

Evaluation of serum calcium differences in hypertensive crises and control patients: A randomly matched case-control study

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Abstract

The role of calcium in blood pressure has been widely studied among hypertensive patients; however, no study has explored the role of calcium in hypertensive crises. The primary objective of this study is to evaluate the differences in serum calcium levels between hypertensive crises patients and a 1:1 random matched controls (age-, sex-, race-, diabetes, and body mass index matched). This study is a single-center, retrospective, chart review, case-control study of patients with hypertensive crises (case group) and patients without hypertensive crises (control group). Patients were included in the case group if they were 18 years of age or older with hypertensive crises and have a documented calcium level. The control group patients were required

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to be 18 years of age or older, have a documented calcium level, and have no diagnosis of hypertensive crises. The primary outcome of the study was to compare the mean serum calcium in patients with hypertensive crises vs patients without hypertensive crises. Five hundred and sixty-six patients were included in the study: 283 patients in both the case group and control group. The primary outcome results showed that serum calcium concentration was not significantly different between the case group (8.99 ± 0.78 mg/dL) and control group (8.96 ± 0.75 mg/dL) ($P = .606$). This study found no significant difference in serum calcium levels in patients with hypertensive crises compared to a random matched control group. Larger observational or experimental studies may be useful to evaluate the effect of calcium on blood pressure in hypertensive crises.

1 | INTRODUCTION

Hypertension is characterized by elevation in the systolic blood pressure (SBP) and/or diastolic blood pressure (DBP).^{1,2} Hypertension definition varies based on clinical practice guidelines cutoff as either SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg³ or SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.^{4,5} The overall global prevalence of hypertension in adults is between 30%-45%, and the prevalence of hypertension among adults in the United States is between 32%-46% depending on the clinical practice guideline cut-points to categorize blood pressure.³⁻⁵ Hypertension is a leading risk factor for cardiovascular diseases (hemorrhagic stroke, ischemic stroke, myocardial infarction, angina, heart failure, peripheral artery disease, and aortic aneurysm), end-stage renal disease (ESRD), death, and disability.¹⁻⁶ Hypertensive crises are defined as SBP >180 mmHg and/or DBP >120 mmHg.^{3,4} Hypertensive crises can be further classified into: hypertensive urgency (absence of target organ damage) and hypertensive emergency (presence of target organ damage).^{3,4} Although hypertensive urgency reflects a marked elevation in blood pressure, it can be managed by optimizing or increasing the dose of oral antihypertensive agents.^{3,4} Hypertensive emergency is however characterized with organ damage and is associated with a one-year mortality rate of 79% or higher, thus necessitating rapid blood pressure reduction with intravenous antihypertensive agents to prevent sustained deterioration of target organ damage.^{3,4}

Calcium is an important cation which plays an important role in a wide spectrum of cellular processes in the body, namely bone metabolism and bone structure, neural transmission, muscular (skeletal, cardiac, and vascular) contraction, endocrine and exocrine secretory functions, blood coagulation, and intercellular adhesion.^{7,8} Total body calcium ranges from 1000 to 1200 g in adult humans with about 99% found in the bone, and the remaining 1% of total body calcium exists in intracellular and extracellular space.⁷ Normal total serum calcium concentration is in the range of 8.9-10.1 mg/dL (2.2-2.5 mmol/L) and is tightly regulated by the dynamic interplay between gastrointestinal absorption, bone resorption/exchange, renal exchange, and the hormones (parathyroid hormone, vitamin

D, and calcitonin).⁷ This range of serum calcium is not an accurate surrogate of total body calcium status. Total serum calcium reflects ionized, free physiologically active form (48%), protein bound (46%), and complexed fractions (7%).⁷ The protein bound fraction of serum calcium is predominantly bound to albumin and globulin; while the complexed fraction of serum calcium is bound to molecules such as phosphate and citrate.⁷ Intracellular calcium in vascular smooth muscle cells may play a role in blood pressure regulation through its effect on vasoconstriction and vascular muscular tone.⁹

