	–1.4 (–3.3 to 0.5)

P=0.0001 for the interaction between treatment status (calcium or placebo) and body mass index ((treatment)×(body mass index)) for both diastolic and systolic blood pressure.
One child in the placebo group did not have a height value for the calculation of the body mass index.

< 3000 g, and > 3000 g). The risk of hypertension and the mean blood pressure values in the calcium and placebo groups showed the same pattern as the total sample.

Overall, there was a non-significant negative association between birth weight and blood pressure of the children (regression coefficient − 0.3 mm Hg/kg for systolic and − 0.9 mm Hg/kg for diastolic blood pressure), with adjustment for sex, age, treatment (calcium *v* placebo), maternal blood pressure at follow up, and children's body mass index. In similar adjusted analyses including only newborn infants born at term (> 37 weeks' gestation) the regression coefficients of birth weight on blood pressure at assessment were − 1.2 mm Hg/kg for systolic and − 1.3 mm Hg/kg for diastolic blood pressure (P > 0.10).

Side effects

The incidence of symptomatic kidney stones in the mothers was 2.3% and 2.7% for the calcium and placebo groups, respectively (not significant). Gall stones were reported by 3.1% of mothers in the calcium group and by 2.3% in the placebo group (not significant). None of the children had symptoms of kidney stones or gall stones. Children whose mothers had received calcium supplements were admitted (at least once) to hospitals at a similar rate to those whose mothers had not (26.7% *v* 27.4%).

Discussion

We show here that calcium supplementation during pregnancy is associated with lower systolic blood pressure in the offspring at age 5 to 9 years, particularly among overweight children. This is the first evidence from a randomised controlled trial of intrauterine programming of childhood blood pressure, mediated by a nutritional intervention during pregnancy.[1 3]

Mothers were blinded to their supplementation status, so they could not have selectively influenced the diet (high calcium or potassium or low sodium) or other health related behaviour of the children. Maternal baseline and newborn characteristics were fairly similar between groups, as were illnesses (information obtained retrospectively) and admission rates of children, occurring at the same rate as in another seven year follow up in a healthy, well nourished population.[9]

In addition to mean blood pressure, we used a normative standard, which offers specific cut off points for sex, age, and height for systolic and the fifth sound of diastolic blood pressure in children.[7] This adds to the external validity and future comparability of our results. Using this standard is unlikely to have introduced bias in the evaluation of the calcium effect because the objective of our study was to compare two arms of a randomised controlled trial rather than to estimate the prevalence of high blood pressure in the study population. Using this standard, however, will result in a higher than expected number of children classified as above the 95th centile. This is perhaps because the values of the standard are consistently lower than those from similar populations to ours[10] and because "single day" measurement in children is associated with higher prevalence of hypertension than repeated screening.[11]

Key messages

- Impaired fetal and maternal nutrition seem to be associated with childhood blood pressure, but most of the evidence comes from uncontrolled studies
- Systolic blood pressure of children aged between 5 and 9 years was lower when mothers took calcium rather than placebo during pregnancy
- The effect is found predominantly among children with a body mass index above the median for this population
- Fetal life seems to be a period for programming blood pressure; the magnitude of the effect observed has health implications among overweight children

The observed effect could therefore reflect a long term programming of blood pressure in utero by calcium supplementation in the mother. This agrees with results from observational studies that an early (fetal and infancy) exposure to calcium reduces blood pressure during childhood.[4 5]

The effect is observed mostly with systolic blood pressure, in agreement with previous reports evaluating the relation between maternal nutritional status[1] or birth weight[12] and blood pressure in children as well as reports of the effect of calcium intake on the blood pressure of young[5] and older[13] children. It is unclear whether this is a true biological differential effect or a statistical artefact resulting from the greater variability within individuals of diastolic compared with systolic pressure.[14]

The age of the children—before puberty—in our study is important for the effect on blood pressure[13] and the prediction of blood pressure during adulthood.[15] Children in the upper level of the distribution of blood pressure in this age range are at increased risk of adult hypertension,[16] and evidence exists of an association between children's blood pressure and adult blood pressure and cardiovascular mortality.[17] Systolic blood pressure is recommended as the primary measurement for screening pre-adolescent children for high risk of high blood pressure in adult life.[14]

We explored an a priori hypothesis of a differential effect among children with high current weight and body mass index because these are well known, strong predictors of high blood pressure in this age group.[18 19] The observation that most of the protective effect of calcium supplementation during pregnancy is concentrated in children with high body mass index, if confirmed, has important preventive implications because this subgroup is at higher risk of raised blood pressure and adult hypertension.

These subgroup analyses, although based on a post-randomisation characteristic, are biologically important[20] because (*a*) they show a clinically important effect, (*b*) they are significant, (*c*) we used an a priori hypothesis, and (*d*) the results are supported by recent independent evidence. Our data are in agreement, for example, with a recent report showing that the inverse relation between birth weight and blood pressure at age 50 in men is much stronger and

consistent among those in the top third of body mass index at assessment.[21] Likewise, the inverse association observed between birth weight and the risk of coronary heart disease is restricted also to men in the top third of body mass index.[22]

The magnitude of the effect on systolic blood pressure may be important. For example, a reduction as low as 2.0 mm Hg in a population is comparable to that achieved in adults by nutritional and hygienic interventions.[23] A reduction of 2-3 mm Hg in the blood pressure distribution may achieve lifesaving benefits similar to antihypertensive treatments.[24] Further research, however, is needed to corroborate these preliminary results.

The mechanism of action is a matter for physiological research. It is not mediated by changes in the birth weight distribution, and birth weight is not an effect modifier in this association. High maternal calcium intake, with lower maternal blood pressure, could reduce fetal exposure to maternal hormones or substances related to high blood pressure. Mothers who have had toxaemia or high blood pressure during pregnancy tend to have children who have high blood pressure until adolescence.[19] The parathyroid gland[25] and parathyroid hypertensive factor[26] could be associated with this effect. Lower levels of these factors could reduce peripheral resistance and pulse pressure during fetal life, protecting against a rise in blood pressure later in life. Our observation that the effect is present after blood pressure during pregnancy is controlled for is in conflict with this hypothesis. Alternatively, high maternal calcium intake could increase the rate of calcium transport to fetal circulation, thereby directly affecting the regulation mechanisms of blood pressure in the fetus in either a similar fashion to that of the mother or by influencing other intrauterine factors that control the developing cardiovascular system.

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Endpiece

Getting away with it

If age, which is certainly
Just as wicked as youth, look any wiser
It is only that youth is still able to believe
It will get away with anything, while age
Knows only too well it has got away with nothing.

W H Auden, *The Sea and the Mirror* (1944)