Acta Scientific Women's Health (ASWH)
ISSN: 2582-3205
DOI: 10.31080/ASWH.2021.03

Research Article

Special Issue 3- 2021

Short-term Effects of Calcium and Vitamin D Supplementation in Postmenopausal Hypertensive Patients in sub-Saharan Africa: A Double Blinded Randomized Controlled Trial

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Received: March 01, 2021
Published: March 08, 2021

Abstract

Background and Aims: Postmenopausal period is linked to an increase in cardiovascular diseases such as hypertension. This study aimed to determine the short-term effect of Calcium and vitamin D supplementation on blood pressure control and inflammation markers in a group of postmenopausal hypertensive patients.

Methods and Results: We conducted a double-blinded randomized controlled trial including postmenopausal hypertensive patients recruited in two hospitals in Yaoundé, Cameroon. These patients were randomly assigned to two arms: one arm receiving 1 000 mg of Calcium daily, the other arm receiving 1 000 mg /800UI of calcium/vitamin D daily. The primary outcome was the diurnal systolic blood pressure, and the secondary outcomes were plasmatic uric acid level and hsCRP level.

A total of 21 patients were included in each group, with similar baseline characteristics except a higher vitamin D baseline level in the Calcium group. After 60 days, we observed a significant decrease in diurnal systolic blood pressure (p = 0.006), plasmatic uric acid level (p = 0.002), and hsCRP (p = 0.001) in the Calcium group. Similar reductions were found in the Calcium+Vitamin D group for diurnal systolic blood pressure (P = 0.006), plasmatic uric acid level (p = 0.001), and hsCRP (p = 0.001). However, Calcium + vitamin D had a higher decrease in uric acid level.

Conclusion: Supplementation of calcium and calcium+vitamin D in postmenauposal hypertensive women is associated with a significant reduction of diurnal blood pressure and inflammatory biomarkers.

Keywords: Hypertension; Menopause; Calcium; Vitamin D; Diurnal Blood Pressure Control; Uric Acid Level

Abbreviations

ABPM: Ambulatory Blood Pressure Measurement; BMI: Body Mass Index; CVD: Cardiovascular Disease; DBP: Diastolic Blood Pressure; ELISA: Enzyme-linked immunosorbent Assay; hsCRP: Highly Sensitive C Reactive Protein; SBP: Systolic Blood Pressure; SPSS: Statistical Package of Social Sciences.

Introduction

Hypertension is the leading modifiable cardiovascular risk factor and premature death cause worldwide. Its prevalence was estimated at 20.5% in 2015, representing an increase of 3.2% from 1990. This hypertension burden is rising more in low- and middle-income countries (LMIC) [1]. In the Sub-Saharan Africa region of the world health organization (WHO), 46 % of the entire population over 25 years of age is affected by hypertension. It represents the highest prevalence across all WHO regions [2]. In 2015, a community-based cross-sectional survey reported a prevalence of 29.7% [3].

Menopause, defined as the permanent cessation of menses for 12 months resulting from estrogen deficiency, is a period where the risk of cardiovascular diseases (CVD) greatly increases. The prevalence of hypertension in postmenopausal women is twice the prevalence in premenopausal women [4,5]. This overall increase of CVD is related to estrogen deficiency through various mechanisms. Estrogen can modulate vascular function by targeting estrogen receptors in endothelial and vascular smooth muscle cells, by triggering the release of nitric oxide and prostacyclin which are both vasodilators. Estrogen also reduce inflammation and can reduce the secretion pro-atherogenic cytokines like tumor necrosis factor alpha [5]. Furthermore, cardiovascular consequences are also linked to low level of vitamin D during menopause. Many factors contribute to a lack of vitamin D in this period, including a thinner skin and lower capacity to produce vitamin D, decrease of intestinal absorption and decrease of vitamin D hydroxylation in the liver and the kidneys, and tendency towards a reduction of outdoor activities [6]. As shown by previous studies, vitamin D deficiency is associated with obesity, and therefore to insulin resistance and diabetes [7]. Although many observational studies has reported an association between vitamin D deficiency and CVD, the effect of vitamin D supplementation on cardiovascular risk factors is less clear. In a cohort of women aged 45 years and above, the incidence of hypertension was lower in subjects with high dietary Calcium and vitamin D intake, but did not change with calcium and vitamin D supplements [8]. However, few randomized controlled trials have shown a beneficial effects of vitamin D supplementation on cardiovascular events and risk factors. More data are needed to better understand the role of vitamin D in cardiovascular risk management, especially in subjects at higher risk like postmenopausal women.