The novel and central focus of our study is to study the role of serum calcium in hypertensive crises; however, much foundational data buttressing our study are drawn from studies evaluating the role of calcium in hypertension. Clinical studies have evaluated the serum calcium difference between hypertensive patients and normotensive controls and/or the relationship between serum calcium and blood pressure. We identified seven studies that compared the mean serum calcium levels between hypertensive vs normotensive patients.¹⁰⁻¹⁶ Three of these studies found significant differences in mean serum calcium between hypertensive vs normotensive patients^{10,13,14} while four studies found no significant difference in mean serum calcium between hypertensive vs normotensive patients.^{11,12,15,16} Of the three studies finding significant differences in mean serum calcium between hypertensive vs normotensive/control patients, two studies found significantly higher serum calcium in hypertensives^{10,13} and one study found a significantly lower mean calcium in hypertensive patients.¹⁴ No study has compared the mean serum calcium levels in patients with hypertensive crises vs other population. Sixteen observational clinical studies have evaluated the correlation between serum calcium and blood pressure in patients with and without hypertension,^{10,15-29} and only one of these studies evaluated a malignant hypertension population that is similar to our hypertensive crises population.²⁰ This indicates the paucity of data on the relationship of serum calcium in hypertensive crises population. Collectively, these correlation studies have revealed conflicting evidence on the relationship between serum calcium levels and blood pressure (SBP, DBP, or both); with most studies showing positive association,^{10,15-18,21-29} few studies reporting negative

association^{19,20} (including the study of patients with malignant hypertension²⁰) and others showing no association.^{15,16,18,21,22,26,27,29} Additionally, the effect of calcium supplementation on blood pressure has been well studied. Two of three studies (a Cochrane review and a meta-analysis) showed that calcium supplementation lowered SBP, DBP, or both^{30,31}; one Cochrane review reported an inconclusive finding on the effect of calcium supplementation on blood pressure due to the heterogeneity of the studies included in their systematic review.³² A recent study in non-pregnant women with previous pre-eclampsia showed that calcium supplementation lowered SBP and mean arterial pressure.³³ This prevailing favorable effect of calcium supplementation in lowering blood pressure and the dominant positive relationship between serum calcium and blood pressure served as the foundational rationale for our study evaluating whether serum calcium is a factor that contributes to the dysregulated high blood pressure in patients with hypertensive crises. We hypothesized that serum calcium will be significantly higher in patients with hypertensive crises and that high serum calcium will be positively associated with blood pressure (SBP and DBP) in patients with hypertensive crises.

The primary objective of this study is to evaluate the differences in mean serum calcium levels between patients with hypertensive crises and matched controls (age-, sex-, race-, diabetes, and body mass index [BMI] matched) in a 1:1 random match. Secondary objectives were used to evaluate the association between serum calcium (and other electrolytes) and blood pressure in patients with hypertensive crises and to determine the effects of covariates on the relationship between serum calcium and blood pressures in patients with hypertensive crises. The aim of the study is to determine the relationship between serum calcium and blood pressure in hypertensive crises. Given that hypertensive crises is a state of profound blood pressure dysregulation, it is important to study and understand the role that factors, such as serum calcium, play in the etiology of hypertensive crises. Data from these studies can be hypothesis generating and provide the foundational evidence for studying potential innovative therapies to manage hypertensive crises, such as serum calcium-modifying therapies.

2 | STUDY DESIGN AND METHODS

This study is a single-center, retrospective, chart review, case-control study conducted at University Medical Center New Orleans (UMCNO) in New Orleans, Louisiana. In this case-control study, patients with hypertensive crises were included in the case group, while the control group consisted of patients without hypertensive crises who were admitted to the hospital during the same time period from August 2013 to August 2015. This study was approved by the Xavier University of Louisiana Institutional Review Board (IRB) and UMCNO Research Review Committee (RRC).

