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The effect of calcium supplementation on blood pressure in non-pregnant women with previous pre-eclampsia: An exploratory, randomized placebo controlled study

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ABSTRACT

Background: Epidemiological findings suggest that the link between poverty and pre-eclampsia might be dietary calcium deficiency. Calcium supplementation has been associated with a modest reduction in pre-eclampsia, and also in blood pressure (BP).
Methods: This exploratory sub-study of the WHO Calcium and Pre-eclampsia (CAP) trial aims to determine the effect of 500 mg/day elemental calcium on the blood pressure of non-pregnant women with previous pre-eclampsia. Non-pregnant women with at least one subsequent follow-up trial visit at approximately 12 or 24 weeks after randomization were included.
Results: Of 836 women randomized by 9 September 2014, 1st visit data were available in 367 women of whom 217 had previously had severe pre-eclampsia, 2nd visit data were available in 201 women. There was an overall trend to reduced BP in the calcium supplementation group (1–2.5 mmHg) although differences were small and not statistically

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significant. In the subgroup with previous severe pre-eclampsia, the mean diastolic BP change in the calcium group (−2.6 mmHg) was statistically larger than in the placebo group (+0.8 mmHg), (mean difference −3.4, 95% CI −0.4 to −6.4; $p = 0.025$). The effect of calcium on diastolic BP at 12 weeks was greater than in those with non-severe pre-eclampsia ($p = 0.020$, ANOVA analysis).

Conclusions: There is an overall trend to reduced BP but only statistically significant in the diastolic BP of women with previous severe pre-eclampsia. This is consistent with our hypothesis that this group is more sensitive to calcium supplementation, however results need to be interpreted with caution.

Background

Calcium intake and pre-eclampsia

Hypertension has been estimated to complicate 5% of all pregnancies and 11% of first pregnancies, half of these being associated with pre-eclampsia, and accounting for 14% of 343 000 maternal deaths annually [1]. Pre-eclampsia, defined as high blood pressure and proteinuria occurring after the 20th week of pregnancy, is considerably more prevalent in poor than in wealthy communities. Two striking exceptions have been identified. More than 50 years ago, a low prevalence of pre-eclampsia was reported from Ethiopia where the diet, among other features, contained high levels of calcium [2]. The observation in 1980 that Mayan Indians in Guatemala, who traditionally soaked their corn in lime before cooking, had a low incidence of pre-eclampsia and eclampsia [3], stimulated interest in the concept that the link between poverty and pre-eclampsia might be dietary calcium deficiency.

The hypothesis that an increase in calcium intake during pregnancy might reduce the incidence of pre-eclampsia was tested in several randomized trials commencing in the late 1980s. Our systematic review showed that calcium supplementation of at least 1 g daily, commencing around mid-pregnancy, is associated with a modest reduction in pre-eclampsia, and notably a reduction in its severe manifestations, particularly among women at increased risk, or with low dietary calcium intake [4]. We recently reviewed evidence from randomized trials of lower doses of calcium (<1000 mg, mainly 500 mg daily) [5]. The limited evidence suggested a similar reduction in pre-eclampsia to that found with larger doses.

A trial nested within the large WHO trial of calcium supplementation (1.5 g daily from approximately 20 weeks' gestation) in pregnant women with low dietary calcium intake, failed to demonstrate an effect of calcium supplementation on biochemical measures commonly elevated in pre-eclampsia: serum urate, platelet count, and urine protein/creatinine ratio [6]. To reconcile the considerable evidence for reduced pre-eclampsia with calcium supplementation, with the absence of evidence of an effect on proteinuria and other markers for pre-eclampsia, we proposed the hypothesis that calcium supplementation in the second half of pregnancy reduces blood pressure and thus, the diagnosis and severe manifestations of pre-eclampsia, without evidence of an effect on the underlying pathology, and the epidemiological association of low dietary calcium with pre-eclampsia might be due to an effect in the first half of pregnancy. To test this hypothesis we are conducting a placebo-controlled randomized trial of calcium supplementation commencing before pregnancy in women with previous pre-eclampsia [7].

