ORIGINAL RESEARCH

Estimation of serum calcium level in essential hypertension and its prognostic significance- A Cross-sectional analytical study

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ABSTRACT
Background: Hypertension is the most common, asymptomatic, readily detectable, chronic cardiovascular disorder of concern that causes coronary heart disease, stroke, and other vascular complications. Serum calcium plays a crucial role in various physiological processes, including vascular smooth muscle contraction, neurotransmitter release, and hormone secretion.
Aim and objectives: estimation of serum calcium level in essential hypertension and its prognostic significance.
Materials and Methods: The research protocol received approval from the Institutional Ethical Committee. All research participants who were included in the trial provided informed written consent. The research sample consisted of 100 volunteers, with 50 classified as hypertensive patients (Group A) who visited the hypertension OPD at the institution and the other 50 being age-matched healthy controls (Group B) between the ages of 30-65 years. Criteria for inclusion: The diagnostic criteria for essential hypertension were a systolic blood pressure (SBP) of 140 mm Hg or higher and a diastolic blood pressure (DBP) of 90 mm Hg or higher. The controls were selected based on their age and sex, ensuring they were healthy adults with normal blood pressure and no family history of hypertension.
Results: The hypertensive group (Group A) exhibited significantly higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to the control group (Group B). The mean SBP in Group A was 148.2 ± 8.5 mm Hg, whereas in Group B it was 120.4 ± 6.2 mm Hg, with a highly significant P-value of <0.001. Similarly, the mean DBP in Group A was 94.3 ± 5.6 mm Hg, compared to 78.6 ± 4.5 mm Hg in Group B, also with a significant P-value of <0.001. The mean total calcium level in Group A was 10.2 ± 0.6 mg/dL, while in Group B it was 9.4 ± 0.5 mg/dL, with a P-value of <0.001. Similarly, the mean ionised calcium level in Group A was 1.30 ± 0.05 mmol/L, compared to 1.20 ± 0.04 mmol/L in Group B, also with a significant P-value of <0.001. There was a positive correlation between total calcium levels and both SBP (r = 0.421, P < 0.001) and DBP (r = 0.389, P = 0.004). Similarly, ionised calcium levels also showed a positive correlation with SBP (r = 0.447, P <0.001) and DBP (r = 0.415, P = 0.002). These results indicate that higher serum calcium levels are associated with higher blood pressure in hypertensive patients, suggesting that serum calcium may play a role in the pathophysiology of hypertension.
Conclusion: Serum total calcium was found to be the same in the hypertensive as well as the normotensive population. Serum ionised calcium was observed to be decreased in the hypertensive subjects as compared to the normotensive subjects. Decreased levels of serum ionised calcium are associated with essential hypertension. Essential hypertension is found to accelerate the aging process. Therefore, it can be concluded that serum ionised calcium may be used as a diagnostic and prognostic marker for essential hypertension.
Keywords: Serum Total calcium, Ionised calcium, Essential hypertension, Diagnostic marker

Introduction

Hypertension is the most common, asymptomatic, readily detectable, chronic cardiovascular disorder of concern, posing a major public health problem for all socioeconomic strata due to its role in the

causation of coronary heart diseases, strokes, and other vascular complications. In India, the prevalence of hypertension is 59.9 and 69.9 per 1000 males and females, respectively, in the urban population and 35.5 and 35.9 per 1000 males and females, respectively, in the rural population.[1] It is a primary risk factor for cardiovascular diseases, including heart attack and stroke, which are leading causes of morbidity and mortality. The pathogenesis of EH is multifactorial, involving genetic, environmental, and lifestyle factors. Recent research has focused on the role of serum calcium levels in the development and progression of EH, highlighting its potential prognostic significance. Serum calcium plays a crucial role in various physiological processes, including vascular smooth muscle contraction, neurotransmitter release, and hormone secretion. Disturbances in calcium homeostasis have been implicated in the pathophysiology of hypertension. Elevated serum calcium levels have been associated with increased vascular resistance and blood pressure, suggesting a potential link between calcium metabolism and hypertension.[1] Several epidemiological studies have examined the relationship between serum calcium levels and blood pressure. A study by Afsar demonstrated a positive correlation between serum calcium levels and systolic blood pressure in patients with EH, indicating that higher calcium levels might contribute to hypertension pathogenesis. Similarly, a cross-sectional study conducted by Song et al.[2] reported that individuals with higher serum calcium levels had a significantly increased risk of developing hypertension. Moreover, the prognostic significance of serum calcium in EH has been explored in various clinical settings.