Therefore, we conducted a trial to determine the short term effect of Calcium and vitamin D supplementation on blood pressure control and inflammation markers in Cameroonians postmenopausal hypertensive women.

Methods

Study design and population

We conducted a double-arm, double-blind, randomized and parallel clinical trial in two references hospitals in Cameroon, namely the University Teaching Hospital of Yaoundé and Pediatric and Gyneco-Obstetric Hospital of Yaoundé. From November 2018 to June 2019, we consecutively included all consented postmenopausal women who have been diagnosed hypertensive according to American College of Cardiology's guidelines [9]. Patients included were on stable antihypertensive therapy for at least 03 months with no class changes. Exclusion criteria were the following: (i) subjects receiving regular supplementation of Calcium or vitamin D; (ii) reported allergy to any of these substances; (iii) known or newly diagnosed diabetes mellitus; (iv) inflammatory diseases and (v) Hypercalcemia.

Randomization, sequence generation, blinding

All consented patients were randomly assigned to one of the two groups in a 1:1 ratio using random allocation software 1.0 with a block size of 2 patients. The first group received a daily oral dose of Calcium 1 000 mg, and the second group received a daily oral dose of Calcium 1 000 mg + Vitamin D 800 UI. The treatment was administered for 60 days. Blinding was maintained by an investigator with no clinical involvement in the trial, who generated the randomization sequence, packed Calcium 1 000 mg and Calcium 1 000 mg + Vitamin D 800 UI in boxes with identical appearance. These boxes were labeled for each patient with his name and randomization number.

Data collection and laboratory procedures

Sociodemographic data, medical history, and anthropometric parameters (body mass index, abdominal and hip circumference) were collected at baseline. Then, a 24-hour ambulatory blood pressure measurement (ABPM) was performed with an electronic sphygmomanometer (Omron HEALTHCARE®). Biological data collected were corrected calcium level using the colorimetric Arsenazo III principle, Vitamin D level assessed by ELISA procedure (ElabScience, USA), and phosphorus level with the colorimetric phosphomolybdate principle. Serum creatinine was also measured by the Jaffe principle, and uric acid level was obtained by a colorimetric uricase principle. The immunoturbidimetric method was used to quantify high-sensitivity C-reactive protein (hsCRP). The follow-up visit was conducted 60 days (D60) after inclusion. At this visit, the same clinical, ABPM, and biological data were collected.

Endpoints

The primary endpoints described in a per-protocol principle were diurnal systolic blood pressure at D60, assessed by the same blinded investigator. Secondary outcomes were uric acid and hsCRP levels at D60.

Statistical analysis

The sample size was estimated at 10 participants per group, using the Whitley and al. formula, with a power of 80%, a type one error of 5%, an expected systolic blood pressure difference of 13.1 mmHg and a standard deviation of 10 mmHg [10].

Categorical data were described with numbers and percentages and compared by a bivariate statistical analysis with Fisher's exact test. Quantitative variables were presented as median with interquartile range (IQR), and the Mann-Whitney U test was used to compare these continuous data between groups. Furthermore, a comparison of baseline and D60 in the different groups was performed using the Wilcoxon signed-rank test. P values less than 0.05 were considered statistically significant for all the analyses performed using Statistical Package for Social Sciences (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

Ethics approval and consent

Ethical clearance was obtained from the Institutional Review Board of High Institute of Health Sciences and West region-Cameroon's regional ethical committee. Administrative authorization was also obtained from the directors of the study hospitals. Before performing any study-related procedure, written informed consent was obtained from all study participants. This clinical trial was registered at the National Library of Medicine website (ClinicalTrials.gov Identifier: NCT04255992).

Results

A total number of 101 hypertensive postmenopausal women were assessed for inclusion. After primary evaluation, 34 were included and randomly assigned to the groups (Figure 1). The median duration of menopause was nine years [2; 20], and the median duration of hypertension was six years [2; 14]. Baseline characteristics of the population are described in table 1. Sociodemographic and clinical parameters were similar in both groups before intervention. Among biological parameters, Vitamin D level was higher in the participants who received Calcium than those who received Calcium + Vitamin D (Table 1).