Calcium intake and hypertension

Low dietary calcium intake is associated with hypertension in the general population [8]. In animal studies, a high calcium diet reduces hypertension associated with oral contraceptive treatment, by improving diuresis and vasorelaxant responses [9]. A high dairy diet has been found to reduce systolic and diastolic blood pressure by about 2 mmHg, an effect correlated with reduction in intracellular calcium [10]. An alternative mechanism whereby calcium supplementation might lower blood pressure is by mitigating the hypertensive effect of sodium chloride (common salt) [11]. Another possible mechanism is via changes in vitamin D and parathyroid hormone concentration [12,13]. Calcium supplementation has also been shown to improve insulin sensitivity in women with Type 2 diabetes and hypertension [14]. In the latter study, blood pressure was not significantly reduced [15].

A meta-analysis published in 1999 of the effect of dietary or non-dietary calcium supplementation on blood pressure found an overall reduction in systolic and diastolic blood pressure of 1.44 and 0.84 mmHg, respectively (4560 participants) [16]. A subsequent randomized placebo controlled trial in 1471 non-hypertensive women with average age 74 years found that 1 g calcium daily was associated with a small reduction in systolic blood pressure at 6 months only. For a subgroup of women with low dietary calcium, the reduction was greater and persisted [17].

Whether calcium supplementation reduces blood pressure in hypertensive patients is not clear. A Cochrane review in 2006 including 13 small trials in men and women (total participants 485, largest trial 90, calcium dosage 400 mg to 2 g, median follow up 8 weeks) concluded that: "Due to poor quality of included trials and heterogeneity between trials, the evidence in favour of causal association between calcium supplementation and blood pressure reduction is weak and is probably due to bias" [18].

We are not aware of any previous randomized trials of calcium supplementation in non-pregnant women with previous pre-eclampsia. If calcium deficiency is a factor in the genesis of pre-eclampsia, it is feasible that women predisposed to pre-eclampsia may be more susceptible to the effects of calcium on blood pressure. This manuscript presents the results of a sub-analysis of the above-mentioned ongoing WHO trial: long term calcium supplementation in women at high risk of pre-eclampsia [7] with the objective to assess the effect of calcium supplementation on systolic and diastolic blood pressure in non-pregnant women with previous pre-eclampsia. Our hypotheses are that (1) calcium supplementation in non-pregnant women with previous pre-eclampsia is associated with reduced systolic and diastolic blood pressure; and (2) the effect of calcium supplementation on blood pressure is greater in women with previous severe pre-eclampsia/eclampsia.

Methods

The WHO long term calcium supplementation in women at high risk of pre-eclampsia trial is a multi-centre randomized, double-blind placebo-controlled clinical trial. Non-pregnant women who had pre-eclampsia or eclampsia in their most recent pregnancy are randomized to receive either 500 mg/day elemental calcium or placebo. The trial started in 2011 and is on-going. It has been approved by the Research Project Review Panel of the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction at the Department of Reproductive Health and Research of WHO, and the WHO Research Ethics Review Committee, Geneva, Switzerland. Ethical approval was obtained from appropriate national and institutional ethical review bodies as applicable for each study site.

The methodology of the trial has been described in the published protocol [7]. A brief description is presented below.

Settings

This is a multi-centre, multi-country trial in hospitals in South Africa, Zimbabwe and Argentina. The sites in Africa are government secondary or tertiary urban referral hospitals with large obstetric units serving urban and rural populations. The South African hospitals are located in Cape Town, East London, Johannesburg and Stellenbosch. In Zimbabwe the two maternity units included are in Harare. In Argentina, the site comprises of one maternity-hospital in Tucuman, two in Buenos Aires and one in the province of Buenos Aires.

Dietary surveys in the East London, Mdantsane and Western Johannesburg populations prior to participation in the 2006 WHO trial of calcium supplementation during pregnancy to prevent pre-eclampsia, found that the median daily dietary calcium of primiparous women was about 600 mg [19]. In the current on-going trial, a nutritional interview is conducted among all women enrolled in the trial who reach 20 weeks gestation to confirm low calcium intake in the study population.