Patients who were 18 years of age or older with an international classification disease ninth revision (ICD-9) code of 401.9 (hypertensive crises: emergency or urgency) and a documented

calcium level on their electronic medical record (during the hypertensive crises hospital admission) were included in the case group. Hypertensive crises were defined as SBP >180 mmHg and/or DBP >120 mmHg. Patients identified as having hypertensive crises based on ICD-9 codes were confirmed to have two occurrences of either SBP >180 mmHg and/or DBP >120 mmHg within 48 hours of the hospital encounter. Hypertensive crises were further categorized as either hypertensive urgency (absence of acute or on-going target organ damage) or hypertensive emergency (presence of acute or on-going target organ damage). Target organ damage by system included neurologic (hypertensive encephalopathy, intracranial hemorrhage), cardiac (acute myocardial infarction, acute left ventricular failure, unstable angina, dissecting aortic aneurysm) and renal (acute kidney injury). All diagnoses of target organ damage were confirmed with both the physician diagnosis documented on the patients' problem list and clinical findings (laboratory results, imaging, signs, and symptoms). Hypertensive encephalopathy diagnosis was verified based on physical examination findings of headache and altered level of consciousness. Diagnosis of intracranial hemorrhage was confirmed using a computed tomography scan (or magnetic resonance imaging) of the head with or without contrast, performed on patients with neurologic symptoms, which included change in mental status or focal neurologic signs indicative of cerebrovascular accident or hemorrhage. Unstable angina diagnosis was made clinically and confirmed with documented new or sudden chest pain, while myocardial infarction diagnosis was confirmed with elevated serum troponin levels and electrocardiogram (EKG) findings. Acute left ventricular failure was diagnosed with echocardiographic findings of a decreased ejection fraction <40% as well as physical examination findings of elevated jugular venous pressures (distension), crackles, or edema. Diagnosis of dissecting aortic aneurysm was confirmed from imaging studies revealing wide mediastinum on chest x-ray and/or chest CT scan with or without contrast. Acute kidney injury was defined as a serum creatinine (SCr) >2 mg/dL, which is new onset in the absence of prior renal disease and/or increase in SCr of 0.5 mg/dL or greater. The control group patients were required to be 18 years of age or older with a documented calcium level on their medical record during the hospital admission. Control group patients were excluded if they experienced a blood pressure fitting the criteria of hypertensive crises, as defined above.

Exclusion criteria were based on patient conditions interfering with serum calcium levels including: chronic kidney disease (CKD) stages 3, 4, and 5, ESRD, primary hyperparathyroidism, secondary hyperparathyroidism, hypoparathyroidism, and hypercalcemia of malignancy. Patients who received calcium supplementation (IV or oral) and/or vitamin D (IV or oral) products (ergocalciferol, cholecalciferol, calcitriol, etc) at home or in the hospital prior to serum calcium level collection were excluded. Additionally, patients who received inotropes or vasopressors (including epinephrine, norepinephrine, dopamine, phenylephrine, vasopressin, dobutamine, or milrinone) prior to blood pressure collection were excluded from the study. Patients who had an unidentifiable glomerular filtration rate (GFR) value were excluded in the final analyses.

All patient data were obtained from UMCNO's electronic medical record. The following demographic data were collected: age, sex, race, BMI, and history of diabetes mellitus. Outcome variables collected included serum calcium (mg/dL), serum phosphorus (mg/dL), serum magnesium (mg/dL), SBP (mmHg), and DBP (mmHg). Corrected calcium (mg/dL) was calculated using the formula: corrected calcium = patient's measured serum calcium in mg/dL + $(0.8 * [4 \text{ g/dL} - \text{patient's measured albumin in g/dL}])$. The adjusted corrected serum used the actual patient's measured serum calcium when albumin was 4 g/dL or greater, while the unadjusted corrected calcium applied the corrected calcium formula regardless of the patient's measured albumin level. All outcome variables for the case group were collected at a time closest to the first documented hypertensive crises' blood pressure during the hospital encounter and is denoted as "at crises." Outcome variables for the control group were collected at a time closest to the first documented blood pressure during the hospital encounter. Additionally, predictor variables were collected and include: at home and hospital use of loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid), at home and hospital use of thiazide and thiazide-like diuretics (hydrochlorothiazide, chlorthalidone, chlorothiazide, metolazone, indapamide), at home and hospital use of bisphosphonates (alendronate, zoledronic acid/zoledronate, pamidronate, etc) inhibitors, albumin levels (gm/dL), Modification of Diet in Renal Disease (MDRD) GFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$), and CKD stages 1, and 2 diagnosis.

