Serum Calcium: Can It Be A Diagnostic And Prognostic Marker In Essential Hypertension?

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ABSTRACT

Context: To evaluate the usefulness of serum calcium in the diagnosis and prognosis of essential hypertension**.** Objectives: To find out the association of serum calcium with the pathophysiology of essential hypertension. **Study Design:** A cross-sectional analytical study. **Materials & Methods:** Concentrations of serum total and ionized calcium were analyzed and compared between hypertensive cases and normotensive controls by using the unpaired two-tailed Student's t test. All statistical analyses were done by using PASW (SPSS) v.18.0. **Results:** The mean levels of serum total calcium were not statistically different between the hypertensive and the normotensive groups (P > 0.05). The hypertensive subjects had significantly lower mean serum ionized calcium levels (P < 0.001) as

compared to the normotensive controls. Correlation studies showed that the serum ionized calcium levels varied negatively with age, both in the hypertensive (r = -0.283, P < 0.01) and the normotensive subjects (r = -0.219, P < 0.01). The Liner regression analysis of serum ionized calcium levels with age indicated that hypertensive subjects had 1.67 times higher variation in serum ionized calcium levels than in the normotensive subjects at a particular age. **Conclusion:** Essential hypertension is associated with perturbations in calcium metabolism, especially with decreased levels of the ionized fraction of serum calcium, thus contributing to the ageing process. Serum ionized calcium can be used as a diagnostic as well as a prognostic marker in essential hypertension.

Key Words: Serum total calcium, Ionized calcium, Essential hypertension, Diagnostic marker, Prognostic marker

INTRODUCTION

Hypertension is the commonest, asymptomatic, readily detectable, chronic cardiovascular disorder of concern, posing a major public health problem to all socioeconomic strata due to its role in the causation of coronary heart diseases, stroke and other vascular complications. In India, the prevalence of hypertension is 59.9 and 69.9 per 1000 in 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]

Calcium levels are found to be altered in essential hypertension. [2] Elevated basal cytosolic free calcium (Cai) levels, as well as defective membrane binding and transport kinetics of calcium, have been identified in platelets [3], erythrocytes [4], lymphocytes [5], and adipocytes [6] of hypertensive subjects, in whom blood pressure levels were closely and directly related to the Cai content. [3],[4] Past studies indicate that extracellular calcium concentrations also may differ between hypertensive and normotensive persons. [7],[8] Some researchers have found a highly significant association between serum calcium and both systolic and diastolic BP in both the genders.[9]

The present study was planned with the objective to study the variation of serum total and ionized calcium levels in the patients of essential hypertension, as compared to the levels in age and sex matched healthy normotensive individuals and to investigate the association of serum calcium with the pathophysiology of essential hypertension.

MATERIALS AND METHODS

The present study was carried out during the period of December 2007 - May 2009 in the Department of Biochemistry, Indira Gandhi Government Medical College, Nagpur. The study protocol was approved by the Institutional Ethical Committee. An informed

written consent was obtained from all the study subjects who were enrolled in the study. The study sample comprised of two-hundred participants; of which hundred were diagnosed to be hypertensive patients (Group A) who attended the hypertension OPD in the institute and other hundred were age-sex matched healthy controls (Group B) who were confined to the age group of 30-65 years.

Inclusion Criteria: The criteria for the diagnosis of essential hypertension was systolic BP (SBP) of ≥ 140 mm Hg and diastolic BP (DBP) of ≥ 90 mm Hg. The criteria for the controls were age and sex matched healthy normotensive individuals without any family history of hypertension.

Exclusion Criteria: 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 supplementations were excluded from the study. The calcium intake of each individual was strictly controlled by the dietician.

BLOOD PRESSURE MEASUREMENT [10],[11]

In a quiet and comfortably seated study subject, two BP readings were taken five minutes apart, on both arms, with a mercury sphygmomanometer (cuff size, 12.5 x 40 cm). The SBP and DBP were read to the nearest 2 mm Hg. The first and fifth phases of Korotkoff's sounds were taken as the criteria for SBP and DBP respectively. The average of two consecutive readings was recorded.

SERUM TOTAL CALCIUM

For the estimation of serum total calcium, 2 ml of fasting, venous, non-haemolysed blood sample was withdrawn without the aid of a tourniquet, in a plain sterile bulb. The blood samples were

analysed immediately. The estimation of serum total calcium was done on a TRANSASIA ERBA CHEM-5 Plus Semi-Automatic Analyzer with the kit based on the O-Cresolphthalein Complexone Method.