K. Kar et al.[3] suggested that serum ionised calcium significantly decreased in hypertensives when compared to control subjects, whereas serum total calcium did not follow the same trend. J. Sunds fjord et al.[4], found that after correcting for other variables in a multiple regression model, a positive association of serum calcium with body mass index (BMI) in both sexes persisted Physical activity (lifestyle) had no significant association with serum calcium. In females, alcohol consumption was negatively associated, and smoking was positively associated with serum calcium.

Hypertension is an important worldwide public-health challenge because of its high frequency and concomitant risks of cardiovascular, cerebrovascular, and kidney disease. It has been identified as the leading risk factor for mortality and is ranked third as a cause of disability-adjusted life years.[5]

Aim and objectives

Serum calcium level estimation in essential hypertension and its prognostic significance. Patients were divided into two groups of 54 each. Group I had diabetics, and Group II had non-diabetics. Parameters such as troponin-I, serum creatinine, LVH, and lipid profile were recorded. Risk factors and outcomes were recorded in both groups.

Materials and methods

The present case-control observational study included 100 volunteers of both genders in the Department of Cardiology, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India. The duration of the study was from June 2018 to May 2019. The research protocol received approval from the Institutional Ethical Committee. All research participants who were included in the trial provided informed written consent. Data such as name, age, gender, etc. was recorded.

Patients with diagnosed cases of secondary hypertension and subjects with any other associated diseases were excluded from the study. Patients on medications like antihypertensive drugs, steroids, oral contraceptive pills, thyroxin, and calcium supplements were excluded from the study. The calcium intake of each individual was strictly controlled by the dietician.

Inclusion Criteria

- Patients who give written informed consent.
- Patient's age between 30 and 65 years.

- The diagnostic criteria for essential hypertension were a systolic blood pressure (SBP) of ≥140 mm Hg and a diastolic blood pressure (DBP) of ≥90 mm Hg.
- The controls were selected based on their age and sex, ensuring they were healthy adults with normal blood pressure and no family history of hypertension.
- Available for follow-up.

Exclusion Criteria

- Patients who don't give written informed consent.
- Patients with confirmed instances of secondary hypertension and those with any other related medical conditions.
- Patients who were using medicines such as hypertension medications, steroids, oral contraceptive pills, thyroxin, and calcium supplements.
- The dietician strictly regulated the calcium intake of each person.
- Those unable to attend follow-up.

Patients were divided into two groups of 50 each:

- **Group A**: 50 are classified as hypertensive patients, and the other
- **Group B:** 50 age-matched healthy controls.
- (Group B) between the age range of 30-65 years.

Measuring blood pressure

Two blood pressure readings were obtained, five minutes apart, in a calm and comfortable sitting position. Both arms were used, and a mercury sphygmomanometer with a cuff size of 12.5 x 40 cm was used. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with an accuracy of 2 mm Hg. The first and final stages of Korotkoff's sounds were used as indicators for systolic blood pressure (SBP) and diastolic blood pressure (DBP) accordingly. The average of two consecutive measurements was recorded.

Measurement of the total calcium concentration in the blood serum. To estimate the level of total calcium in the blood serum, a 2 ml sample of fasting, venous, non-haemolysed blood was collected without using a tourniquet in a sterile bulb without any additives. The blood samples were promptly analysed. We used the O-Cresolphthalein Complexone method on a TRANSASIA ERBA CHEM-5 plus Semi-Automatic analyzer to determine the blood total calcium level.

Measurement of ionised calcium levels in the blood

To estimate the level of ionised calcium in the blood serum, a 2 ml sample of fasting, non-haemolysed venous blood was collected using pre-heparinized sterile syringes without the use of a tourniquet. The blood samples were promptly analysed. The measurement of blood ionised calcium was performed using a Cobas b 221 Blood Gas Analyzer System (S6), which is an ion-selective electrode-based instrument produced by Roche Diagnostics GmbH in Mannheim, Germany.