2.1 | Outcomes

The primary outcome of the study was to compare the mean serum calcium in patients with hypertensive crises vs patients without hypertensive crises. Secondary outcomes of the study were to assess the correlation between serum calcium (and other electrolytes) on blood pressures (SBP and DBP) in patients with hypertensive crises and to determine the effects of covariates (age, race, sex, BMI, history of diabetes mellitus, use of bisphosphonates, use of loop diuretics at home, use of loop diuretics at hospital, use of thiazide diuretics at home, use of thiazide diuretics at hospital, CKD staging, albumin, and GFR) on the relationship between serum calcium and blood pressure.

2.2 | Statistical analyses

The control group was randomly matched to the cases in a 1:1 ratio based on the covariates of age, sex, race, history of diabetes mellitus, and BMI. The matching for race was performed using two categories of African Americans and non-African Americans (Whites, Asians, Native Hawaiian/Pacific Islanders, American Indian/Alaskan Native, and racial category of "other") because the sample size for the non-African American races, except Whites, was small. The matching for BMI was performed using BMI categories of: underweight ($\text{BMI} < 18.5 \text{ kg}/\text{m}^2$), normal ($18.5\text{-}24.9 \text{ kg}/\text{m}^2$),

overweight ($25.0\text{-}29.9 \text{ kg}/\text{m}^2$), obesity I ($30.0\text{-}34.9 \text{ kg}/\text{m}^2$), obesity II ($35.0\text{-}39.9 \text{ kg}/\text{m}^2$), and obesity III ($\geq 40.0 \text{ kg}/\text{m}^2$).

Descriptive statistical analysis was performed on demographic characteristics. A chi-square test or Fisher's exact test was used to compare between group differences for categorical variables in the baseline characteristics. Student's t test was used to compare the continuous variables between groups (mean serum calcium levels, mean corrected calcium levels, mean albumin levels, MDRD GFR, and BMI) between the case and control group. Simple linear regression was performed to assess the correlation (r) and coefficient of determination (R^2) between serum calcium, corrected calcium, serum phosphorus, and serum magnesium on blood pressures (SBP and DBP) in patients with hypertensive crises. Multivariable linear regression was performed to assess the effects of calcium on blood pressures (SBP and DBP) at the time of hypertensive crises while adjusting for covariates. Logistic regression analysis was performed to assess the odds of having either abnormally high ($>10.3 \text{ mg}/\text{dL}$) or low ($<8.4 \text{ mg}/\text{dL}$) serum calcium in cases compared to matched controls. Statistical analyses were performed using SAS[®] version 9.4. An alpha value of <0.05 was considered statistically significant.

3 | RESULTS

There were 566 patients who were included in the study: 283 patients in both the case group and the randomly matched control group (see Figure 1). Baseline demographics were similar between groups for the matched variables of age, sex, race (using two categories of African Americans and non-African Americans), history of diabetes mellitus, and BMI using 6 BMI categories (see Table 1). There were 80 non-African Americans in the case group and control group, respectively. Majority (~75%) of the non-African Americans were White in each group. Altogether Asians, Native Hawaiian/Pacific Islanders, American Indian/Alaskan Native, and racial category of "other" made up the remainder of the racial category. There were significant differences between the case and control group in the use of hospital loop diuretics, use of hospital thiazide diuretics, and MDRD GFR. The use of hospital loop diuretic, home thiazide diuretics, and hospital thiazide diuretics were all significantly higher in cases compared to controls. GFR was significantly lower in the case group compared to the control group. Consistent with the case-control study design, the SBP at crises and DBP at crises in the case group differed significantly from SBP and DBP in the control group (Table 1). The blood pressure average and ranges are reported in Table 1 and reflects that patients may have met the hypertensive crises definition through either SBP $>180 \text{ mmHg}$, DBP $>120 \text{ mmHg}$, or both SBP $>180 \text{ mmHg}$ and DBP $>120 \text{ mmHg}$. The lower values in the range account for the likelihood of patients meeting the hypertensive crises definition through one of the criteria: either SBP or DBP alone.

