Study of Serum Calcium Levels in Newly Detected Patients with Essential Hypertension

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ABSTRACT

Introduction: Calcium is a key factor in regulating cardiovascular function and alteration in calcium metabolism and has been shown to be associated with human hypertension. Serum calcium levels are found to be significantly lowered in hypertensives. The aim of the study was to estimate total and corrected serum calcium levels in patients with newly detected hypertension and determine its correlation with systolic and diastolic blood pressures.

Material and methods: This was a hospital based cross sectional study in which newly detected patients with essential hypertension were enrolled. Corrected Serum calcium levels were estimated in all patients at the time of the study. Calcium levels were correlated with systolic and diastolic pressure, age, gender, family history of hypertension, sedentary life style, smoking, alcohol intake and BMI.

Results: A total of 100 patients were studied. 71% were over 60 years. 51% were males. Family history of hypertension was present in 54%. 38% were smokers and 24% consumed alcohol. 38% had a BMI of 25 and above. 60% had a sedentary life style. Corrected serum calcium levels were decreased in 65% of patients with hypertension. Significant negative correlation was found between corrected serum calcium levels and systolic and diastolic blood pressures.

Conclusions: Corrected serum calcium levels were reduced in patients with essential hypertension and significant negative correlation was seen between corrected serum calcium levels and systolic and diastolic blood pressures.

Keywords: Serum Calcium, Decreased Levels in Essential Hypertension, Correlation with Systolic and Diastolic Pressure

INTRODUCTION

Hypertension is a chronic condition which accounts for a majority of morbidity and mortality across the globe. Affecting about 1 billion people worldwide, systemic hypertension is one of the major risk factors for heart disease and stroke, thus becoming the number one attributable risk for death worldwide, approximately 7.1 million deaths per year.[1] Lifestyle changes and escalating trends of obesity both in developed and developing counties increased the global burden of hypertension and is projected to affect 1.5 billion people, about one third of the world's population, by 2025.[2] Hypertension has an asymptomatic course which delays the diagnosis. Even in patients diagnosed with hypertension there is no single disease-causing mechanism that can be identified as the disease pathogenesis is decided by many factors like genetic, environmental and others. Observational studies have shown the association between essential hypertension and disturbed calcium metabolism. Studies have shown that there is increased intracellular calcium, decreased serum ionized calcium levels and also increased urinary excretion of calcium in patients with essential hypertension. (Touyz 1995).[3-6] One of the largest studies regarding this topic was done by National Health And Nutrition Examination Survey (NHANES). This study concluded that there is a threshold of 400-600 mg per day of dietary calcium, the risk of high blood pressure increasing dramatically at levels below this threshold, while the cardiovascular benefits modestly increase at higher intake.[7] This value can vary with the population studied. This threshold value was found to be elevated in other races and pregnancy.

In this study total serum calcium levels and corrected serum calcium levels of newly detected essential hypertensives are estimated and correlated with variables like stages of hypertension, age, gender, family history of hypertension, BMI, lifestyle, smoking and alcohol intake.

Objective of the study was to estimate the total and corrected serum calcium levels in patients with newly detected essential hypertension, to compare the corrected serum calcium levels of patients with newly detected essential hypertension and its relation with factors like age, gender, family history of hypertension, life style, smoking, alcohol intake and BMI, to determine the correlation of corrected serum calcium levels with systolic blood pressure in patients with essential hypertension and to correlate corrected serum calcium levels with diastolic blood pressure in patients with essential hypertension.

MATERIAL AND METHODS

This study was carried out in the Department of General Medicine at Government Stanley Medical College and Hospital, Chennai during the period between March 2016 and August 2016. This study was approved by the Institutional Ethical Committee.

This study was a cross sectional study, enrolling 100

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newly detected essential hypertension patients as per JNC 7 guidelines. Cases were selected from those who visited hypertension clinic and those who were admitted in Medical wards during the study period. Newly detected cases of essential hypertension and known cases of essential hypertension, not on treatment with antihypertensive drugs were included in this study. Hypertensive patients with chronic kidney disease, ischemic heart disease, congestive cardiac failure, secondary causes of hypertension, stroke, peripheral vascular disease, age less than 30 years, BMI < 18.5 Kg/m², patients on calcium supplements and those who had undergone parathyroidectomy were excluded from this study.