Participants

Women are eligible if they had pre-eclampsia or eclampsia in their most recent pregnancy, if they are in a sexual relationship, not pregnant, not using contraception and if they give informed consent. Exclusion criteria are: less than 18 years of age; chronic hypertension with persistent proteinuria; calcium supplement intake; and history or symptoms of urolithiasis, renal disease or parathyroid disease.

The intervention

Women in the intervention group take one chewable tablet containing 500 mg elemental calcium daily from enrolment (before pregnancy) until 20 weeks' gestation. The women are asked to chew the tablet during the day, not close in time to taking food or iron supplements. Women in the control group receive placebo tablets identical in shape, colour and taste to the intervention tablet. The women are encouraged not to take any additional calcium supplements. All women receive unblinded calcium supplementation (1.5 g) from 20 weeks' gestation until delivery, according to WHO recommendations [20].

Data acquisition for blood pressure measurement

Blood pressure measurement was standardized at the beginning of the trial according to recommendations by the British Hypertension Society (http://www.bhsoc.org/latest-guidelines/how-to-measure-blood-pressure/). Blood pressure is measured and recorded for all women at recruitment (baseline) and in all subsequent trial visits. The visits are scheduled every 12 weeks until the woman becomes pregnant, then at 8, 20, and 32 weeks of pregnancy.

Blood pressure is measured with a standard mercury sphygmomanometer at the sites in Africa and with an automated sphygmomanometer at the sites in Argentina.

Sub-study population and methods

For the current sub-study, routine data collected during the trial visits were analysed. Women recruited in the trial with blood pressure data available for baseline and at least one subsequent follow-up trial visit while still not pregnant up to September 2014 were included. To eliminate the effect of recent pre-eclampsia, women with their previous delivery at less than 6 weeks prior to baseline (randomization) were excluded.

Baseline data were compared between the calcium and placebo groups for the study population to ensure no selective loss to follow-up. Due to the high number of comparisons we used 0.025 as indicating statistical significance. We used an intention-to-treat (ITT) approach for this analysis.

Two comparisons were computed: between baseline and 1st trial visit (approximately 12 weeks after baseline); and between baseline and 2nd trial visit (approximately 24 weeks after baseline). For each woman, the changes in systolic and diastolic blood pressures were calculated by

subtracting the measurement at baseline from the measurement at the first and second follow-up visit. The mean change in systolic and in diastolic blood pressures were compared between the calcium and placebo groups for the first follow-up visit minus baseline and for the second follow-up visit minus baseline. The mean changes were expressed as mean differences with 95% confidence intervals. For each woman, the 1st visit (or 12 week visit) was considered as the visit occurring between 6 and 18 weeks, and the 2nd visit (or 24 week visit) was considered as the visit occurring between 18 and 30 weeks.

Sub-group analyses were performed to compare the effect of calcium supplementation on blood pressure at the first visit after admission between women with a history of severe pre-eclampsia and women without such a history. A history of severe pre-eclampsia in the previous pregnancy was defined as: (i) eclampsia, or (ii) HELLP syndrome, or (iii) systolic blood pressure higher than 160 mmHg or (iv) diastolic blood pressure higher than 110 mmHg or (v) onset of pre-eclampsia earlier than 28 weeks, or (vi) ICU admission. An ANOVA analysis on both systolic and diastolic blood pressures was conducted controlling for treatment received (placebo vs. calcium) and history of severe pre-eclampsia (yes/no).

Using preliminary information, we decided that for this secondary analysis we would need no less than 180 subjects per arm (360 patients in total) to be able to detect a systolic blood pressure difference of 5 mmHg between the placebo and calcium groups (130 and 125 mmHg respectively), and with a common SD of 16 mmHg. With an alpha value of 0.05, this sample size would allow us to detect this difference with 90% power. SPSS version 20 was used for all analyses.