The primary outcome result is displayed on Table 2 and showed that serum calcium concentration was not significantly different between the case group and control group. The same finding of no

FIGURE 1 Flow chart of patient selection into the case group and random matched control group

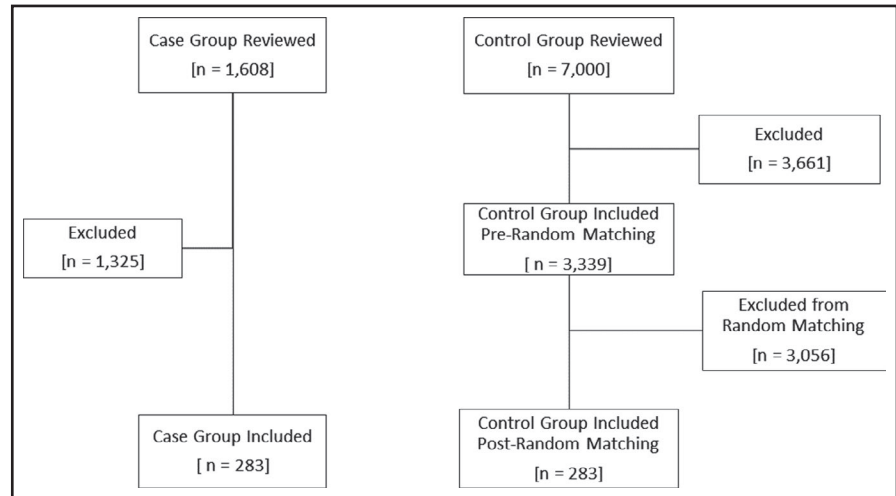


TABLE 1 Baseline demographics

Baseline demographics			
	Cases (N = 283)	Controls (N = 283)	P-value
Age (Mean ± SD years; [range])	57.85 ± 12.29 (26-96)	56.01 ± 14.59 (18-98)	.105
Gender	Male 178 (62.9%)	Male 174 (61.48%)	.729
	Female 105 (37.1%)	Female 109 (38.52%)	
Race	African American 203 (71.73%)	African American 203 (71.73%)	1.000
	Non-African American 80 (28.27%)	Non-African American 80 (28.27%)	
History of diabetes mellitus	Diabetic: 76 (26.86%)	Diabetic: 78 (27.6%)	.850
	Non-diabetic: 207 (73.14%)	Non-diabetic: 205 (72.4%)	
BMI category	Underweight 8 (2.83%)	Underweight 10 (3.53%)	.992
	Normal 80 (28.27%)	Normal 83 (29.33%)	
	Overweight 78 (27.56%)	Overweight 79 (27.92%)	
	Obesity I 52 (18.37%)	Obesity I 51 (18.02%)	
	Obesity II 34 (12.01%)	Obesity II 32 (11.31%)	
	Obesity III 31 (10.95%)	Obesity III 28 (9.89%)	
Mean BMI (kg/m ²)	29.93 ± 8.74	29.43 ± 7.98	.479
Diagnosis	Urgency 229 (80.92%)	N/A	N/A
	Emergency 54 (19.08%)		
Systolic blood pressure (Mean ± SD mmHg; [range])	194.3 ± 23.61 (132-300)	128.4 ± 21.87 (63-180)	<.0001
Diastolic blood pressure (Mean ± SD mmHg; [range])	114 ± 20.02 (63-182)	79.95 ± 14.59 (38-118)	<.0001
Use of home loop diuretic	27 (9.54%)	37 (13.07%)	.184
Use of hospital loop diuretic	109 (38.52%)	52 (18.37%)	<.0001
Use of home thiazide diuretic	39 (13.78%)	25 (8.83%)	.063
Use of hospital thiazide diuretic	98 (34.63)	21 (7.42)	<.0001
Use of bisphosphonates	5 (1.77%)	2 (0.71%)	.450
CKD staging	Stage 1:1 (0.35%)	Stage 1:3 (1.06%)	.056
	Stage 2:9 (3.19%)	Stage 2:2 (0.71%)	
	No CKD: 272 (96.45%)	No CKD: 278 (98.23%)	
Albumin (Mean ± SD g/dL)	3.52 ± 0.72 (N = 276)	3.53 ± 0.65 (N = 257)	.814
MDRD GFR (Mean ± SD mL/min/1.73 m ²)	64.54 ± 27.10	73.88 ± 23.36	<.001

