Effects of calcium supplementation on markers of preeclampsia: randomized clinical trial

Efeitos da suplementação do cálcio sobre marcadores da pré-eclâmpsia: ensaio clínico randomizado
Efectos de los suplementos de calcio en marcadores de preeclampsia: ensayo clínico aleatorizado

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Abstract

Objective: To analyze the effects of calcium supplementation on markers of preeclampsia over time by comparing the use of high- and low-dose calcium in hypertensive pregnant women.

Methods: This is a randomized clinical trial, placebo controlled, with three parallel groups carried out at the reference outpatient clinic for high-risk prenatal care in the South Region of Brazil, with intention-to-treat analysis and follow-up after four and eight weeks. The intervention consisted of ingesting calcium 500mg/day, calcium 1500mg/day and placebo. Data were analyzed according to a generalized mixed equation estimation model adopting α 0.05.

Results: The effect of low- and high-dose calcium on evolution over time was maintained between groups, even after adjustment for confounding factors. There was a significant difference in the parameters analyzed in the time and group interaction (p <0.000) and a decrease in the means of 12.3 mmHg in SBP, 9.2 mmHg in DBP, 3.2 mg/dl creatinine and 7.2 mg/dl proteinuria for the 500mg calcium/day group. The results were similar for the maximal supplementation group.

Conclusion: Calcium improved vascular prognosis in hypertensive pregnant women by reducing blood pressure levels and markers of preeclampsia.

Resumo

Objetivo: Analisar os efeitos da suplementação de cálcio nos marcadores da pré-eclâmpsia ao longo do tempo, comparando o uso de cálcio em alta e baixa dosagem em mulheres grávidas com hipertensão.

Métodos: Trata-se de ensaio clínico randomizado com três grupos paralelos, placebo controlado realizado no ambulatório de referência para o pré-natal de alto risco na Região Sul do Brasil, com análise de intenção de tratar e seguimento após quatro e oito semanas. A intervenção consistiu na ingestão de cálcio 500mg/dia, cálcio 1500mg/dia e placebo. Os dados foram analisados segundo um modelo generalizado de estimação de equações mistas adotando α 0,05.

Resultados: O efeito do cálcio em baixa e alta dosagem na evolução ao longo do tempo foi mantido entre os grupos, mesmo após o ajuste para os fatores de confusão. Houve diferença significativa nos parâmetros analisados na interação tempo e grupo (p <0,000) e diminuição nas médias de 12,3mmHg na PAS, 9,2 mmHg na PAD, 3,2 mg/dl creatinina e 7,2 mg/dl proteinúria para o grupo cálcio 500mg/dia. Os resultados foram semelhantes para o grupo com suplementação máxima.

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Conflicts of interest: Although Schirmer J is the Editor-in-Chief of Acta Paulista de Enfermagem, she did not participate in the peer review process of the aforementioned article.

Conclusão: O cálcio melhorou o prognóstico vascular em mulheres grávidas com hipertensão ao reduzir os níveis pressóricos e os marcadores da pré-eclâmpsia.

Resumen

Objetivo: Analizar los efectos de los suplementos de calcio en los marcadores de preeclampsia a lo largo del tiempo, comparando el uso de calcio en dosis altas y bajas en mujeres embarazadas con hipertensión.

Métodos: Se trata de un ensayo clínico aleatorizado con tres grupos paralelos, placebo controlado realizado en consultorios externos de referencia en el control prenatal de alto riesgo en la Región Sur de Brasil, con análisis de intención de tratar y seguimiento luego de cuatro y ocho semanas. La intervención consistió en la ingesta de calcio 500 mg/día, calcio 1500 mg/día y placebo. Los datos se analizaron de acuerdo con un modelo generalizado de estimación de ecuaciones mixtas adoptando α 0,05.

Resultados: El efecto del calcio en dosis bajas y altas en la evolución a lo largo del tiempo se mantuvo entre los grupos, inclusive después de los ajustes por los factores de confusión. Hubo diferencia significativa en los parámetros analizados en la interacción tiempo y grupo (p <0,000) y reducción de los promedios de 12,3 mmHg en la PAS, 9,2 mmHg en la PAD, 3,2 mg/dl creatinina y 7,2 mg/dl proteinuria en el grupo calcio 500 mg/día. Los resultados fueron parecidos en el grupo con suplemento en dosis máxima.

Conclusión: El calcio mejoró el pronóstico vascular en mujeres embarazadas con hipertensión al reducir los niveles de presión y los marcadores de preeclampsia.

Introduction

Preeclampsia (PE) is considered one of the most important complications of the pregnancy-puerperal cycle, and the main cause of maternal death in developing countries by eclampsia-related complications.[1] The potential mechanisms of hypertensive disorders appear to be directly related to maternal concentrations of micronutrients, including calcium.