Results

A total of 836 women were randomized in the CAP study database dated 9 September 2014 (Fig. 1). Blood pressure at admission was compared with blood pressure in the 1st follow-up visit (approximately 12 weeks after admission) in 367 women, and with blood pressure in the 2nd follow-up visit (approximately 24 weeks after admission) in 201 women. In both comparisons, there were 94% of women recruited in the African sites and 6% of women recruited in the Argentinean sites. In the 12 week sub-group with severe pre-eclampsia, 217/367 women versus 150/367 women without severe preeclampsia were analysed.

Fig. 1 shows the trial profile of the sub-study. From 836 women randomized, 469 were excluded from the 1st visit versus admission comparison for the following reasons: 168 had a previous pregnancy less than six weeks before enrolment and 388 had blood pressure missing at admission and/or in the 1st trial visit (e.g. not yet due for 12 week visit, or missed visit). None were pregnant at the 1st visit. For the comparison between the 2nd visit and admission, an additional 166 women were excluded from the analysis because blood pressure was missing at this visit (e.g. not yet due for visit or missed visit).

Table 1 shows data for selected baseline characteristics comparing the calcium and placebo groups for trial participants who were included (first row) and excluded (second row) from the comparisons at 1st and 2nd visit. Results are presented as means or percentages depending on the variable, with p values. There were no statistically significant differences at the $p < 0.025$ level between the calcium versus placebo groups included in this sub-study. We did not statistically quantify the differences at baseline between women who were included in the sub-study versus women excluded but Table 1 shows the characteristic of both groups.

Table 2 shows the changes in systolic and diastolic blood pressure at the 1st and 2nd visit stratified by calcium and placebo groups. There was an overall trend to reduced blood pressure at the follow-up visits, except for the placebo group diastolic pressure at the 1st visit. The reductions in blood pressures were consistently greater in the calcium than in the placebo groups, however the differences were small (1–2.5 mmHg) and none were statistically significant.

Table 3 shows the results for the subgroup with history of severe pre-eclampsia. The mean reduction in diastolic blood pressure in the calcium group (−2.6 mmHg) is statistically larger than the corresponding change in the placebo group (+0.8 mmHg), (mean difference −3.4, 95% confidence interval −0.4 to −6.4; $p = 0.025$) but the other differences are not statistically significant. In the ANOVA analysis controlling for treatment received (placebo vs. calcium) and history of severe pre-eclampsia (yes/no), the only statistically significant result was the interaction between the two predictors for DBP ($p = 0.020$).

We used an intention-to-treat (ITT) approach for this analysis. Nevertheless, compliance was similar and above 80% in both groups. At the 1st visit, compliance was 81.1% and 82.4% in the calcium and placebo groups, respectively. At the 2nd visit, compliance was 83.2% and 82% in the calcium and placebo groups, respectively.

Discussion

Due to the exploratory nature of this sub-study and the multiple comparisons performed, the results need to be interpreted with caution. This sub-study did not confirm an overall effect of calcium supplementation on blood pressure. We found a consistent trend to greater blood pressure reductions in the calcium than the placebo group at both trial visits (at 12 weeks and 24 weeks after randomization) which is consistent with such an effect, but the differences were not statistically significant except for diastolic pressure in the sub-group of women with previous severe pre-eclampsia. These women with previous severe forms of pre-eclampsia (including eclampsia and HELLP syndrome) may be more sensitive to the effects of calcium supplementation on diastolic blood pressure than women with previous non-severe pre-eclampsia. The latter finding is consistent with our hypothesis that women who are susceptible to pre-eclampsia may be uniquely sensitive to calcium deficiency, either because of greater dietary deficiency or because of an inherent sensitivity to calcium deficiency. Once completed, the CAP study should provide sufficient data to test this hypothesis in an independent dataset.