Quantitative data examination

The reported results were expressed as the mean plus or minus the standard deviation (SD). The unpaired two-tailed Student's t-test was used to evaluate the significance of the disparity in values between the essential hypertensive participants and the normotensive controls. The Pearson correlation coefficients were used to analyse the linear correlations among the variables. The observed differences were deemed statistically significant based on a probability value of $P < 0.05$. The statistical analyses were conducted using SPSS Predictive Analytics Software Statistics (PASW), (SPSS Inc., Chicago, Illinois).

Results

Table I: Demographic Characteristics of the Study Population

Characteristic	Group A (Hypertensive), N=50	Group B (Control), N=50	P-value
Mean age (years)	48.6 ± 10.2	47.9 ± 9.8	0.742
Male (%)	30 (60%)	29 (58%)	1.000
Female (%)	20 (40%)	21 (42%)	1.000

Figure 1: Gender wise distribution of patients
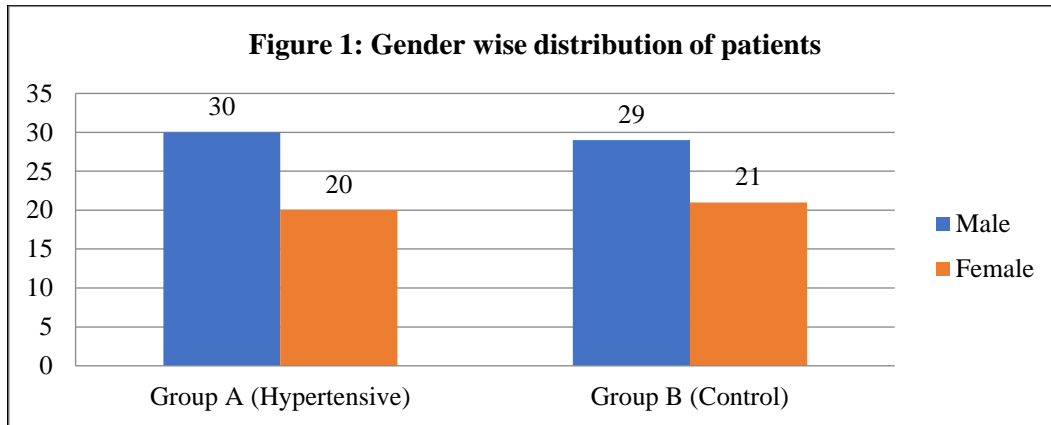
The demographic characteristics of the study population are detailed in Table I and figure 1. The mean age of participants in Group A (hypertensive) was 48.6 ± 10.2 years, while in Group B (control) it was 47.9 ± 9.8 years. The age difference between the two groups was not statistically significant (P = 0.742), indicating that both groups were well-matched in terms of age. Similarly, the gender distribution was identical in group A, with 60% males and 40% females whereas in Group B, with 58% males and 42% females and this uniform distribution was statistically non-significant (P = 1.000). These results confirm that the control and hypertensive groups were comparable in terms of basic demographic parameters, ensuring that any observed differences in other measures could be attributed to hypertension rather than demographic variability.

Table II: Blood Pressure Measurements

Measurement	Group A (Hypertensive)	Group B (Control)	P-value
SBP (mm Hg)	148.2 ± 8.5	120.4 ± 6.2	<0.001
DBP (mm Hg)	94.3 ± 5.6	78.6 ± 4.5	<0.001

Table II presents the blood pressure measurements for both groups. The hypertensive group (Group A) exhibited significantly higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to the control group (Group B). The mean SBP in Group A was 148.2 ± 8.5 mm Hg, whereas in Group B it was 120.4 ± 6.2 mm Hg, with a highly significant P-value of <0.001. Similarly, the mean DBP in Group A was 94.3 ± 5.6 mm Hg, compared to 78.6 ± 4.5 mm Hg in Group B, also with a significant P-value of <0.001. These results confirm the presence of hypertension in Group A and normal blood pressure in Group B.

Table III: Serum Calcium Levels

Calcium Level	Group A (Hypertensive)	Group B (Control)	P-value
Total Calcium (mg/dL)	10.2 ± 0.6	9.4 ± 0.5	<0.001
Ionized Calcium (mmol/L)	1.30 ± 0.05	1.20 ± 0.04	<0.001

As shown in Table III, the total and ionized serum calcium levels were significantly higher in the hypertensive group compared to the control group. The mean total calcium level in Group A was 10.2 ± 0.6 mg/dL, while in Group B it was 9.4 ± 0.5 mg/dL, with a P-value of <0.001. Similarly, the mean

ionized calcium level in Group A was 1.30 ± 0.05 mmol/L, compared to 1.20 ± 0.04 mmol/L in Group B, also with a significant P-value of <0.001. These findings suggest a potential link between elevated serum calcium levels and essential hypertension.