Applying all these criteria, 100 essential hypertensive patients were selected and included in the study after taking their informed consent. Secondary hypertension was ruled out by thorough history, clinical examination, appropriate hematological investigations, urine analysis and radiological investigation. Serum Calcium estimation was done at the time of enrolment in the study. The social and demographic details recorded were age, gender, family history of hypertension, occupation and income, assessment of sedentary behaviour, alcohol intake and smoking index. On clinical examination, BMI, BP recording and thorough general and systemic examination was done.

Blood pressure was recorded with the patient seated quietly for 5 min in a quiet room after emptying the bladder, with the arm bared and supported at the level of the heart with the back resting against a chair. A mercury manometer with appropriate cuff size was used to measure the blood pressure. Korotkoff sounds phase I (appearance) was taken as systolic BP while phase V (disappearance) was taken as a measure of diastolic blood pressure. Two sets of BP readings were taken 30 min apart in both arms in sitting posture, if the pressures differed the arm with the higher pressure was taken. Lower limb BP was also taken in patients less than 40 years of age. Supine and standing BP recordings for postural hypotension were measured in individuals more than 60 years.

Investigations done in all patients were complete blood count, urine routine analysis, urine spot protein-creatinine ratio, random blood sugar, fasting lipid profile, urea, creatinine, electrolyte estimation, serum albumin, ECG, X-ray chest and ultrasound abdomen.

Estimation of serum Calcium levels

Arsenazo III method was used for the estimation of serum calcium. This method is based on principle that calcium binds to the dye arsenazo III at an acidic P_H to form blue-purple colored complex. Intensity of the color of the complex is directly proportional to the amount of calcium in the sample. In the kit there is a standard sample with 10 mg/dl of calcium in it. This is taken as the control. A solution with distilled water is also prepared taken as blank. Absorption photospectroscopy of both test and control is measured against the blank at 650nm in room temperature within one hour and compared. Linearity of this test is upto 15mg/dl. Serum calcium (mg/dl) = (Abs of test/ Abs of control) x 10. In this study calcium levels were corrected using the below
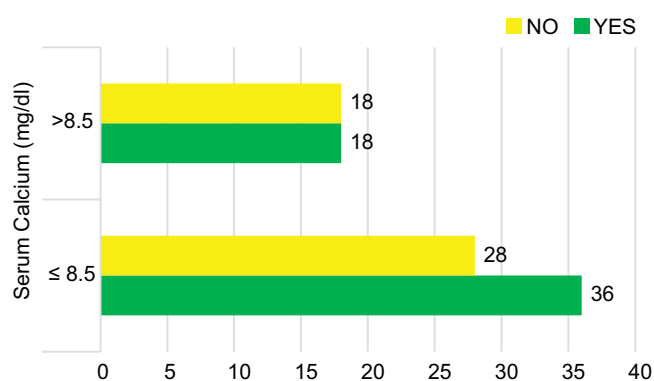
formula. Corrected Serum Calcium = Serum Calcium (mg/dl) + {0.8 [4 – Serum Albumin (gm/dl)]}

STATISTICAL ANALYSIS

Collected data was analyzed statistically in SPSS software version 11.5. Results were considered significant if the $P < 0.05$. The tests used for statistical analysis were Chi- square test, Student– t test, Analysis of variance (ANOVA) and Pearson's correlation.

RESULTS

Age and Gender Distribution: In the present study out of the 100 patients studied, 71% were of the age group </- 60 years and 29% were more than 60 years. Mean age of the

Graph–1: Bar graph showing correlation of serum calcium vs family history of hypertension
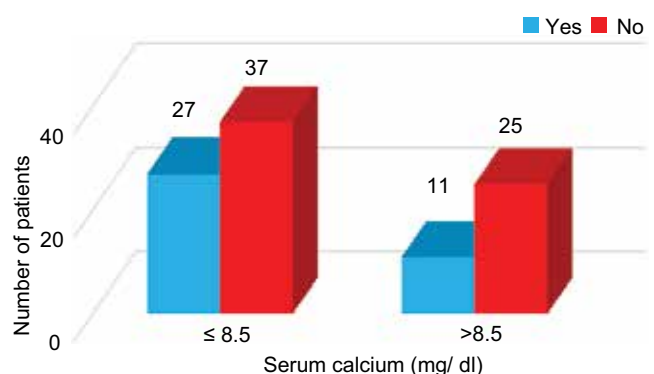
Graph–2: Correlation of corrected serum calcium with smoking
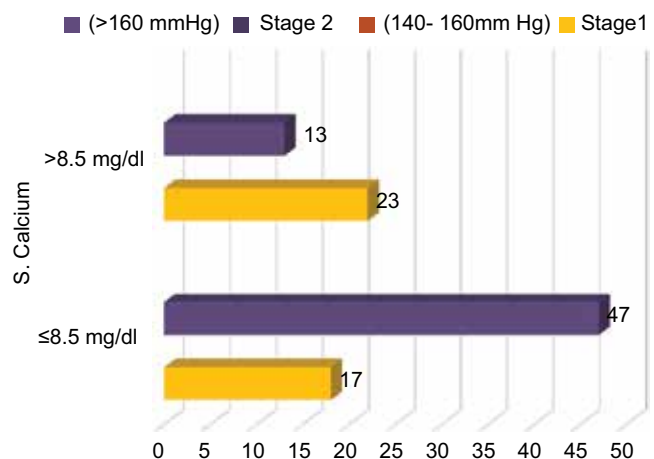
Graph–3: Bar diagram depicting the correlation between serum calcium levels and systolic blood pressure