Calcium supplementation has been tested in several randomized trials starting in the late 1980s, suggesting a promising beneficial effect in hypertensive disorders of pregnancy. Based on these first results, a series of randomized clinical trials were performed to evaluate the effectiveness of calcium supplementation in reducing blood pressure levels and PE-related complications.[2-4]

For this reason, strategies to reduce the risk of hypertensive disorders of pregnancy have received considerable attention. The World Health Organization (WHO) has published guidelines that recommend calcium supplementation with 1.5g-2g of elemental calcium per day for pregnant women with low dietary calcium in low- and middle-income countries.[5]

This recommendation raised questions about optimal calcium dosing and the safety of an effective dosage. Some intervention studies have addressed calcium supplementation at 1,500mg/day and obtained satisfactory results in reducing the risk of PE.[1-3] On the other hand, other studies have highlighted the benefits of supplementation at lower dosages (800mg/day), raising doubts regarding dosage and suspicions regarding the risks of excessive supplementation.[6,7] The WHO recognizes that implementation of this recommendation requires close monitoring of women's total daily calcium intake to avoid exceeding the established tolerable upper intake level locally or internationally.[5]

Excessive calcium consumption can increase the risk of urinary stones and urinary tract infections, and reduce the absorption of other essential micronutrients.[8,9] Although women's response to calcium supplementation is heterogeneous, in terms of magnitude of the effect, a consistent protective response to the intervention was identified in previous studies.[3,10] There is evidence that the mineral prevents the activation of endothelial cells induced by the invasion of placental trophoblastic dendrites, and minimizes blood pressure by reducing parathyroid hormone and the release of renin by the kidneys, leading to vasodilation.[4]

Although calcium supplementation is recommended from 20 weeks for pregnant women at risk in low-income countries, universal calcium supplementation for pregnant women is not part of antenatal care services in Brazil. The development of this study is justified by the non-existent practice of supplement prescription and the scarcity of essential intervention offers.

Note that the dietary calcium intake of pregnant women in developing countries, such as Mexico, Brazil, Ecuador, Argentina and African countries is low, less than 600 mg per day.[11,12] Therefore, exploring strategies to compensate for nutritional and dietary limitations in pregnant women with potential risks for hypertensive complications is highly recommended, as it can be an acceptable alternative to avoid side effects and worse outcomes.

Given the limited availability of calcium rich foods in the eating habits of Brazilian pregnant women and as the conflicting effects on the action of calcium still fall on the recommended dosage and duration of use of the supplement, the assumption in this study was that low doses of calcium (500mg) may affect vascular prognosis in pregnant women at risk by reducing blood pressure levels and adjusting markers of PE.

Studies on the minimum effective calcium supplementation to prevent PE are also needed to determine if lower doses can be recommended.[6] Therefore, identifying the effect of calcium can support standardized clinical practice, encourage its prescription, and provide subsidies to review and update the actions of public health services during antenatal care offered to pregnant women at potential risk of developing hypertensive syndromes.

The aim of this study was to analyze the effects of calcium supplementation on markers of PE over time, comparing the use of high- and low-dose calcium in hypertensive pregnant women.

Methods

Randomized placebo-controlled clinical trial with three parallel groups conducted from June 2018 to July 2019 at the reference outpatient clinic for high-risk antenatal care in the South Region of Brazil linked to the Unified Health System (SUS).

The territory chosen for the development of the study is a reference in health actions and comprises the Grande Fronteira do Mercosul region (Meso Mercosul). On average, the outpatient clinic serves around 300 pregnant women/month classified as high risk, who are assisted by specialist doctors (gynecologists and obstetricians). These pregnant women are referred via the regulatory system of the municipality through the Basic Health Units (UBS).

The study included pregnant women over 18 years of age with a single fetus, primiparous, diagnosed with gestational hypertension (characterized by an increase in blood pressure levels equal to or above 140 mmHg for systolic blood pressure/SBP; and equal to or above 90 mmHg for diastolic blood pressure/DBP identified in Korotkoff phase V after week 20), overweight/obese before pregnancy (BMI between 25 kg/m² and 29.9 kg/m²), at least 20 weeks pregnant, with low socioeconomic factor (less than four years of study and income less than one minimum wage) and low dietary calcium intake (less than 800 mg/day), and not using medications that could interfere with calcium absorption (for example: corticosteroids, thiazides and thyroid hormones).

Participants who presented polyhydramnios, severe anemia, fetal death, history of hypertension before pregnancy, placental abruption, premature rupture of membranes (PROM), altered umbilical artery Doppler and uteroplacental insufficiency were excluded from the study. These clinical conditions contraindicate the follow-up of pregnant women in the high-risk outpatient clinic, and they are referred to the high-complexity hospital service.

The sample size was calculated based on the primary results of calcium supplementation in pregnant women from previous studies.[1,4] The difference between the group means in the reduction of systolic and diastolic blood pressure and proteinuria was considered (4% in the placebo group, 8% in the 500mg calcium/day group and 12% in the 1,500mg calcium/day group), with a type I (α) error of 0.05%, type II (beta) error of 0.20% and a study power of 80%. The calculated necessary sample totaled 175 pregnant women. However, considering probable losses, the sample calculation was expanded by 10%, totaling 193 pregnant women subdivided into three groups.