significant difference between the case and control group was seen with corrected calcium (both adjusted and unadjusted). Tables 3 displays the relationship between calcium and SBP or DBP in a simple linear regression analysis performed only on the case group. The results show that there is no significant association between calcium and either SBP at crises or DBP at crises. Additionally, the simple linear regression results of the relationship between several electrolytes (corrected calcium [adjusted and unadjusted], phosphorus, and magnesium) and SBP at crises or DBP at crises are reported on Table 3. None of the electrolytes assessed significantly correlated with either SBP at crises or DBP at crises.

In the results from multivariable regression analysis performed only on the case group (Table 4), after adjusting for covariates (age, sex, race, history of diabetes mellitus, BMI, use of diuretics (loop and thiazides) at home and hospital, use of proton pump inhibitors at home and hospital, CKD staging, Albumin, GFR), calcium was not significantly correlated with either SBP at crises or DBP at crises in patients with hypertensive crises. The results of the logistic regression analysis are reported on Table 5. The odds of having either abnormally high serum calcium or abnormally low serum calcium was not significantly different in the case group vs the control group.

4 | DISCUSSION

This study contributes to the sparsely available knowledge on the role of calcium in patients with hypertensive crises. Our study found no significant serum calcium difference between the case group and the matched control group. This finding is consistent with the majority of studies that compared mean serum calcium in hypertensive patients compared to normotensive individuals; similar to our finding, four of these studies revealed no significant difference in serum calcium levels among hypertensive patients and controls.^{11,12,15,16} However, our study result is divergent from a few studies which showed statistically significant higher^{10,13} or lower¹⁴ serum calcium level in hypertensive patients compared to normotensive individuals. It is plausible to consider that our exploratory study was not adequately powered to detect significant differences in serum calcium between patients with hypertensive crises and matched controls without hypertensive crises.

The major secondary outcome of our study evaluated the relationship between serum calcium and blood pressures (SBP and DBP) in patients with hypertensive crises. Our study did not find a significant correlation between calcium and either SBP or DBP in both a simple linear regression analysis (Table 3) and multivariable linear regression analysis (Table 4). This finding conflicts with majority of correlation studies of serum calcium and blood pressure which has predominantly shown significant positive correlation.^{10,15-18,21-29} However, our finding of no significant association between calcium and either SBP or DBP has been found in part in some studies.^{15,16,18,21,22,26,27,29} Among the additional electrolytes (corrected calcium [adjusted and unadjusted], phosphorus, and magnesium) that were assessed for a relationship with blood pressures

TABLE 2 Differences in serum calcium, and corrected calcium between hypertensive crises patients and controls