SERUM IONIZED CALCIUM

For the estimation of serum ionized calcium, 2 ml of fasting, non-haemolysed, venous blood sample was withdrawn by using pre-heparinized sterile syringes without the aid of a tourniquet. The blood samples were analysed immediately. The estimation of serum ionized calcium was done on a Cobas b 221 Blood Gas Analyzer System (S6) (Ion Selective Electrode Based) which was manufactured by Roche Diagnostics GmbH, Mannheim, Germany.

STATISTICAL ANALYSIS

All values were reported as mean ± SD. The unpaired Two-tailed Student's t test was used to assess the significance of the difference in the values in the essential hypertensive subjects and in the normotensive controls. Pearson's correlation coefficients were used to analyse the linear correlations between the variables. The differences were considered as statistically significant at a probability value, $P < 0.05$. All statistical analyses were performed by using SPSS Predictive Analytics Software Statistics (PASW) version 18.0 (SPSS Inc., Chicago, Illinois) [12].

RESULTS:

The demographic profile of the study subjects is depicted in [Table/Fig 1], [Table/Fig 4]. The cases consisted of 58 males and 42 females with a male-to-female ratio of 1.38:1 and the controls consisted of 62 males and 38 females with a male-to-female ratio of 1.63:1. The cases had a mean age of 43.26 ± 7.67 years as compared to a mean age of 44.40 ± 7.37 years in the controls [Table/Fig 1], [Table/Fig 4].

	Group A (Cases)	Group B (Controls)
Male	58	62
Female	42	38
M:F Ratio	1.38:1	1.63:1
Age (yr)	43.26 ± 7.67	44.40 ± 7.37

[Table/Fig 1]: Age and gender distribution of the study groups

Parameter	Group A (Cases)	Group B (Controls)	Test of Significance (P value)
SBP (mm of Hg)	152.14 ± 7.88	119.80 ± 7.31	P < 0.001
DBP (mm of Hg)	105.60 ± 9.04	76.96 ± 3.50	P < 0.001

[Table/Fig 2]: Comparison of SBP and DBP in study groups

The clinical and the laboratory characteristics of the study subjects are reported in [Table/Fig 2] and [Table/Fig 3], respectively.

Parameter	Group A (Cases)	Group B (Controls)	Test of Significance (P value)
Serum Total Calcium (mg/dl)	9.19 ± 0.52	9.26 ± 0.60	P = 0.374
Serum Ionized Calcium (mg/dl)	4.43 ± 0.45	4.91 ± 0.31	P < 0.001

[Table/Fig 3]: Comparison of serum total & ionized calcium in study groups
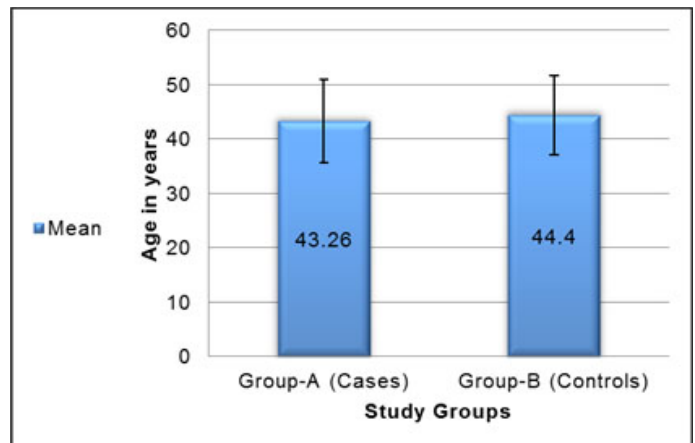

[Table/Fig 4]: Age-wise distribution of study groups.