Randomization was performed by a statistician unrelated to the trial using the online calculator (http://randomization.com/) via permuted block-

ing. Treatment assignments within blocks were determined randomly in order, with the desired allocation ratio achieved within each 1:1:1. The generated codes were allocated to packages containing the coding generated by randomization.

Participants were randomly allocated and masked regarding the dosage received from 20 weeks of pregnancy until delivery. A third person was responsible for administering and prescribing the pills. The study investigators were not masked for calcium measurement since masking does not interfere with the primary outcome of this study, which consists of clinical and laboratory measurements.

The intervention consisted of prescribing two pills with 250mg of elemental calcium each, totaling 500mg per day (500mg calcium/day group), two pills with 750mg of elemental calcium each, totaling 1,500mg per day (1,500mg calcium/day group) and two pills with 250mg of microcrystalline cellulose each, totaling 500mg for the control group. The placebo pills were indistinguishable from calcium pills in appearance and taste.

The pills were provided to participants at each follow-up of the study. Recommendation was to consume calcium with water, preferably between the two main meals (lunch and dinner) to minimize possible interference with the absorption of other minerals. None of participants received or used antihypertensive medication during the study period.

Pregnant women were instructed to continue with the supplementation until delivery, asked not to change their regular food intake during the study nor take any supplements other than those provided by the investigator.

Envelopes containing the pills were given to participants with the exact number of pills to last four weeks. After the first assessment (baseline), sequential assessments occurred every four weeks after the start of the trial. Thus, every four weeks, new pills were offered and clinical and laboratory parameters were evaluated. Follow-up monitoring was performed until delivery.

Adherence to treatment was calculated by dividing the number of blisters used by the total number of pills that should have been taken since the last count, expressed as a percentage. Adherence was classified as low when the participant took less than 50% of the prescribed medication; regular for between 50% and 69% of the medication and optimal for more than 70%.[13]

Participants were screened according to the inclusion criteria. After giving their consent to participate in the study, they were randomized for further assessment, intervention and follow-up. Once recruited, participants were asked to return to the study site on a day and time scheduled by the researchers after a 12-hour fasting for clinical evaluation and collection of laboratory tests.

The clinical evaluation comprised the application of the research questionnaire containing demographic data and socioeconomic factors (age, education, income), in addition to a dietary recall questionnaire. During clinical evaluation, anthropometric measurements (weight and height) were taken and blood pressure was measured.

All dietary recalls were applied using the Multiple-Pass Methods (MPM), according to which the interviewer conducts the interview by listing foods by time and meal.[14] This method reduces the bias of the dietary measurement, as it helps the interviewee remember the food eaten in the previous day. Information on drinks consumed was also included in the record.

The estimate of habitual calcium intake was calculated with the dietWin® software, version 2012. Food quantification for the inclusion of values was performed according to the Brazilian Table of Food Composition (TACO) and the Dietary Reference Intakes (DRI).[15]

Blood pressure was measured manually, using the Littmann Classic III 5620 Stethoscope Kit and Welch Allyn Durashock DS44-BR sphygmomanometer, standardized in accordance with recommendations of the British Hypertension Society (BHS).[16]

The nutritional status was classified using the patient's body weight and height, according to the WHO criteria for body mass index (BMI) per gestational week.[17] To this end, body weight was measured with the pregnant woman barefoot and not wearing any accessory, using a portable digital scale model HCM 5110 M (GAMA Italy Professional,

San Pietro in Casale, Italy) previously calibrated, with a capacity of 150kg and a sensitivity of 100g. The portable stadiometer used had a maximum capacity of 200cm and a resolution of 1mm. All interviewees were weighed and measured following the standard procedure described in the literature.[18]

For laboratory evaluation, blood and urine samples were collected for analysis of tests such as complete blood count, urea, creatinine, proteinuria, microalbuminuria, parathyroid hormone (PTH) and ionized calcium. The laboratory's standardized analytical procedure was used for the dosages in accordance with the protocol defined by the manufacturer of the commercial kits used for each specific exam. The laboratory samples were collected by the team of technicians from the health clinic's exam collection room and sent to the research support laboratory for subsequent analysis.

The groups were accompanied by a research assistant every week to monitor the safety of participants. In the presence of serious adverse events such as hypertensive peaks and severe PE, participants were duly referred to hospital units and treated. Such events were not observed throughout the study.

As an incentive strategy to improve participant retention, a home visit was performed to emphasize the benefits of calcium intake. After childbirth, research team members extracted neonatal outcome data from hospital records.

Repeated observations were obtained over time for each participant; at baseline, at four weeks, and at eight weeks of supplementation.