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study population was 56.02 +/- 10.76 years (table-1). Out of the 71 patients in the age group < / - 60 years, 40 had low calcium levels. Out of the 29 patients in the age group of > 60 years, 24 had low calcium levels (table-2). *P* value was 0.01 which was statistically significant. Chi square test was 6.238. Thus statistically significant correlation was

Age group (years)	Number	Percentage	Mean	Std. deviation	Std. Error
<ary - 60	71	71	56.02	10.76	1.076
>60	29	29			
Total	100	100			
Table-1:					

Age	S. Calcium ≤8.5 mg/dl	S. Calcium>8.5 mg/dl
≤ 60 years	40	31
>60 years	24	5
Table-2: Correlation of corrected serum calcium with age groups		

Gender	Serum calcium ≤ 8.5 mg/dl	Serum Calcium > 8.5 mg/dl
Male	36	15
Female	28	21
Table-3: Correlation of corrected serum calcium with gender		

Alcohol intake	Serum Calcium (mg/ dl) ≤ 8.5	Serum Calcium (mg/ dl) >8.5
Yes	18	6
No	46	30
Table-4: Correlation of corrected serum calcium with alcohol intake		

Body Mass Index (BMI) kg/m²	Number	Percentage	Mean	Std. Deviation	Std. Error
18.5-22.9	30	30	24.41	2.76	0.276
23- 24.9	32	32			
>25	38	38			
Total	100	100			
Table-5: Distribution of body mass index					

BMI	S. Calcium ≤ 8.5 mg/dl	S. Calcium > 8.5 mg/dl
18.5-22.9	19	11
23-24.9	22	10
>25	23	15
Table-6: Correlation of corrected serum calcium with BMI		

Sedentary lifestyle	S. Calcium ≤ 8.5 mg/dl	S. Calcium > 8.5 mg/dl
Yes	38	22
No	26	14
Table-7: Correlation of corrected serum calcium with lifestyle		

Serum Calcium (mg/dl)	Number	Percentage	Mean	Std. Deviation	Std. Error
≤ 8.5 mg/dl	64	64	8.39	0.509	0.509
>8.5 mg/dl	36	36			
Total	100	100			
Table-8: Distribution of corrected serum calcium in the study sample					

Systolic blood pressure	Number	Percentage	Mean	Std. Deviation	Std. Error
Stage 1 (140- 160mm Hg)	40	40	166.16	15.076	1.508
Stage 2 (>160 mmHg)	60	60			
Total	100	100			
Table-9: Systolic and diastolic blood pressure distribution					

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Diastolic blood pressure	Number	Percentage	Mean	Std. Deviation	Std. Error
Stage 1 (90-100mm Hg)	44	44	102.43	12.42	1.243
Stage 2 (>100 mmHg)	56	56			
Total	100	100			
Table-10:					

noted between corrected serum calcium levels and age. 51% were males and 49% were females in the patients studied. Decreased calcium levels were present in 36% of males and 28% of females (table-3). *P* value was 0.21, which was not statistically significant. Chi square test is 1.961. There was no statistically significant association noted between corrected calcium levels and gender of the patient.

Distribution of family history of hypertension: Family history of hypertension was obtained in 54%. Among the 64% of patients with decreased calcium levels, 36 patients had family history of hypertension and 28% did not have positive family history (graph-1). P value was 0.06, which was not statistically significant. Chi square test was 0.362. There was no statistically significant association noted between corrected calcium levels and family history of hypertension.