The SBP of the cases i.e. 152.14 ± 7.88 mm of Hg was significantly higher (P < 0.001) than that of the controls i.e. 119.80 ± 7.31 mm of Hg [Table/Fig 2] [Table/Fig 5]. The cases had a DBP of 105.60 ± 9.04 mm of Hg, which was significantly higher (P < 0.001) as compared to that of the controls, which was 76.96 ± 3.50 mm of Hg [Table/Fig 2], [Table/Fig 6].
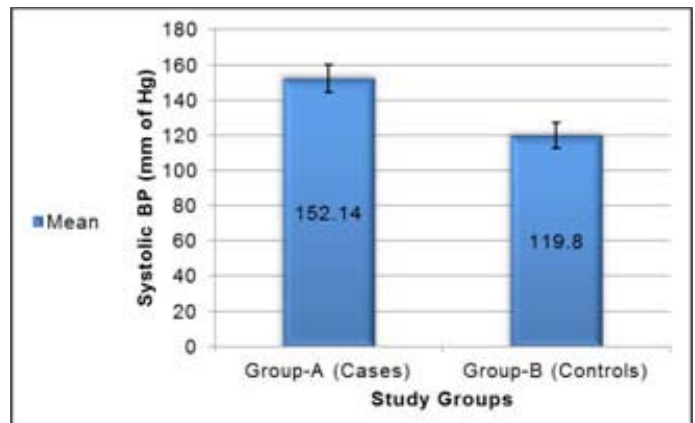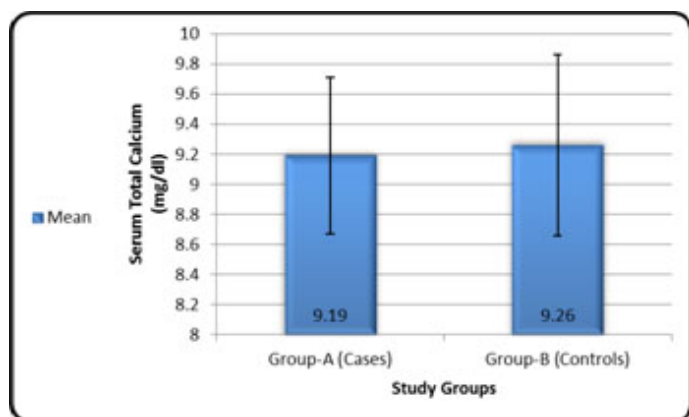

[Table/Fig 5]: Comparison of SBP in study groups

Lower levels of serum total calcium were observed in the cases, i.e. 9.19 ± 0.52 mg/dl as compared to the levels of serum total calcium in the controls i.e. 9.26 ± 0.60 mg/dl [Table/Fig 3], [Table/Fig 7], but the difference between the mean levels of serum total calcium of the cases and the controls was statistically non-significant (P = 0.374 i.e. P>0.05). The cases has significantly lower (P < 0.001) levels of serum ionized calcium, which was 4.43
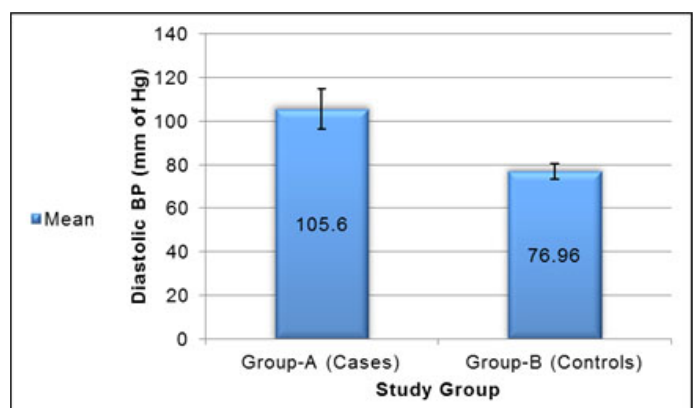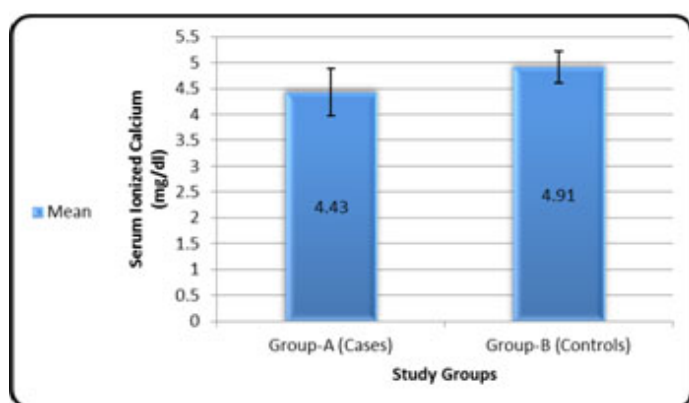