The primary outcome of the study was the improvement of vascular prognosis through the reduction of blood pressure levels and markers of PE measured by levels of proteinuria, urea, creatinine, protein/creatinine ratio and parathyroid hormone (PTH). Secondary outcomes were low birth weight (< 2,500g) and prematurity (< 37 weeks).

Taking into account the follow-up of study participants over time at three different moments of data collection, the dependent variable was defined based on the assessed markers of PE and the independent variables were time (baseline, four weeks and eight weeks) and calcium dosage (500mg/day, 1,500mg/day and placebo).

Analyzes were conducted using the Statistical Package for the Social Sciences (SPSS) software, version 20.0. An automatic check of data was carried out at the time of typing using the Check function. Data cleaning was carried out to identify and correct coding, review and typing inconsistencies, thereby obtaining the frequencies of the variables collected in the program itself.

Descriptive data analysis was used to characterize the studied population. Mean and standard deviation were calculated for continuous variables and frequency and percentage for categorical variables. Data normality was tested using the Shapiro-Wilk test.

The analysis of variance (ANOVA) of independent samples was performed to study the differences between the groups before the intervention, followed by the Bonferroni post-test. The Pearson's chi-square test was used for categorical variables.

In longitudinal analyzes, repeated assessments of each patient were used for all outcomes (dependent variables) generalized linear mixed models (GLMM). When using GLMM, all observations are considered, including those of discontinued patients. The model made it possible to evaluate the fixed factors time (baseline, week four and week eight) and group factors (500mg calcium/day, 1,500mg calcium/day and placebo), as well as a possible interaction effect between time and group.

The model was fitted with gamma distribution with log link, considering individuals as a random effect and first-order autoregressive covariance matrix (AR1). The best fit was defined by the Akaike Information Criterion (AIC). The Normal and Tweedie probability functions were also tested. The assumption of normality of residuals was assessed with the QQ plot with confirmatory results and the analysis of multiple pairwise comparisons was performed using the Bonferroni test.

For the variables with a significant difference between the groups as measured by the GLMM, the intragroup and intergroup P were calculated at each time point separately. The size of the effect of the intervention was investigated on the studied variables that behaved differently over time.

The intention-to-treat analysis was adopted. In cases where treatment was interrupted, patients

were first invited to perform only the assessments. For patients who refused to return for assessments, previously collected data were repeated in subsequent assessments.

The necessary ethical requirements were met in the study, respecting the guidelines and regulatory standards for research with human beings. The research protocol was submitted for consideration by the National Council for Scientific and Technological Development (CNPq) and received financial assistance, in accordance with a notice from the Ministry of Science, Technology, Innovations and Communications/National Council for Scientific and Technological Development (MCTIC/CNPq) 28/2018 – Universal. This study was also financed by the Support Fund for the Maintenance and Development of Higher Education (FUMDES). The study funders had no role in study design, data collection, data analysis, data interpretation or writing of the report (Universidade Federal de São Paulo: Opinion Number: 2.659.764/ Certificate of Presentation of Ethical Review: 81829417.3.0000.5505).

Results

During the recruitment and allocation of 193 eligible participants, five were excluded before randomization because they did not meet the inclusion criteria, 11 refused to participate and two had severe anemia. Therefore, 175 pregnant women were randomized and randomly allocated into three groups preliminarily divided into the placebo group (n=59), the 500mg calcium/day group (n=58) and the 1,500mg calcium/day group (n=58). During follow-up after four weeks, there were 44 losses, 12 in the placebo group, 15 in the 500mg calcium/day group and 17 in the 1,500mg calcium/day group. In the analysis of the total number of pregnant women who started the research protocol, 83 completed all stages. Figure 1 presents the flow diagram of the study participants. For patients who did not attend reassessments, data from the last evaluation were repeated to perform the intention-to-treat analysis. Table 1 shows the homogeneity between

groups before the intervention according to sociodemographic, clinical and laboratory characteristics. The results suggest that randomization was not affected by discrepancies between groups. At the end of the study, after eight weeks, low adherence to treatment was significant in the group with maximum supplementation.

In analyzing the effect of low- and high-dose calcium on the evolution of preeclampsia markers over time, the GLMM was used and adjusted considering the participants as a random effect. The analysis showed a significant effect of calcium on the group and time interaction for SBP ($p<0.000$), DBP ($p<0.005$), creatinine ($p<0.000$), proteinuria ($p<0.000$), PTH ($p<0.005$) and calcium ($p<0.000$), with intragroup and intergroup differences in relation to placebo (Table 2).

