Serum Calcium Level in Hypertension

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Abstract

Background: The alterations in extracellular calcium level may influence intracellular calcium level and possibly play a role in the pathogenesis of essential hypertension. Aim: The purpose was to find out the association between serum calcium levels and hypertension; and to compare the serum calcium levels between normotensive controls, hypertensive subjects on calcium channel blockers, and hypertensive subjects on antihypertensive medication other than calcium channel blockers. Materials and Methods: Thirty one individuals including normotensives (n = 12) and hypertensives (n = 19) were enrolled for the study and their blood pressure recorded. Hypertensive group was sub divided into two: hypertensives on calcium channel blockers and hypertensives on antihypertensive medication other than calcium channel blockers. Serum calcium levels were measured by Accucare Calcium Arsenazo III kit. Differences between the groups were analyzed using ANOVA. Results: No significant difference in serum calcium level was found between normotensive and hypertensive groups; and no correlation was found between calcium levels and the blood pressure. Also the difference in serum calcium levels in hypertensive group on calcium channel blockers and those on antihypertensive other than calcium channel blockers was insignificant. Conclusions: Serum calcium levels are tightly regulated. Subtle changes in serum levels do not affect blood pressure.

Keywords: Antihypertensive medication, Calcium channel blocker, Hypertension, Normotension, Serum calcium

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Introduction

The overall prevalence of hypertension (HTN) in the population has been reported between 6% and 32%.[1] Disturbed calcium metabolism may play an important role in the pathophysiology of essential hypertension. Ionized calcium (Ca\(^{2+}\)) acts as an intracellular second messenger in excitation-contraction coupling in vascular smooth muscle (VSM) cells. The free intracellular calcium concentration determines the tension in VSM cells, thereby contributing to peripheral vascular resistance (PVR). Increased PVR is found in HTN.[2] Touyz et al.[3] showed significantly increased intracellular calcium levels in HTN. Zidek et al.[4] also found an increased intracellular calcium activity in normotensive subjects with a familial hypertensive disposition in comparison with normotensives without family history of HTN. Recent studies[5,6] indicate that extracellular calcium concentrations also differ between hypertensive and normotensives. Three extracellular calcium fractions: ionized, protein-bound, and complexed calcium are in equilibrium with one another in the serum. Ionized calcium (Ca\(^{2+}\)) is the physiologically active form whereas protein-bound calcium is apparently inactive. The function of complexed calcium, which is bound to small anions such as bicarbonate, citrate, phosphate, and lactate, is uncertain.[7]

Treatment of HTN is multi-dimensional comprising of dietary modification, weight reduction, regular exercise, and medication. The calcium channel blockers (CCBs) namely nifedipine, amlodipine, diltiazem, verapamil, etc., form one of the mainstay treatments in HTN because they considerably reduce the morbidity and mortality in HTN and coronary artery disease. CCBs block the voltage-gated calcium channels in VSM cells resulting in vasodilatation and decrease in peripheral resistance.[8] Since CCBs act on sarcolemma and reduce the entry of Ca\(^{2+}\) from extracellular fluid (ECF) to intracellular fluid.
(ICF), it is assumed that the serum (extracellular) calcium levels may be altered in hypertensive individuals who are on CCBs. This study may give an insight into the role of deranged calcium homeostasis in HTN.

**Materials and Methods**

A total of 31 individuals including 19 hypertensive patients and 12 normotensive subjects in the age group of 35–70 years and belonging to both genders attending the out-patient department of General Medicine were enrolled into the study after taking written informed consent and approval from institutional ethics committee. Hypertensive patients were grouped into two: those who were on CCBs \( n = 9 \) and those who were on antihypertensive medication other than CCBs \( n = 10 \). Systolic blood pressure (SBP) more than 140 mmHg and/or diastolic blood pressure (DBP) more than 90 mmHg with or without previous diagnosis of hypertension were included in hypertensive group. Subjects with SBP less than 140 mmHg, DBP less than 90 mmHg, and without previous diagnosis of hypertension were considered normotensive. Individuals on supplementation with calcium and vitamins including vitamin D were excluded from the study. Subjects with history of diabetes mellitus, ischemic heart disease, retinopathy, neuropathy, and nephropathy were also excluded.

**Blood pressure measurement**

The blood pressure (BP) was measured in the right arm of the subject in sitting position using sphygmomanometer (Diamond Company, Pune, India) after adequate relaxation. SBP and DBP were recorded, pulse pressure (PP) and mean arterial blood pressure (MABP) calculated.

**Estimation of serum calcium**

Venous blood was collected in plain vacutainers and serum was immediately separated by centrifugation. The serum samples were then stored at 4°C and analyzed within 24 hours.

Ionized calcium (Ca\(^{2+}\)) was measured by Accucare Calcium Arsenazo III kit (Lab-Care Diagnostics Pvt. Ltd., Sarigam, India) according to manufacturer’s instructions.\(^{[9]}\) At a neutral pH, Ca\(^{2+}\) forms a complex with Arsenazo III, the color intensity of which is directly proportional to the concentration of calcium in the sample. The normal reference range is 8.8–10.2 mg/dL.