[Table/Fig 6]: Comparison of DBP in study groups

± 0.45 mg/dl, as compared to the levels in the controls, which was 4.91 ± 0.31 mg/dl [Table/Fig 3], [Table/Fig 8].
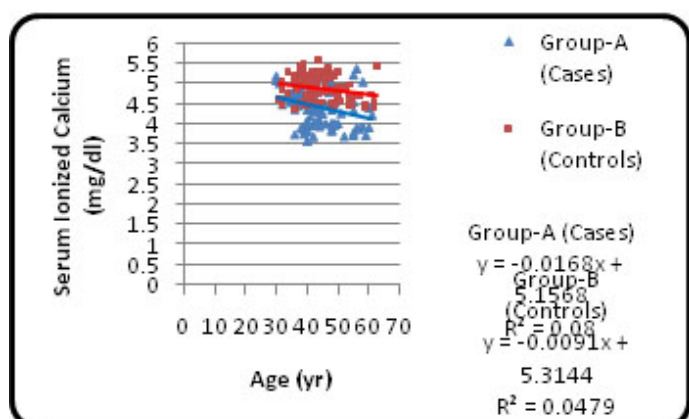

[Table/Fig 7]: Comparison of levels of serum total calcium in study groups.

[Table/Fig 8]: Comparison of levels of serum ionized calcium in study groups

The correlation study of age with the levels of serum ionized calcium indicated that age was significantly negatively correlated with the levels of serum ionized calcium in the cases (r = -0.283, P < 0.01) as well as in the controls (r = -0.219, P < 0.05) [Table/Fig 9]. The linear regression analysis of age with serum ionized calcium levels [Table/Fig 9] showed that the R2 change which was observed for the cases and the controls were 0.08 and 0.0479 respectively.

[Table/Fig 9]: Comparison of levels of serum ionized calcium in study groups

It shows that the variation in the serum ionized calcium levels because of age in the cases and the controls was 8% and 4.79% respectively, accounting for 1.67 times higher variation in serum ionized calcium in the cases than was observed in the controls.

DISCUSSION

Essential hypertension is a complex multifactorial disorder of BP regulation, which is characterized by an increase in BP which is more than the optimal level, resulting from a multitude of causes. Recent studies which were focused on the association of serum total and ionized calcium with essential hypertension have indicated that serum calcium levels have a role in the pathophysiology of hypertension.[13],[14]

The present study was undertaken to find out the association or a causal relationship between serum total and ionized calcium and essential hypertension. Other confounding factors which might have influenced the above parameters in this study were minimized, 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 regards to their daily exercise patterns and their dietary intake of calcium was as prescribed by the dietician.

The hypertensive cases showed lower levels of serum total calcium as compared to the normotensive controls [Table/Fig 3], [Table/Fig 7], but the difference between the mean levels of serum total calcium in the hypertensives and the normotensives was statistically non-significant (P = 0.374 i.e. P > 0.05). David A. McCarron [7], Aaron R. Folsom et al [15], Kazushi Tsuda et al [16] and Markus Kosch et al [17] have fairly supported the present study.

The findings of Rolf Jorde et al [9] and K. Sudhakar et al [18] showed some disparity with our results, as Rolf Jorde et al had included hypertensive patients with a history of myocardial infarction, which could have changed the pattern of serum ionized calcium levels in the hypertensive patients. K. Sudhakar et al [18] found that serum total calcium levels were significantly decreased in patients with essential hypertension and their first degree relatives, which can be attributed to the different dietary habits and the different genetic pools of the populations in which the study had been carried out.

Hypertensives had significantly lower levels of serum ionized calcium as compared to the normotensives (P < 0.001) [Table/Fig 3], [Table/Fig 8]. Our study coincided well with the studies carried out by David A. McCarron [7], Aaron R. Folsom et al[15], Andreas Hvarfner et al[19], Andreas Hvarfner et al[20] and Mario Barbagallo et al [21].

Correlation studies of serum ionized calcium with age [Table/Fig 9] have shown that there was a significant negative correlation between serum ionized calcium and age in the cases (r = -0.283, P < 0.01) and the controls (r = -0.219, P < 0.05). Linear regression analysis showed that the variation in the serum ionized calcium levels because of age in the hypertensives was 8%, whereas that in the normotensives was 4.79% [Table/Fig 9]. It is obvious that age accounts for 1.67 times higher variation in serum ionized calcium in the hypertensives than the variation which was observed in the normotensives. This higher change in serum ionized calcium levels because of age in the hypertensive cases can be ascribed to the mechanisms leading to the pathology of hypertension.