When analyzing the effect of calcium on the blood pressure levels of individuals within each group, a reduction of 12.3 mmHg in SBP and 9.2 mmHg in DBP for the 500mg calcium/day group was observed, while for the 1,500mg calcium/day group, the reduction was of 9.4 mmHg in SBP. The effect of calcium on markers of PE over time showed a reduction of 3.2 mg/dl in creatinine and 7.2 mg/dl in proteinuria for the 500 mg calcium/day group and a reduction of 8.6 mg/dl in creatinine and 4.5mg/dl in proteinuria for the 1,500mg calcium/day group compared to the placebo group. At the end of eight weeks, there was a reduction of 4.7 pg/ml in PTH in the 500 mg calcium/day group and a reduction of 3.1 pg/ml in the 1,500 mg calcium/day group (Figure 2). Regarding calcium, there was an increase in both groups after eight weeks compared to the placebo group.

The secondary outcomes at the end of eight weeks, such as birth weight (g), gestational age (weeks), premature labor and admission to the neonatal ICU showed no differences between the groups, nor worsening of birth conditions regardless of the supplemented dosage. Throughout the protocol, no pregnant woman experienced serious adverse reactions such as hypertensive peak, severe PE, HELLP syndrome (hemolysis, elevation of liver enzymes and thrombocytopenia), kidney failure, eclampsia or fetal death. In the group supplement-
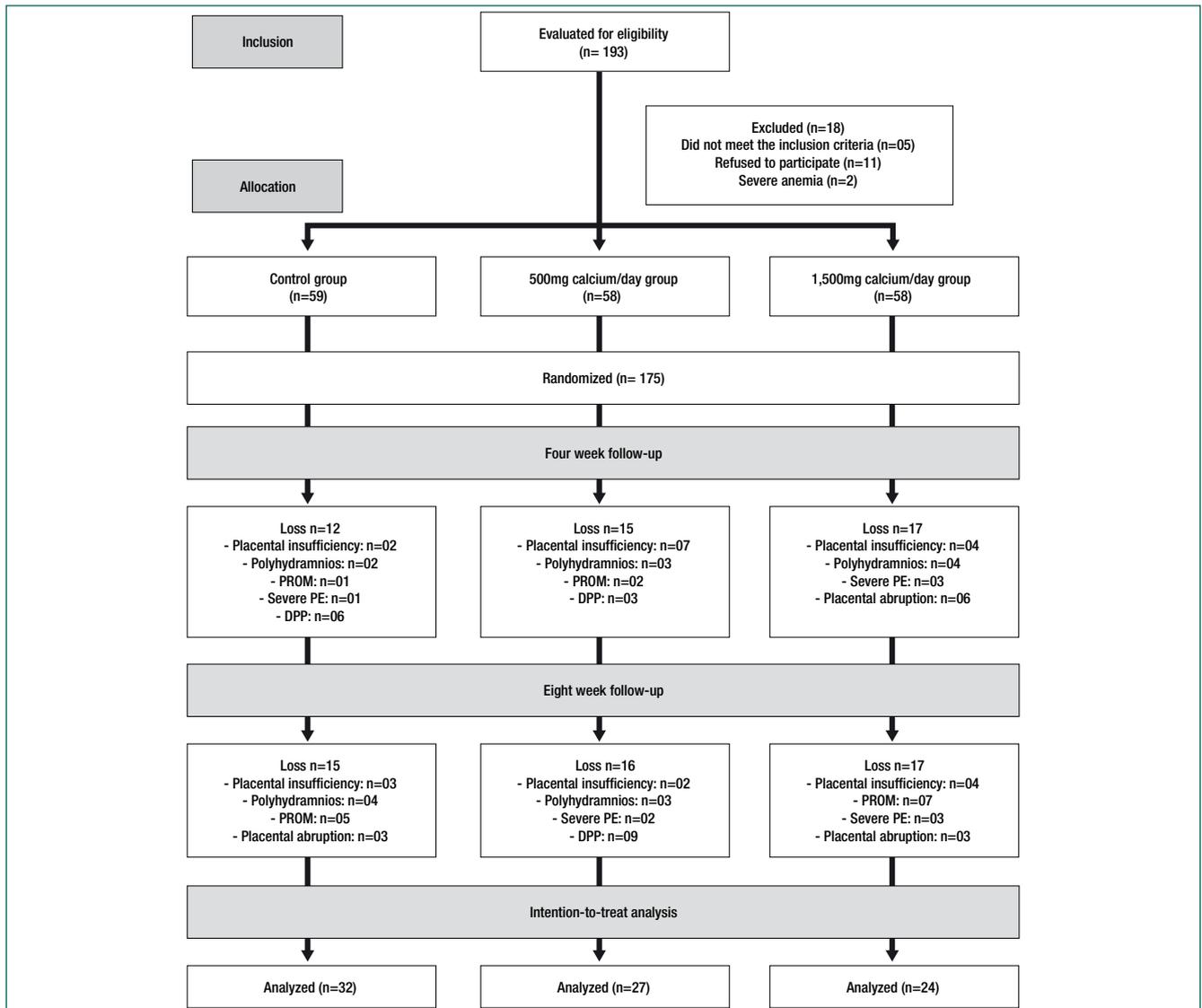
Figure 1. Flow diagram of the study design and allocation of CONSORT participants

ed with 1,500mg calcium/day, three participants complained of heartburn after eight weeks.