Although the trial includes sites in Africa and Argentina, we would like to note that the majority of the population

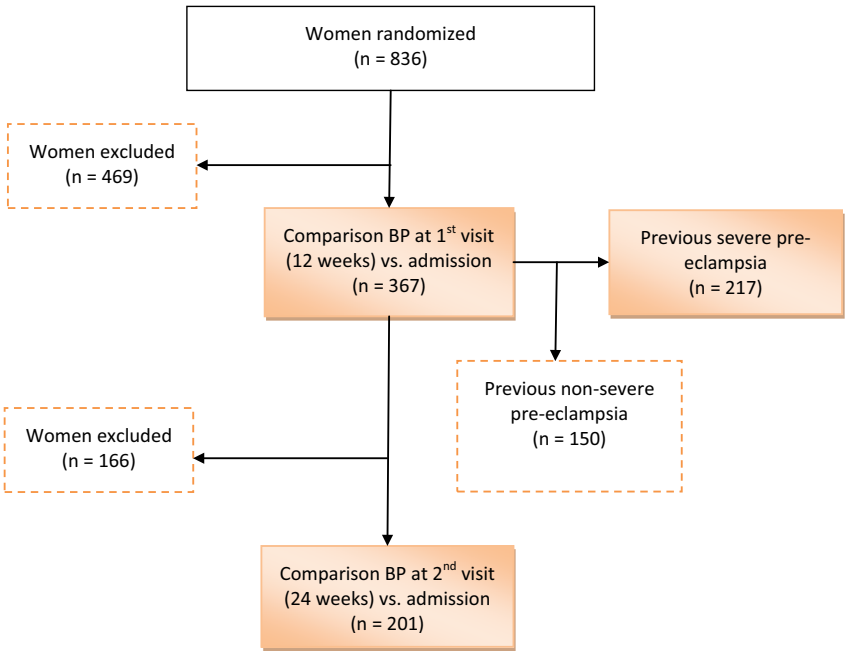

Fig. 1. Trial profile for the blood pressure sub-study (BP: blood pressure). Reasons for exclusions are presented in the results section.

Table 1
Baseline data expressed as percentages (%) or mean values with standard deviations (SD). Incl: trial participants included in this analysis; Excl: trial participants excluded from this analysis.

		1st Trial visit (12-weeks follow up) vs. admission							2nd Trial visit (24-weeks follow up) vs. admission						
		Placebo			Calcium			p^{**}	Placebo			Calcium			p^{**}
		n	Mean (%)	SD	*n*	Mean (%)	SD		*n*	Mean (%)	SD	*n*	Mean (%)	SD	
Age (years)	Incl	186	30.3	5.5	181	30.5	5.6	0.700	104	30.3	5.6	97	31.7	5.5	0.074
	Excl	231	29.5	6.2	237	29.7	6.0		313	29.7	6.0	321	29.5	5.9	
Parity	Incl	186	1.9	1.1	181	2.0	1.1	0.256	104	1.9	1.1	97	2.2	1.3	0.042
	Excl	231	2.0	1.2	237	1.9	1.1		313	2.0	1.1	321	1.8	1.0	
SBP at admission (mmHg)	Incl	186	126.1	16.3	181	127.4	17.2	0.463	104	126.8	16.0	97	131.0	19.6	0.095
	Excl	229	126.8	19.9	235	125.7	20.2		311	126.4	19.1	319	125.0	18.5	
DBP at admission (mmHg)	Incl	186	81.6	11.5	181	81.5	13.0	0.962	104	81.9	11.4	97	83.6	14.5	0.371
	Excl	229	81.7	14.3	235	81.8	14.2		311	81.5	13.6	319	81.1	13.4	
Weight (kg)	Incl	183	79.4	18.4	178	76.1	18.0	0.085	103	78.9	17.1	95	77.5	17.6	0.566
	Excl	219	74.4	18.2	222	74.8	19.1		299	75.9	18.8	305	74.7	18.9	
Months since (last) birth with PE	Incl	186	26.2	28.4	181	22.9	26.6	0.265	104	21.2	19.3	97	22.6	24.3	0.664
	Excl	207	21.9	37.8	209	17.7	23.2		289	24.9	37.6	293	19.3	25.1	
Onset PE <28 weeks	Incl	152	52.6%		143	46.9%		0.381	91	54.9%		84	44%		0.197
	Excl	176	50.0%		188	49.5%			237	49.8%		247	49.8%		
Eclampsia*	Incl	179	17.3%		176	14.2%		0.510	100	21.0%		95	10.5%		0.071
	Excl	220	19.1%		222	22.5%			299	17.4%		303	21.5%		
HELLP*	Incl	151	15.2%		153	15.7%		1.000	80	17.5%		88	20.5%		0.772
	Excl	190	13.2%		192	14.1%			261	13.0%		257	12.8%		
Baby born alive	Incl	186	54.3%		181	53.6%		0.975	104	52.9%		97	51.5%		0.961
	Excl	231	44.2%		237	44.3%			313	47.3%		321	47.4%		