Distribution of smoking: 38% of individuals were smokers. Out of the 38 smokers, 27 had low serum calcium levels and 37 out of 62 non - smokers had low serum calcium levels. *P* value was 0.28, which was not statistically significant. Chi square test was 1.323. There was no statistically significant association noted between corrected serum calcium levels and smoking (graph-2).

Distribution of alcohol intake: History of alcohol intake was present in 24% of the study group. Out of the 24 patients who consumed alcohol, 18 had low serum calcium levels and 46 out of the 76 patients who did not consume alcohol had low calcium levels. P value is 0.23, which was not statistically significant. Chi square test was 1.658. There was no statistically significant association noted between corrected serum calcium levels and alcohol intake (table-4).

Distribution of Body Mass Index: was over 25 in 38%, between 23 and 24.9 in 32% and less than 23 in 30%. Mean BMI of the study population was 24.41+/- 2.76 (table-5). Low calcium levels were present in 19 out of 30 patients, 22 out of 32 patients and 23 out of 38 patients respectively among the three groups. P value was 0.10, which was not statistically significant. Chi square test was 4.449. There was no statistically significant association noted between corrected serum calcium levels and Body mass index (table-6).

Distribution of life style- 60% of the study group had a sedentary life style. Among the 64% who had decreased calcium levels, 38 patients had history of sedentary life style and 26 were physically active. P value was 0.006, which was not statistically significant. Chi square test was 0.550. There was no statistically significant association noted between corrected calcium levels and sedentary lifestyle (table-7).

Distribution of corrected serum calcium: Serum calcium levels were less than 8.5 mg/dl in 64% of the patients. Mean serum calcium in our study group was 8.39 +/- 0.509 mg/ dl (table-8).

Systolic and Diastolic blood pressure distribution: Out of the 100 hypertensives studied, systolic BP of 40 patients were in stage 1 hypertension and 60 were in stage 2 hypertension. Mean systolic BP was 166.16 +/- 15.08 (table-9).

56% of patients had stage 2 diastolic hypertension and 44% had stage 1 diastolic hypertension. Mean diastolic BP was 102.43 +/- 12.42 mm of Hg (table-10).

Among the 60 patients with stage 2 systolic hypertension, 47 had decreased calcium levels and 13 had normal levels (graph-3). Among the 56% of patients with stage 2 diastolic hypertension, 42 patients had reduced calcium levels, in comparison to 14 patients with normal levels.

Serum calcium levels were lowered in 47 out of 60 patients with Stage 2 systolic hypertension and this association was statistically significant (p value of 0.001). Among the 56% of patients with stage 2 diastolic hypertension, 42% had low calcium levels. The correlation coefficient was -0.289 and p value is 0.001 which was also statistically significant. Thus both systolic and diastolic blood pressure had statistically significant negative correlation with serum calcium levels.

DISCUSSION

Systemic hypertension remains the most common, readily identifiable

and reversible risk factor for myocardial infarction, stroke, heart failure, atrial fibrillation, aortic dissection and peripheral arterial disease. Evidence is growing that calcium physiology is altered in essential hypertension, but whether this is a secondary association or a causal relationship is unresolved. Intracellular calcium ions are known to have direct effects on peripheral vascular tone and it has been reported in various trials that hypertensive persons have increased concentrations of intracellular free calcium that decrease to normal levels with antihypertensive drugs. Various epidemiological studies have stated that the calcium status of humans with essential hypertension and genetic animal models of hypertension is characterized by low serum total and ionized calcium concentration, increased intracellular calcium, increased urinary calcium excretion, and increased parathyroid hormone (PTH) concentration.[3-6,17] Calcium is a key factor in regulating cardiovascular function and alteration in calcium metabolism has been shown to be associated with human hypertension. This study used corrected serum calcium, which is an alternative but not a substitute to serum ionised calcium. In this study the mean corrected serum calcium was 8.39 +_0.509 mg/dl.

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Statistical analysis revealed that the corrected serum calcium levels were significantly lowered in patients with essential hypertension. This observation is supported by some of the following studies.

According to K. Sudhakar et al.,[5] the mean total serum calcium levels

were significantly (P<0.01) decreased in males and females in the hypertensive group when compared with normotensive controls. In first-degree relatives also the total serum calcium levels were significantly decreased (P <0.01) when compared with the controls.