Discussion

Given the results presented in this study, a positive effect of calcium was observed in pregnant women with hypertension, showing a significant reduction in markers of PE, even with a short period of use and low dosage.

However, it was not possible to assess the prevalence of under- and over-reporting of food consumption throughout the study, as food intake was compared only to examine the likely differences between the groups at the beginning of the study, which could be a limitation. Furthermore, the findings of this study cannot be generalized to the population of pregnant women with hypertension in high-income countries given the contrast in eating habits in the population of developed countries.

The strong points of the study are the comparison of longitudinal data, attributing to the specific group of pregnant women with gestational hypertension and risk for PE favorable evidence to suggest that calcium positively influences the endothelial and inflammatory processes of this population.

Table 1. Sociodemographic, clinical and laboratory characteristics between groups before the start of the trial (baseline)

Variables	500mg calcium/day group (n=58)	1,500mg calcium/day group (n=58)	Placebo group (n=59)	p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	30.2 (5.1)	30.4 (5.1)	28.6 (4.7)	0.327
Education (years of study)	12.4 (5.5)	12.4 (4.6)	13.9 (5.3)	0.427
Gestational age (weeks)	26.9 (4.0)	26.3 (4.7)	28.2 (5.0)	0.299
Initial weight (Kg)	94.2 (17.3)	86.5 (16.3)	87.7 (17.9)	0.227
Initial BMI (Kg/m²)	35.7 (5.9)	32.6 (7.1)	32.7 (6.2)	0.161
Dietary calcium (g)	531.5 (315.7)	731.5 (477.0)	569.7 (310.1)	0.135
Initial SBP (mmHg)	131.6 (13.8)	131.5 (11.2)	127.8 (12.6)	0.416
Initial DBP (mmHg)	84.2 (9.3)	83.8 (13.2)	81.3 (8.9)	0.531
Platelets, mg/dl	236.380 (50.3)	238.436 (57.6)	262.144 (60.9)	0.105
Urea, mg/dl	16.2 (4.8)	19.2 (6.2)	17.1 (4.3)	0.098
Creatinine, mg/dl	76.4 (36.9)	82.9 (38.8)	79.8 (23.2)	0.932
Proteinuria, mg/dl	26.4 (32.5)	24.9 (37.1)	26.4 (32.2)	0.076
P/C ratio	0.2 (0.2)	0.2 (0.1)	0.1 (0.5)	0.302
Microalbuminuria	7.7 (6.3)	8.7 (2.7)	6.2 (3.0)	0.212
PTH, pg/ml	20.2 (19.0)	23.4 (12.2)	22.9 (10.2)	0.987
Ionized calcium, mg/dl	9.1 (0.2)	9.1 (0.2)	9.4 (0.2)	0.832
After eight weeks	**n (%)**	**n (%)**	**n (%)**	
Low adherence to treatment	4 (2.2)	14 (8)[#]	3 (1.7)	0.026[#]
Loss of follow-up	31 (17.7)	34 (19.4)	27 (15.4)	0.890

ANOVA – independent samples / [#] Qui- square. SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; P/C ratio – protein/creatinine; PTH – parathyroid hormone

Table 2. Generalized Mixed Model Analysis on markers of PE between groups (500mg calcium, 1,500mg calcium and placebo), time (baseline, week four, week eight) and group/time interaction

| Factors	Intercept		Groups		Time		Group/Time	
Parameters	F[§]	p**	F[§]	p**	F[§]	p**	F[§]	p**
SBP, mmHg	7.68	0.000	1.04	0.355	19.25	0.000	7.74	0.000
DBP, mmHg	8.91	0.000	1.84	0.160	25.56	0.000	8.64	0.000
Platelets, mg/dl	1.74	0.088	2.24	0.108	2.00	0.137	1.51	0.199
Urea, mg/dl	4.96	0.000	0.04	0.956	3.39	0.035	8.86	0.000
Creatinine, mg/dl	4.10	0.000	10.8	0.000	4.30	0.014	1.57	0.181
Proteinuria, mg/dl	10.8	0.000	18.7	0.000	18.0	0.000	6.0	0.000
P/C ratio	2.86	0.004	5.95	0.003	3.03	0.049	2.04	0.089
Microalbuminuria	2.80	0.005	8.50	0.000	1.98	0.139	0.87	0.481
PTH, pg/ml	2.08	0.037	2.01	0.135	3.81	0.023	2.09	0.008
Ionized calcium, mg/dl	6.31	0.000	3.01	0.051	19.23	0.000	5.84	0.000

§F = Snedecor's F distribution; **$p < 0.05$

The effect of 500mg calcium/day supplementation was similar to that of high-dose supplementation after eight weeks in some parameters. There was a reduction in blood pressure levels, as well as in creatinine and proteinuria concentrations similar to what was found in previous clinical trials. [19,20] This reinforces the favorable effect of the supplement, even at a low dosage in high-risk pregnant women in low-income countries. [9]

The decrease in blood pressure levels, in turn, can result in a reduced risk of chronic inflammation and important kidney markers for the progression of the risk of PE. [1] The findings reinforce the effects of calcium in reducing blood pressure and in the prevention of PE in high-risk pregnant women.