SBP, systolic blood pressure; DBP, diastolic blood pressure; PE, pre-eclampsia.
* Those unsure were excluded.
** *t*-Test for independent means, or chi-square test with continuity correction. Due to the high number of comparisons, we used 0.025 as indicating statistical significance.

in this sub-study constitutes of women recruited in the African sites (94% versus 6%). The small number of women recruited from sites in Argentina did not allow us at the time of this sub-study to study differences, if any, in sensitivity to calcium supplementation and calcium deficiency among these two populations.

While emphasising the need for caution in interpreting the results of exploratory research with several outcomes measured, these findings are consistent with the possibility of a role for calcium deficiency in the aetiology of pre-eclampsia and justify further research in this field.

Table 2
Change in blood pressure at 1st and 2nd trial visit (12 weeks and 24 weeks, respectively) compared with baseline, expressed as mean values with standard deviation (SD). Differences between calcium and placebo groups expressed as mean differences (MD) with 95% confidence intervals (CI).

	Calcium			Placebo			Difference	
	N	Mean	SD	*N*	Mean	SD	MD	95% CI
Change after 12 weeks (1st trial visit)								
Week after randomization	181	12.4	1.3	186	12.6	1.5		
Systolic BP (mmHg)	181	−4.1	14.7	186	−2.7	14.4	1.4	−1.6–4.4
Diastolic BP (mmHg)	181	−0.8	11.6	186	0.2	11.3	1.0	−1.3–3.4
Change after 24 weeks (2nd trial visit)								
Week after randomization	97	24.4	1.9	104	24.9	1.9		
Systolic BP (mmHg)	97	−5.9	18.5	104	−3.3	12.7	2.5	−1.9–6.9
Diastolic BP (mmHg)	97	−2.5	14.2	104	−1.2	11.3	1.4	−2.2–4.9

Table 3
Change in blood pressure at 12 weeks compared with baseline, expressed as mean values with standard deviation (SD). Differences between calcium and placebo groups expressed as mean differences (MD) with 95% confidence intervals (CI) for women with and without severe pre-eclampsia in the previous pregnancy. In the case of diastolic BP, the interaction between treatment and severity of previous pre-eclampsia was statistically significant ($p = 0.20$, ANOVA analysis).

	Calcium			Placebo			Difference	
	N	Mean	SD	*N*	Mean	SD	MD	95% CI
With severe pre-eclampsia in previous pregnancy								
Week after randomization	105	12.4	1.2	112	12.5	1.5		
Systolic BP (mmHg)	105	−6	14.7	112	−2.8	15.6	3.2	−0.9–7.3
Diastolic BP (mmHg)	105	−2.6	10.9	112	0.8	11.3	3.4*	0.4–6.4
Without severe pre-eclampsia in previous pregnancy								
Week after randomization	76	12.4	1.4	74	12.6	1.8		
Systolic BP (mmHg)	76	−1.4	14.3	74	−2.4	12.4	−1.1	−5.4–3.3
Diastolic BP (mmHg)	76	1.7	12.2	74	−0.6	11.4	−2.3	−6.1–1.5

* Statistically significant.

Ethics statement

Ethical approval was obtained from appropriate national and institutional ethical review bodies as applicable for each study site. The protocol of this trial has been approved by the Research Project Review Panel of the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction at the Department of Reproductive Health and Research of WHO, and the WHO Research Ethics Review Committee, Geneva, Switzerland.

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Competing interests

The authors have declared that no competing interests exist.

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