Differences in serum calcium between hypertensive crises patients and controls			
	Cases (N = 283)	Controls (N = 283)	P-value
Mean serum calcium levels (mg/dL)	8.99 ± 0.78	8.96 ± 0.75	.606
Mean corrected calcium (adjusted)	9.45 ± 0.68 (N = 276)	9.47 ± 0.65 (N = 257)	.811
Mean corrected calcium (unadjusted)	9.38 ± 0.68 (N = 276)	9.41 ± 0.65 (N = 257)	.662

TABLE 3 Relationship between calcium (other electrolytes) and SBP at crises or DBP at crises—cases

Relationship between calcium and SBP at crises or DBP at crises (N = 283)			
Variables	r	R ²	P-value
SBP at crises			
Calcium	0.104	0.011	.080
Corrected calcium (adjusted) (N = 276)	-0.041	0.002	.496
Corrected calcium (unadjusted) (N = 276)	-0.051	0.003	.398
Phosphorus (N = 230)	-0.002	0.000	.970
Magnesium (N = 220)	0.043	0.002	.523
DBP at crises			
Calcium	0.003	0.000	.959
Corrected calcium (adjusted) (N = 276)	-0.099	0.010	.100
Corrected calcium (unadjusted) (N = 276)	-0.095	0.009	.117
Phosphorus (N = 230)	0.007	0.000	.921
Magnesium (N = 220)	-0.019	0.000	.781

TABLE 4 Relationship between serum calcium and SBP at crises or DBP at crises – cases (adjusted for covariates)

Relationship between calcium and SBP at crises or DBP at crises (N = 283)		
Variables	β ± SE	P-value
SBP at crises		
Calcium	0.025 ± 2.116	.991
DBP at crises		
Calcium	-1.705 ± 1.711	.320

Note: Adjusted for covariates: age, sex, race, history of diabetes mellitus, BMI, use of bisphosphonates, use of loop diuretics at home, use of loop diuretics at hospital, use of thiazide diuretics at home, use of thiazide diuretics at hospital, CKD staging, albumin, and GFR.

TABLE 5 Odds of having abnormally high serum calcium (>10.3 mg/dL) or abnormally low serum calcium (<8.4 mg/dL) in cases vs controls

	Estimate	Standard error	Odds ratio	95% Confidence interval	P-value
Odds of abnormally high serum calcium (>10.3 mg/dL)	0.158	0.5628	1.171	0.388, 3.537	.779
Odds of abnormally low serum calcium (<8.4 mg/dL)	-0.025	0.2231	0.975	0.629, 1.512	.911

(Table 3), none was significantly correlated to either SBP or DBP at crises. These are secondary outcomes and should be interpreted cautiously. Magnesium was measured because of its strong linkage with blood pressure, especially in concert with calcium,^{3,10,19,29,34-36} while phosphorus was measured because its homeostasis is closely regulated with calcium.^{7,24} Altogether, our study did not detect a significant association between calcium and blood pressure (SBP or DBP) in patients with hypertensive crises which suggests that serum calcium may not play a pronounced role in the dysregulated blood pressure seen in patients with hypertensive crises.

We also performed a logistic regression and found no significant difference in the odds of having an abnormally high or low serum calcium among patients with hypertensive crises compared to matched controls (Table 5). This finding is glaringly different from many studies which have revealed higher odds of incident hypertension or elevated blood pressure in patients with high serum calcium levels.^{13,17,21,37,38} It is worth noting that few studies have found either lower odds of hypertension³⁹ or no significant difference in odds of hypertension in patients with hypertension.²²

The strengths of our study include its case-control study design, use of statistical tests to create randomly matched groups, and employment of diverse statistics that explored between group differences and association within group, and the pilot/exploratory nature of our study. The case-control study design allowed us to investigate whether there is a true difference in mean serum calcium between the hypertensive crises patients and control group. Additionally, we performed correlation analysis to examine the association between serum calcium and blood pressure in patients with hypertensive crises. The random matching process also allowed us to have a control group similar to the cases on the covariates of age, sex, race, history of diabetes mellitus, and BMI which is anticipated to attenuate the effects of these covariates on the study outcomes and thus improved our study's internal validity. This study as a pilot/exploratory study is hypothesis generating which can provide population estimates to help determine the appropriate power and sample size to study calcium effect on hypertensive crises in future studies.