The exact mechanisms by which calcium may influence vascular processes are unclear. It is assumed that the nutrient acts on the release of PTH, reducing renin secretion by the kidneys and glomerular permeability with a consequent decrease in the release of biomarkers of renal function, such as urea, creatinine and proteinuria. [21] In this study, the reduction of proteinuria and creatinine were significant for both the low-dose supplemented group and the high-dose supplemented group. The protein/creatinine ratio has been increasingly used as an effective measure for predicting PE in high-risk pregnant women. [3,7]

Even though the WHO recommends calcium supplementation starting at 1,500mg/day, the ef-
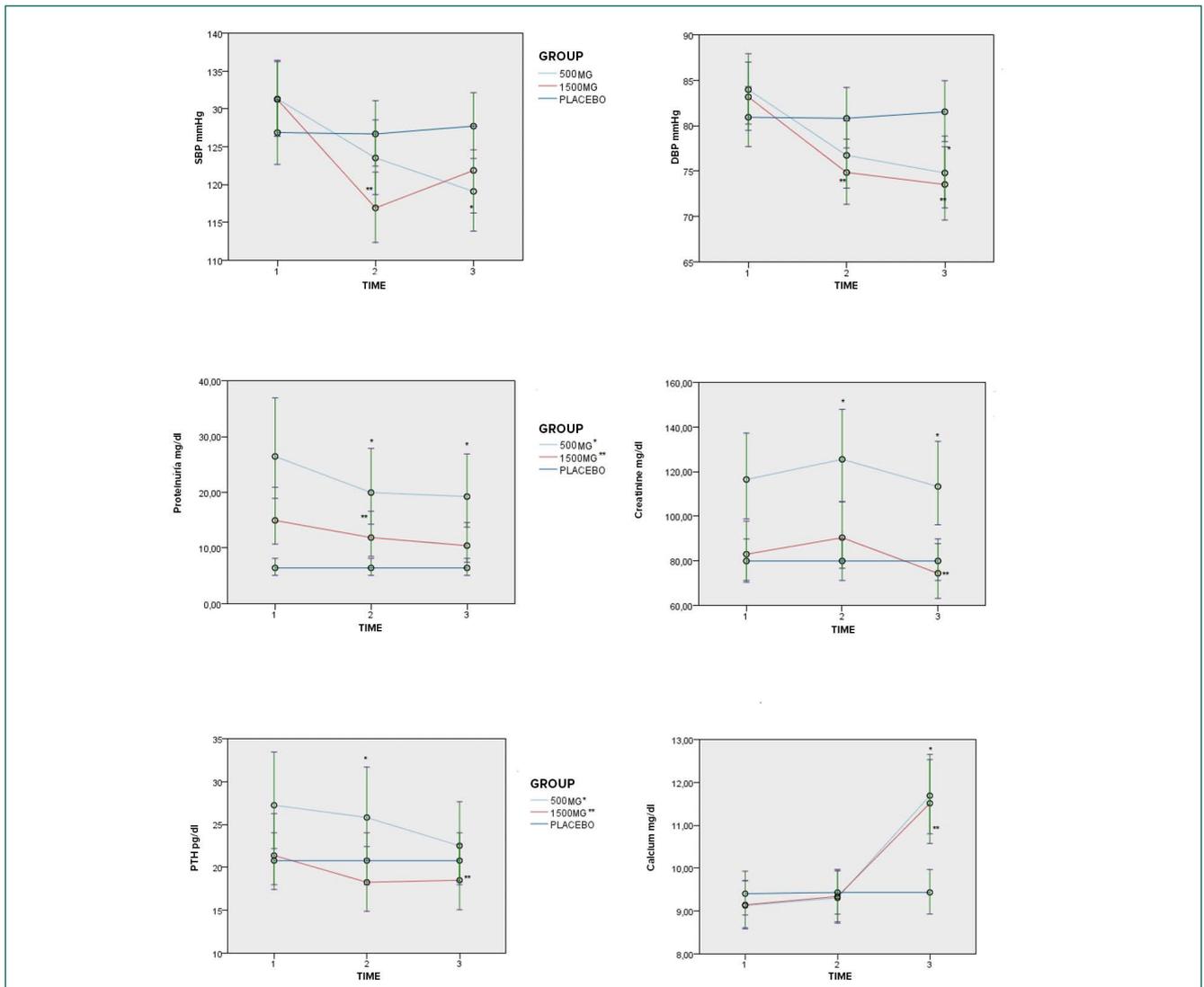
The laboratory protocol for carrying out the analyzes is described in the methodology. Data were expressed as mean ± standard deviation (GLMM, followed by Bonferroni post-test, * indicates p.<0.05) intragroup, ** indicates p<0.05 intergroup

Figure 2. Effects of varying the mean values of blood pressure (mmHg), creatinine (mg/dl), proteinuria (mg/dl), parathyroid hormone (pg/ml) and calcium (mg/dl) over time according to the groups

fects of calcium were also satisfactory in the group that received the lowest dosage. A lower dosage can result in fewer side effects, greater adherence to treatment, easier ingestion and less cost to health services, which should be considered especially in developing countries.[22] Low adherence to treatment can lead to losses in blood pressure control and expose pregnant women to the risk of complications.