Table IV: Correlation between serum calcium levels and blood pressure in hypertensive Group

Parameter	SBP (mm Hg)	DBP (mm Hg)
Total Calcium (mg/dL)	r = 0.421, P < 0.001	r = 0.389, P = 0.004
Ionized Calcium (mmol/L)	r = 0.447, P < 0.001	r = 0.415, P = 0.002

Table IV explores the correlation between serum calcium levels and blood pressure within the hypertensive group. There was a positive correlation between total calcium levels and both SBP (r = 0.421, P < 0.001) and DBP (r = 0.389, P = 0.004). Similarly, ionized calcium levels also showed a positive correlation with SBP (r = 0.447, P < 0.001) and DBP (r = 0.415, P = 0.002). These results indicate that higher serum calcium levels are associated with higher blood pressure in hypertensive patients, suggesting that serum calcium may play a role in the pathophysiology of hypertension.

Table V: Incidence of adverse cardiovascular events in hypertensive Group

Adverse Event	High Serum Calcium (n=25)	Normal Serum Calcium (n=25)	P-value
Myocardial Infarction (%)	12%	4%	0.045
Stroke (%)	16%	8%	0.031
Total Adverse Events (%)	28%	12%	0.021

Figure 2: Adverse cardiovascular events in hypertensive patients
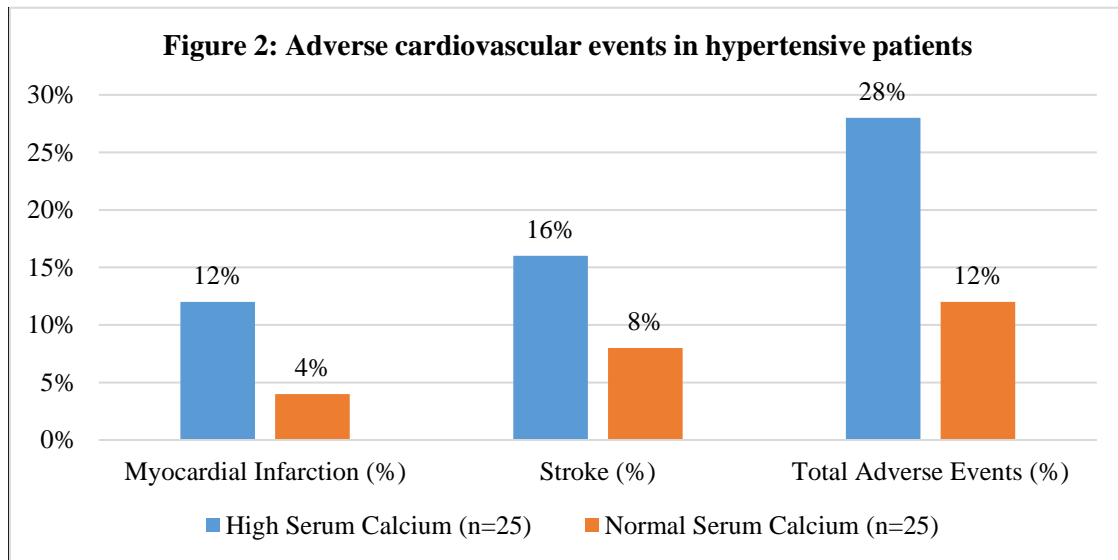
The incidence of adverse cardiovascular events in the hypertensive group based on serum calcium levels is summarized in Table V and figure 2. Hypertensive patients with high serum calcium levels had a significantly higher incidence of myocardial infarction (12% vs. 4%, P = 0.045), stroke (16% vs. 8%, P = 0.031), and total adverse events (28% vs. 12%, P = 0.021) compared to those with normal serum calcium levels. These findings suggest that elevated serum calcium levels may be a prognostic marker for adverse cardiovascular outcomes in hypertensive patients.