Our study has several limitations which impact its internal and external validity. First, this study is a single-center study and as such limits the generalizability of our study to patients across institutions. The findings from this single-center study should be extrapolated cautiously to individual patients and patient populations with hypertensive crises. The inclusion and exclusion criteria of the study weaken the external validity of our study which must be considered in the extrapolation of our study to different populations. It

is worth mention that the mean BMI was high in both groups in our study because of the matching of the control group BMI to the case group. Prior to the matching of BMI, the case group had a higher BMI compared to the controls which is consistent with the literature showing higher BMI correlates with high blood pressure.^{40,41} Although the BMI matching in our study was done to control for the potential confounding effect of BMI on blood pressure and serum calcium based on our preliminary statistical analysis and literature review,⁴⁰⁻⁴³ this poses a threat to the external validity of our study since matching for BMI deviates from real-world setting where BMI is higher in hypertensive patients. The matched control group in our study included patients who were either normotensive or hypertensive. This may weaken the internal validity of the study given the heterogeneity of our matched control group and the lack of result delineation between normotensive vs hypertensive patients in our study. This study was a retrospective study which introduces variability on the time when variables were collected, as variables were not collected uniformly at narrow and specific times. Our study was also a non-interventional/non-experimental study which impacts the internal validity and excludes our study from the ability to assess causation. Our study was not a randomized study and confounding variables may have impacted our study results given that some baseline characteristics were significantly different between groups. Given the non-randomized and retrospective design of our study, some notable variables were not accounted for or controlled and may confound our main study variables (calcium and/or blood pressure). These potential confounding variables include, but are not limited to: use of diuretics therapy, type of treatment used to manage hypertension or hypertensive crises, underlying primary etiology of hypertension or hypertensive crises, use of oral contraceptives in females, etc. Additionally, not matching the estimated GFR status for the case and control group is a limitation of our study as patients' GFR status impacts serum calcium and phosphorus levels and is a likely confounder. Another important limitation of our study is that calcium plays most of its physiological role as an intracellular cation and given that intracellular calcium is not routinely measured clinically at our hospital, the serum calcium level obtained from our electronic hospital record may not be a good reflection of patients' calcium stores.⁷ Lastly, our study had a small sample size (n = 566), which increases the probability of type II errors—a weakened probability to detect significant differences that may exist in the true population of patients from which our sample population was obtained. Our inability to detect significant differences in the serum calcium levels between the case and control groups of our study may be linked to the small sample size of our study.

Overall, when considering the strengths and limitations of our study design and the negative results of our study, we recommend that critical assessment of serum calcium levels should be avoided in patients with hypertensive crises in the clinical setting. Furthermore, since calcium levels are part of standard chemistry panel ordered routinely in medical laboratories, we suggest that calcium reporting patterns should not deviate from the current clinical practice consensus among hospitalized patients.

5 | CONCLUSIONS

This study found no significant difference in serum calcium levels in patients with hypertensive crises compared to a random matched control group. In our tests of association (simple or multivariable), calcium was not significantly correlated with either SBP or DBP in patients with hypertensive crises. Association of calcium with blood pressure in hypertensive crises may be insignificant based on our study. Larger studies may be useful to evaluate the true effect of calcium on blood pressure in hypertensive crises and to generate the hypothesis for an experimental study testing the therapeutic utility of serum calcium altering (supplementation or depletion) therapy in patients with hypertensive crises.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Ifeanyi Onor contributed to the study conception, study design, data analysis/interpretation, and first manuscript draft preparation. John Okogbaa, Christopher Gillard, Daniel Sarpong, Mihran Naljayyan, Shane Sanne, and Shane Guillory participated in the study design and data analysis/interpretations. Robbie Beyl contributed primarily to the statistical analysis of the data set and data interpretation. Rose Duchane, Casey Payne, Hannah Naquin, DeMaurian

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