**Statistical analysis**

Statistical analysis was performed using SPSS version 13.0 (SPSS Inc., IL, USA) and Origin Pro version 8.0 (Origin Lab, MA, USA). Levene statistic was performed to test the homogeneity of variances. Differences between the groups were analyzed using analysis of variance (ANOVA) followed by Tukey honest significant difference (HSD) post hoc test. Statistical significance was set at \( P < 0.05 \).

**Results**

Table 1 shows the demographic and test parameters of the participants. Table 2 shows the difference between the normotensives and hypertensives. Serum calcium levels were slightly lower in hypertensives compared with normotensives. Nevertheless, in patients on CCB treatment, serum Ca\(^{2+}\) is more compared with patients on antihypertensive medication other than CCB but these differences are statistically not significant [Figure 1]. Spearman’s correlation between HTN and serum calcium levels is not significant \( (P = 0.18) \). Also linear regression revealed that MABP is not affected by serum Ca\(^{2+}\) levels.

**Discussion**

HTN is a multi-factorial disorder in which various physiological mechanisms participate to elevate BP.\(^{[10]}\) Many hypotheses were proposed about the possible mechanisms underlying essential HTN including derangements in serum electrolytes and water balance. One of the physiologically important ions in the serum is calcium. The present study shows no significant difference in serum calcium in hypertensive group compared with normotensive group which is consistent with the findings of Kosch \textit{et al.}\(^{[11]}\) However the results are contradictory with that of others\(^{[5,12]}\) who reported a significant decrease in serum calcium in patients with essential HTN compared with normotensive subjects. Serum calcium levels were significantly decreased in both males and females with essential HTN and their first-degree relatives when compared with the normotensive controls.\(^{[2]}\) Reichel \textit{et al.}\(^{[13]}\) also reported reduced calcium in males with elevated DBP.

In the present study the serum calcium levels did not correlate with the levels of BP. Serum calcium was found to be significantly correlated with SBP only among those under the age of 40 years.\(^{[14]}\)

Abnormal cellular ion transport resulting in altered membrane control over intracellular calcium may be related to essential HTN. Calcium interacts with other ions—sodium, potassium, magnesium in affecting BP.\(^{[15]}\) Changes in magnesium levels may contribute to altered cell membrane calcium binding in essential HTN.\(^{[16]}\) The free intracellular calcium concentration determines the tension in VSM cells, and thus peripheral vascular resistance. Calcium has direct effect on peripheral vascular tone.\(^{[17]}\)
Increased serum calcium is observed in hyperparathyroidism, vitamin D intoxication, multiple myeloma and some neoplasic diseases of bone. Decreased serum calcium is observed in hypoparathyroidism, vitamin D deficiency, steatorrhea, nephrosis, and nephritis. Increased calciuria is also a feature of the essential hypertensive patients. Alternations in intracellular calcium are thought to be involved in the common pathway mediating the secretion and action of many hormones, including the pressor action of catecholamines and angiotensin II. Intracellular calcium may be involved in regulation of BP. The effects of abnormal calcium and calcium regulating hormone levels may extend to the BP control centers of the central nervous system (CNS), particularly the nucleus tractus solitarius.

Conclusions

No significant difference exists in serum calcium level between normotensive and hypertensive groups. Hypertensive patients on CCB have serum calcium levels more than those on antihypertensive medications other than CCB, although the difference is statistically not significant. A larger sample size may reveal the difference clearly. Serum calcium levels do not correlate with severity of HTN. Derangement in serum calcium levels were observed but cannot delineate the pathogenic mechanism.

Limitations of the study

First, the sample size in each group is small. Second, hormones regulating calcium homeostasis were not measured. Third, intragroup difference based on the specific CCB is not done.

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Table 1: Demographic and test parameters of the participants

| Parameters                  | Normotensives (n = 12) | Hypertensives on CCB (n = 9) | Hypertensives without CCB (n = 10) |
|-----------------------------|------------------------|-----------------------------|-----------------------------------|
| Age (years)                | 52±8                   | 51±12                       | 48±10                             |
| Male gender (%)            | 33.33%                 | 22.22%                      | 50%                               |
| Body mass index (kg/m²)    | 26.58±6.42             | 23.9±3.20                   | 26.58±2.87                        |
| Duration of HTN (years)    | -                      | 5.7±5.7                     | 6.4±2.2                           |
| Systolic BP (mmHg)         | 128±13                 | 150±10                      | 139±25                            |
| Diastolic BP (mmHg)        | 83±7                   | 91±6                        | 89±14                             |
| Pulse pressure (mmHg)      | 45±9                   | 59±6                        | 50±17                             |
| Mean arterial BP (mmHg)    | 98.3±7.98              | 110.74±6.82                 | 105.60±16.73                      |
| Serum calcium (mg/dL)      | 8.97±0.73              | 9.00±0.35                   | 8.56±1.09                         |

Numbers represents mean ± standard deviation except specified as percentage (%) which represents percentage of subjects

Table 2: Differences in serum calcium levels between normotensives and hypertensives

| Parameter          | Normotensives (n = 12) | Hypertensives (n = 19) | P value |
|--------------------|------------------------|------------------------|---------|
| Serum Calcium(mg/dL) | 8.97±0.73             | 8.77±0.83              | 0.50    |

Figure 1: Serum Ca²⁺ levels in different groups
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