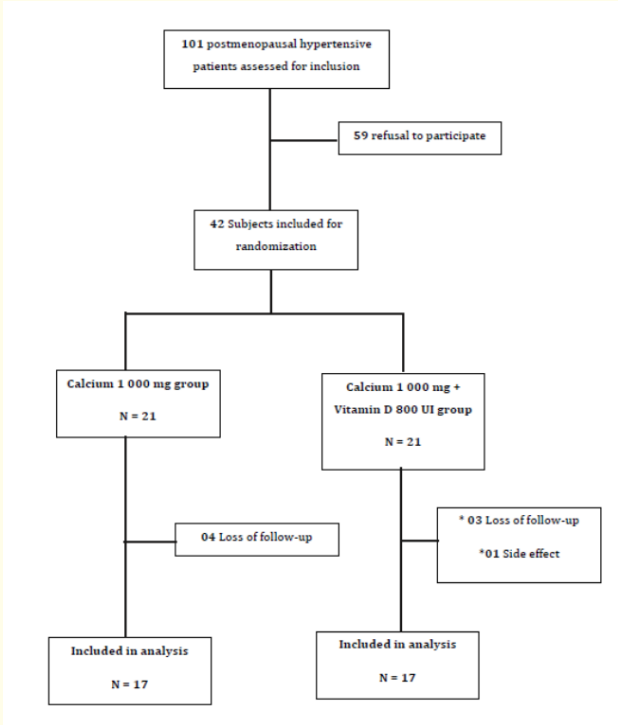

Figure 1: Study's participants flow chart.

Variables*	Calcium group (n = 21)	Calcium +Vitamine D group (n = 21)	p value
Age (years), Median	59 [52 - 66]	61.5 [57.75 - 68.75]	0.421
Office SBP (mmHg)	155.5 [127 - 158.75]	148 [126 - 152.75]	0.423
Office DBP (mmHg)	87 [78 - 97]	82.5 [73 - 89.5]	0.334
24h ABPM SBP	134 [117.60 - 144.40]	126.6 [109.87 - 135]	0.190
24h ABPM DBP	77.70 [65.60 - 86.60]	73.80 [65.2 - 79.50]	0.330
Diurnal SBP (mmHg)	132 [121 - 142]	130 [120 - 141]	0.850
Diurnal DBP (mmHg)	73.20 [62.20 - 82.70]	71.80 [62.27 - 78.90]	0.790
Nocturnal SBP (mmHg)	131.80 [120.60 - 143.10]	125.80 [113.22 - 135.40]	0.300
Nocturnal DBP (mmHg)	73.20 [62.20 - 82.70]	71.80 [62.27 -7.90]	0.790
BMI (Kg/m^2)	30.86 [26.38 - 33.32]	31.14 [27.34 - 33.76]	0.735
Abdominal circumference(cm)	102 [91.25 - 105.75]	98 [87 - 103]	0.336
Hip crcumference (cm)	107.5 [101.5 - 114.75]	106 [92 - 112.50]	0.518
Calcemia (mg/L)	85.25 [73.36 - 95.09]	94.39 [84.75 - 99.09]	0.090
Phosphoremia (mg/L)	30[23 - 33]	29[27 - 33]	0.570
Vitamin D level (ng/L)	26.35 [12 - 31]	12.75 [6.25 - 21]	0.040
HsCRP (mg/L)	3.54 [2 - 12]	2.57 [1.60 - 7.13]	0.470
Uric acid level (mg/L)	57[53 - 65]	62.96 [56 - 74.50]	0.102

Table 1: Baseline characteristics of study population.
*All quantitative variables are described as median [interquartile range];
SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ABPM: Ambulatory Blood Pressure Measurement; BMI: Body Mass Index; HsCRP: High-sensitivity C-Réactive Protein.

In the group receiving Calcium, we observed at D60 a diurnal systolic blood median decrease of 4.7[-2.5; 10] mmHg (p = 0.006), a plasmatic uric acid level median decrease of 11[8; 18] (p = 0.002) and a hsCRP median decrease of 1.68 [0.43; 5.58] mg/L (p = 0.001) (Table IV). For The Calcium + vitamin D group, the median decrease of diurnal systolic blood pressure was 4.7 [0.6; 8.1] mmHg (P = 0.006), median plasmatic uric acid level decrease was 16[9.63; 24] mg/L (p = 0.001) and hsCRP median decrease was 1.46[0.36; 2.63] mg/L (p = 0.001) (Table 2).