The WHO recognizes that low adherence to therapy negatively impacts the results of treatments for chronic diseases, consequently increasing healthcare costs and representing an important public health problem.[5] In this study, the low adherence to treatment was evident in the group that received maximum supplementation hence, this could be another argument in favor of low dose supplementation. Considering the likelihood of low adherence among women with high doses of the supplement, at least the minimum effective dose must be considered and guaranteed.

Excessive supplementation may be related to other adverse events such as increased bone density, kidney stones, constipation, gastrointestinal diseases, cardiovascular events, among others.[8]

Furthermore, the cost of calcium is moderately high compared to supplements such as iron and folate, and its unit dosage can have important implications on the final cost, especially in developing countries.[1] Therefore, a lower calcium dose in pregnant women at risk for PE should be considered.

Note that calcium supplementation in any dosage is not part of the protocol in health services in most Brazilian regions and states, neither is it part of the protocol where this study was carried out. Plasma calcium homeostasis plays a vital role in maintaining human life activities, such as the growth of fetal bone mass, maternal bone density, the stimulation of nerve impulses, muscle contraction, blood clotting, vascular activities, among others.[9] In this study, baseline blood calcium levels assessed after eight weeks of supplementation were significant when compared to the placebo group, reinforcing the favorable supplementation of this nutrient.

Even knowing that calcium absorption depends on several factors, such as vitamin D levels, type of diet, amount of protein ingested, among others, it was possible to observe an increase in the blood value of the nutrient, which may have contributed to better maternal outcomes in the pregnant women studied.[23]

After eight weeks of supplementation, there was no association between the dosages received and low birth weight, prematurity, type of delivery or admission to the neonatal ICU. The premature births in this study were spontaneous and, regardless of the dosage received, the disease in question did not worsen exposure to risk nor did it worsen neonatal outcomes.

Note that in addition to being hypertensive, pregnant women participating in this study were obese. Although weight loss is discouraged during pregnancy,[24] obesity predisposes to a pro-inflammatory state and is a potentially modifiable risk factor for the occurrence of PE. On the other hand, calcium appears to reduce and/or minimize the prevalence of complications arising from PE involved in hypertensive disorders of pregnancy.

Calcium in the diet is more beneficial for health than supplements, in addition to being easier to absorb. However, the favorable role of calcium in pregnant women at potential risk for hypertensive disorders in low- and middle-income countries, where the consumption of the nutrient in the diet is below the recommended needs, is evident.

Calcium supplementation should be prescribed and taken with caution, considering the risks and benefits for each patient. It is important to balance the advantages and disadvantages of supplementation in pregnant women with hypertension, since the literature presents several questions about the safety between the beneficial and side effects of calcium.

Even though obstetric care presupposes interdisciplinary and team action for comprehensive actions, nurses can play a fundamental role in reducing or avoiding complications arising from hypertensive disorders by knowing the benefits of calcium, encouraging its intake in the diet of hypertensive pregnant women and recommending its prescription by professionals.

In this way, qualified nurses who are committed to the work process, based on actions of health promotion and the control of frequent pathologies during provision of antenatal care to women will achieve greater effectiveness in their practice.

The findings of this study should be limited to individualized approaches for pregnant women at potential risk. Solid recommendations can be made in different contexts, respecting health conditions and supplement contraindications, as excess can cause other harm. Further studies need to be conducted to determine the cost and benefits of strategies to improve calcium intake in this population.

Conclusion

Daily calcium supplementation after eight weeks reduced blood pressure, proteinuria, creatinine and PTH levels in pregnant women with hypertension, contributing to reduce the risk of PE caused by the systemic reaction of gestational hypertension. The low prevalence of serious complications was expected as two groups were supplemented with calcium, which is known to reduce

serious complications in hypertensive disorders. Given the similarity of groups before clinical judgment, the favorable outcomes found may be the result of supplemented calcium. The effect of low-dose calcium supplementation (500mg/day) was similar to that of high-dose supplementation after eight weeks, suggesting the positive effect of calcium even after a short period of use. Although the minimum effective dose has not been determined yet, based on the results found, it represents the lowest risk for a universal excess calcium supplementation without neonatal harm.

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Collaborations

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