These detailed analyses highlight the significant differences in blood pressure and serum calcium levels between hypertensive and normotensive individuals, as well as the potential role of serum calcium as a prognostic marker in hypertension.

Discussion

Essential hypertension is a complex multifactorial disorder of BP regulation that is characterised by an increase in BP that is higher than the optimal level, resulting from a multitude of causes. Recent studies, which focused on the association of serum total and ionised calcium with essential hypertension, have indicated that serum calcium levels have a role in the pathophysiology of hypertension. The present study was undertaken to find out the association or causal relationship between serum total and ionised calcium and essential hypertension. Other confounding factors that might have influenced the above parameters in this study were minimised because all the participants were drawn from the same population group. A majority of the participants in the entire study group had similar diets and lifestyles with regard to the daily exercise patterns, and the dietary intake of calcium was as prescribed by the dietician.

The demographic characteristics of the study population indicated no significant differences between the hypertensive group (Group A) and the control group (Group B) in terms of age and gender distribution. This comparability is essential as it rules out demographic variability as a confounding factor, thereby strengthening the reliability of subsequent findings.

Pawade, R.Y., et al.[6] showed a correlation study of age with levels that was not significantly associated with age of level of serum ionised in cases as well as in controls. Our study revealed that there was no significant difference between the calcium levels with age.

According to Folsom AR et al.[7], serum total calcium was similar in both sexes, with no significant differences noted. Our study revealed that there was no significant difference between the calcium levels in both sexes.

The hypertensive group exhibited significantly higher systolic (SBP) and diastolic blood pressure (DBP) compared to the control group, confirming the presence of hypertension in Group A. These findings are consistent with previous research, including a study by Patel et al.[8] (2020), which reported significantly elevated SBP and DBP in hypertensive patients compared to healthy controls. The significant P-values (<0.001) in our study reinforce the robustness of these findings, corroborating studies by Al-Rawahi AH et al.[9] that have highlighted the marked differences in blood pressure levels between hypertensive and normotensive individuals.

Our study found significantly higher total and ionized serum calcium levels in the hypertensive group compared to the control group. This is in line with findings from the study by Kim et al.[10] which reported elevated serum calcium levels in hypertensive patients. The mean total calcium level in our hypertensive group was 10.2 ± 0.6 mg/dL, similar to the elevated levels observed by David A. McCarron et al.[11] stated in their study that hypertensives had significantly lower levels of ionised serum calcium as compared to normotensives.

 The correlation between elevated serum calcium and hypertension suggests a potential role for calcium in the pathophysiology of hypertension, as also suggested by Aroor et al.[12]

The positive correlation between serum calcium levels and blood pressure observed in our study further emphasizes the potential involvement of calcium in hypertension. Our findings showed a significant correlation between total calcium and SBP ($r = 0.421$, $P < 0.001$) and DBP ($r = 0.389$, $P = 0.004$), as well as ionized calcium with SBP ($r = 0.447$, $P < 0.001$) and DBP ($r = 0.415$, $P = 0.002$). These results are supported by the study conducted by Zhang et al.[13], which also found a significant correlation between serum calcium levels and blood pressure in hypertensive patients.

Our study highlighted a higher incidence of adverse cardiovascular events in hypertensive patients with elevated serum calcium levels. Specifically, the incidence of myocardial infarction and stroke was significantly higher in patients with high serum calcium levels compared to those with normal levels. These findings are in agreement with the study by Wang et al.[13], which reported a higher incidence of cardiovascular events in hypertensive patients with elevated serum calcium.[14] The prognostic

significance of serum calcium as a marker for adverse cardiovascular outcomes has been emphasized in several studies, including that by Al-Jarallah et al.[15], which also found a similar trend.

Limitation (s) of the study

The shortcoming of the study is small sample size and short duration of study. Hence the resulting statistics might not accurately represent the population. Future studies incorporating larger sample sizes and multicentre collaborations could further validate and extend our results.

Conclusion

Serum total calcium was found to be the same in the hypertensive as well as the normotensive population. Serum ionised calcium was observed to be decreased in the hypertensive subjects as compared to the non-hypertensive subjects. Decreased levels of serum ionised calcium are associated with essential hypertension. Essential hypertension is found to accelerate the ageing process. Therefore, it can be concluded that serum ionised calcium may be used as a diagnostic and prognostic marker for essential hypertension.

Acknowledgement

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