Variables	Baseline	D60	p value
	Calcium group (n = 21)		
Diurnal SBP (mmHg)	132 [121 - 142]	127.6 [122.5 - 132]	0.006
HsCRP (mg/L)	3.54 [2 - 12]	1.86 [1.57 - 6.42]	0.001
Uric acid level (mg/L)	57 [53 - 65]	46 [45 - 47]	0.002
	Calcium + Vitamin D group (n = 21)		
Diurnal SBP (mmHg)	130 [120 - 141]	125.3 [119.4 - 124.9]	0.006
HsCRP (mg/L)	5.2 [2.3 - 7.13]	3.74 [1.94 - 4.5]	0.001
Uric acid level (mg/L)	62.96 [56 - 74.50]	47 [46.3 - 50.5]	0.001

Table 2: Comparison endpoint parameters between baseline and D60 in the two groups.
*All quantitative variables are described as median [interquartile range]; SBP: Systolic Blood Pressure; HsCRP: High-sensitivity; C: Réactive Protein.

As shown in table 3, the decrease of the uric acid level was more significant in the Calcium+Vitamin D group than the Calcium group (p = 0.020).

Discussion

Our objective was to determine Calcium's short-term effect and calcium/vitamin D supplementation on blood pressure control and inflammatory biomarkers. After 60 days of follow-up, supplementation in both groups was associated with a significant decrease in diurnal blood pressure and reduced inflammation biomarkers. There was a more significant decrease in the uric acid level in the group of participants who received Calcium + vitamin D.

Variables	Calcium (n = 21)	Calcium +VitamineD (n = 21)	p value
Diurnal SBP mmHg	4.7 [-2.5 - 10]	4.7 [0.6 - 8.10]	0.630
Uric acid level mg/l	11[8 - 18]	16 [9.63 - 24]	0.020
HsCRP mg/l	1.68 [0.43 - 5.58]	1.46 [0.36 - 4.63]	0.540

Table 3: Comparison of endpoints decrease between the two groups.

*All quantitative variables are described as median [interquartile range]; SBP: Systolic Blood Pressure; HsCRP: High-sensitivity; C-Réactive Protein.

It is well known that menopause is associated with the burden of cardiovascular disease, including hypertension [5]. In this study, we found a significant reduction in diurnal systolic blood pressure in both groups, like Pfeifer and al. in 2001 [11]. These results emphasized the fact that calcium and vitamin D interacts with the blood pressure regulation system. Physiological studies done in mouse have shown that the extracellular Calcium sensitive receptor was expressed by vessels and smooth muscles. This receptor was directly implicated in blood pressure regulation, and an alteration of this receptor was associated with hypertension [12].

Administration of calcium and calcium+vitamin D was associated with decreased uric acid level with a more significant effect in the calcium/vitamin D group. Although this result was different from that of Dalbeth N and al. in 2009, it suggests a hypouricemic effect of calcium and vitamin D [13]. Further studies are needed to explore this potential effect better. HsCRP level significantly decreased in both groups after 60 days. Menopause is associated with chronic inflammation related to low estrogen levels. This result is consistent with the high cytokines level found by Erin and al. in postmenopausal women [14].

We identified some limits in this study, mainly the short duration of intervention, which prevents us from determining Calcium's longtime effect and calcium/vitamin D supplementation. Nevertheless, this study is scarce in the Sub-Saharan population, and with a randomized controlled trial design, we minimize bias.

Conclusion

Supplementation of calcium and vitamin D in postmenopausal hypertensive women is associated with a significant reduction of diurnal systolic blood pressure and inflammatory biomarkers. These findings may help in designing new guidelines for the better management of such patients.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

- CNNG, VJAM, CAP designed the study
- VJAM, INK, RY, GSW collected data and performed data analysis
- CNNG, VJAM, CAP, GSW, RY, INK, APM drafted and revised the manuscript
- All the study was done under the supervision of APM
- All authors read and approved the final manuscript.

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