The correlation and regression analysis of serum ionized calcium with age in the hypertensive patients and in the normotensive controls was well supported by Mario Barbagallo et al[21]. These findings in the present study indicate that the reduction in serum ionized calcium levels because of aging is physiological and that the pathology which was related to hypertension had significantly contributed to the process of aging. The same reduction in serum

ionized calcium levels which was expected at an older age in the normotensive population was observed at quite a younger age in the hypertensive patients, which can be credited to the pathological process of hypertension.

Kazushi Tsuda et al[16] found no significant difference in serum ionized calcium between the hypertensive and the normotensive subjects, as the racial and regional differences like dietary habits and genetic variation might have contributed to the difference in the reference levels of serum ionized calcium.

It is becoming evident that the physiology of calcium is altered in essential hypertension. Membrane fluxes and intracellular concentrations of calcium have an acknowledged role in the normal function of both the cardiac and the vascular smooth muscle cells. [7],[13],[14] Data from animal models have further suggested that in hypertension, the smooth muscle is hyper-responsive to changes in extracellular calcium concentrations and that the vascular membrane permeability to calcium is increased.[13]

Calcium exists in 3 major forms in plasma. Approximately 50% is in the free or ionized form, which is the physiologically important fraction, 40% is bound to plasma proteins, and the remaining 10% is in soluble complexes with anions such as bicarbonate, phosphate, and lactate.[22],[23] About 80% of the protein-bound calcium is associated with albumin, with the remaining 20% being associated with globulins.[22] Physiologically, calcium is classified as either intracellular or extracellular. Extracellular calcium provides calcium ions for the maintenance of intracellular calcium levels, bone mineralization, blood coagulation, and plasma membrane potential. Calcium stabilizes the plasma membranes and influences the permeability and excitability. A decrease in the serum free calcium concentration causes increased neuromuscular excitability and tetany; an increased concentration reduces neuromuscular excitability.[22]

Several other investigators have reported positive associations between blood pressure levels and the concentrations of serum total calcium.[9],[24]-[27] On the other hand, some,[7],[15] but not all[9] investigators have noted that, as compared to the normotensive subjects, the essential hypertensive subjects had lower serum ionized calcium concentrations even when the total calcium levels were similar. Our findings generally support this observation. The maintenance of a normal concentration of serum total calcium but a low concentration of ionized calcium suggests an abnormality in the protein binding of extracellular calcium.[7]

It has been hypothesized that due to aberrant transmembrane calcium transport, lower serum ionized calcium levels in the hypertensive subjects may in fact reflect increased levels of intracellular ionized calcium, which would account for the arteriolar vasoconstriction in hypertension.[8],[28]-[33] Blaustein hypothesized that the increase in intracellular calcium levels in hypertension was due to the altered sodium-calcium exchange across the cellular membranes of the smooth muscles.[14] Undertaking epidemiological and clinical studies to measure the effect of calcium on blood pressure are difficult, in part, because other factors such as sodium, potassium, magnesium, parathyroid hormone, and renin may influence the calcium-blood pressure association. Sodium and potassium intake could confound serum calcium levels, because serum calcium levels have been reported to be negatively correlated with 24-hour sodium excretion and positively correlated with potassium excretion.[34]

The possible importance of our observations for the pathogenesis

of hypertension should be assessed in the context of the published observations which are related to the effects of extracellular calcium on the vascular-tissue physiology. In vitro studies have demonstrated membrane stabilization and the consequent relaxation of the vascular smooth muscles by increasing the extracellular levels of ionized calcium.[35],[36] Within populations, the dietary intake of calcium generally, is negatively associated with blood pressure levels. Lower levels of dietary calcium exposure may be a predictor for the development of hypertension.[26],[37]-[44] These views were further confirmed by studies in which calcium supplementations were given to hypertensive patients were found to lower the blood pressure in those patients. [45]

The present findings are also consistent with the comparatively high levels of parathyroid hormone which was noted in patients with essential hypertension.[46] The observed depression in serum ionized calcium may be the proximate stimulus for increased hormone synthesis and release by the parathyroid glands of hypertensive human beings and animals. [47]

All these studies have concluded that serum calcium, particularly ionized calcium, plays an important role in the pathogenesis of essential hypertension. An abnormality of calcium metabolism may be a common denominator for the myriad of the presumably disparate abnormalities of cellular physiology which are associated with essential hypertension. Serum ionized calcium is decreased in essential hypertension and can be controlled with the help of calcium supplementations. In summary, essential hypertension is associated with a variety of perturbations in calcium physiology.

SUMMARY AND CONCLUSIONS

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

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