AR Folsom et al.,[9] studied the serum calcium fractions in essential hypertensive and matched normotensive subjects. In their study he observed hypertensive subjects had lower mean serum levels of ultra filterable calcium (P = 0.01), ionized calcium (P = 0.09), and complexed calcium (P = 0.04) and higher levels of protein-bound calcium (p = 0.07). Calculated serum concentrations of complexed calcium were significantly lower in hypertensive subjects (P = 0.04), while protein bound calcium concentrations were higher (P = 0.07). Serum phosphorus and albumin concentrations, as well as estimated dietary calcium intake, were not different between the two groups. Erne P, Bolli P, et al.,[11] in their study on "correlation of platelet calcium with blood pressure: effect of antihypertensive therapy" reported a decrease in the serum total calcium concentration in essential hypertensive patients.

Bande et al[8], conducted a study in Karnataka taking 50 hypertensive cases and 50 healthy controls. Calcium levels were significantly low in hypertensive group compared to controls. Strazzullo P et al.,[10] Erne P., Bolli P., et al.,[11] Touyz, R.M.,et al.,[4] also showed a decrease in the total serum calcium concentration in essential hypertensive patients in their corresponding studies.

Several studies had showed an association of dietary calcium intake with blood pressure but the potential benefit of treating hypertension with dietary supplements of calcium remains controversial. However certain populations have been shown to be benefited from calcium supplementation.

Correlation of corrected serum calcium levels with systolic blood pressure

In this present study a correlation between calcium levels and systolic blood pressure was attempted and found that the corrected serum calcium levels had a significant negative correlation with systolic blood pressure (P < 0.01). Ottar Hals[14] in his study found that pretreatment systolic blood pressure was inversely correlated to serum ionized calcium (r = - 0.44 and P = 0.05) with findings similar to our study. According to Morris, C.D.et al[15], and Christina Martinez[16], there was a clear inverse relationship between calcium levels and both the prevalence of hypertension and the level of blood pressure.

Correlation of corrected serum calcium levels with diastolic blood pressure

In our study we also attempted a correlation between the calcium levels and diastolic blood pressure and found that there was a significant negative correlation between the corrected serum calcium levels and diastolic blood pressure. AR Folsom et al.,[9] studied the serum calcium in essential hypertensive and matched normotensive subjects. In the study, the hypertensive group comprised 28 subjects whose diastolic blood pressure was greater than 90 mm Hg and not taking antihypertensive medication were chosen. One normotensive control was matched to each hypertensive subject. Controls were required to be of the same race, age and sex as the matched hypertensive subject. Hypertensive subjects had lower mean serum levels of ultrafilterable calcium and ionized calcium. Calculated serum concentrations of complexed calcium were significantly lower in hypertensive subjects, while protein bound calcium concentrations were higher. Serum phosphorus, serum albumin and dietary calcium intake were not different between the two groups.

Correlation of corrected serum calcium levels with various subsets of study group

Our study also had an objective of assessing corrected serum calcium levels in various subsets of essential hypertensive population like age, sex, smoking, alcohol intake, family history of hypertension, lifestyle and BMI. After statistical analysis, it was revealed that there was no significant difference between the calcium levels in the above mentioned except for age. Age factor had a significant correlation with corrected serum calcium levels. According to AR Folsom et al.,[9] and Staessen J, Sartor F, et al.,[18] serum total calcium was similar in both the sexes and no significant difference was noted. C Brot.,et al.,[19] noted that there was no difference between serum ionized calcium between smokers and non-smokers in their study. Physical activity (lifestyle) had no significant association with serum calcium. K. Sudhakar et al.,[5] found that the first-degree relatives of essential hypertensive patients had a significantly decreased (P <0.01) total serum calcium levels when compared with the controls. The limitation of this study was the small sample size and lack of follow up of cases as it was a cross sectional study. Serum ionized calcium, cytosolic calcium, urinary calcium, serum parathormone levels, serum renin levels, and serum Vit D3 levels were not measured due to constraints. Calcium supplementation was not attempted in the patients due to ethical reasons.

CONCLUSION

The corrected serum calcium levels were significantly lowered in newly detected essential hypertensive patients. The corrected serum calcium levels have a significant negative correlation with the level of systolic blood pressure in newly

detected essential hypertensive patients. The corrected serum calcium levels have a significant negative correlation with the diastolic blood pressure also in newly detected

essential hypertensive patients. The corrected serum calcium levels showed no significant correlation with gender, BMI, life style, smoking, alcohol intake and family history of hypertension.

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