



## “A STUDY OF SERUM TOTAL CALCIUM AND SERUM CALCIUM TO PHOSPHORUS RATIO IN ESSENTIAL HYPERTENSION”

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### ABSTRACT

Hypertension is an increasingly important medical and public health burden globally. Worldwide, hypertension is estimated to cause 7.7million deaths, which is about 12- 15% of all total deaths. In recent years a various models of calcium metabolism involving cellular calcium level, membrane binding transport, altered permeability and transport kinetics have been described in individuals with hypertension and in animal models as well. The objective for identifying variations in levels of calcium and phosphorus in hypertensive patients helps to address and reduce risk of Cerebrovascular disease, Coronary artery disease, Chronic kidney disease and Peripheral vascular diseases and thereby morbidity and mortality worldwide. In this study, we attempt to review the evidence that calcium metabolism, thereby change in serum calcium levels that are implicated in primary hypertension in patients visiting medicine OPD and admitted under Department of Internal medicine in Mahatma Gandhi Memorial Hospital, Warangal.

**KEYWORDS :** essential hypertension, serum total calcium, serum calcium phosphorus ratio.

### INTRODUCTION

Hypertension significantly increases the risk of mortality and morbidity of cerebrovascular accidents (both ischaemic and haemorrhagic), coronary artery disease, congestive heart failure, chronic kidney failure, and peripheral vascular diseases.<sup>1,2</sup> More than 140 million people are said to be suffering from hypertension in India and it has been estimated to overhaul the 214 million mark by 2025.<sup>3</sup>

The World Health Organization estimated in 2008 that 33 % men and 32 % women older than 25 years in India suffer from hypertension.<sup>4</sup> Recent estimates have suggested the number of patients with hypertension could increase as much as by 15 to 20%, which could reach close to 1.5 billion by 2025. Essential hypertension is that type of hypertension, for which, no cause can be identified, affecting around 95% of all hypertensive individuals.<sup>5</sup> The primary characteristic of essential hypertension is an increased tone in vascular smooth muscle which results in an increase in total peripheral resistance.

The national family health survey was aimed to evaluate the prevalence of hypertension among young and middle- aged men and women using a representative sampling from all over the country. The study reported an overall prevalence of hypertension as 13.6% and 8.8% in men and women, respectively, between the ages of 15 and 59 years. The study also reported a significantly greater prevalence in the urban populations in comparison to the rural.<sup>6</sup>

### Major Determinants of BP in Primary Hypertension Mechanism Of Essential Hypertension

Hypertension is due to specific causes in a small fraction of cases, but in the vast majority of individuals (≈90%), its etiology cannot be determined; therefore, the essential hypertension term is employed.<sup>7,8</sup>

### Some mechanisms implicated in causing hypertension are:

**Genetic basis of Essential Hypertension:** Common genetic variants influencing BP have been identified at over 300 independent genetic loci. However, these genetic variants typically have effects on the order of only 1.0 mm Hg SBP and 0.5 mm Hg DBP per BP-raising allele. Individually, these genetic variants each explain <0.1% of BP phenotype and collectively <3.5% of total BP variance.<sup>9,10,11</sup>

### Vascular reactivity and remodelling:

Hypertensive patients show greater response to norepinephrine than normotensive individuals. The downregulation of noradrenergic receptors is impaired in hypertension.

### Endothelial dysfunction:

Nitric oxide, a potent vasodilator, which is released by endothelial cells in response to changes in blood pressure, is decreased in hypertensive patients.

**Sympathetic nervous system:** Hypertensive patients have increased sympathetic activity with decreased parasympathetic tone. Alteration

in baroreceptor and chemoreceptor pathways occur both at central and peripheral levels resetting to a higher pressure.

### Inherited cardiovascular factors and hyperinsulinemia:

Approximately, 40% of the hypertensive patients have hypercholesterolemia. There is a strong association between hypertension and type 2 diabetes mellitus.

**Altered calcium metabolism:** Primary hypertension is strongly linked with altered calcium metabolism. Calcium ion acts as an intracellular second messenger in the contractility of cardiac muscle and smooth muscle cells. A rise in total peripheral vascular resistance is a common finding in all forms of hypertension irrespective of the causes. The free intracellular calcium level determines the tension in vascular smooth muscle cells which leads to in peripheral vascular resistance. Calcium affects on the peripheral vascular tone directly.

Disturbed calcium metabolism may play an important role in the pathophysiology of essential hypertension. Ionised calcium (Ca<sup>2+</sup>) 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.* showed significantly increased intracellular calcium levels in HTN.<sup>12</sup>

**Potential role of phosphate in vascular damage:** The endothelial dysfunction caused by a long-term excessive phosphate burden (from a Western diet) may constitute the link between high-normal phosphate levels and cardiovascular mortality in the general population. The mechanisms of phosphate-induced vascular calcification (VC) and endothelial dysfunction (ED). eNOS, endothelial nitric oxide synthase; ICAM, intercellular adhesion molecule; ROS, reactive oxygen species; VCAM, vascular cell adhesion molecule.<sup>13</sup>

### Definition And Classification:

BP is a quantitative trait that is highly variable<sup>1</sup>; in population studies, BP has a normal distribution that is slightly skewed to the right.<sup>14</sup>

### Blood Pressure Classification In Adults (jnc 7)

BP CLASSIFICATION	SBP (mm of Hg)	DBP ( mm of Hf)
<b>NORMAL</b>	< 120	And < 80
<b>Pre hypertension</b>	120- 139	Or 80-089
<b>Stage 1 Hypertension</b>	140-159	Or 90-099
<b>Stage 2 Hypertension</b>	>/= 160	Or >/= 100

### American College of Cardiology (ACC) guidelines

JNC VII criteria was used to define hypertension in the study population. Cut off value for normotensives were taken as Systolic BP <120 mmHg and Diastolic BP

<80 mmHg. Informed consent was taken from all the subjects. A detail history including diet, smoking and alcohol habits, lifestyle, drug, and treatment history were taken into account.

**Pathological Consequences of Hypertension:**

Hypertension is a well-known risk factor for all the clinical manifestations associated with atherosclerosis. It is an independent predisposing factor of congestive heart failure, coronary heart disease, cerebrovascular accident, kidney disease and peripheral vascular diseases.

**Materials And Methods**

**Source of Data:** Patients coming to Mahatma Gandhi Memorial Hospital, Warangal

**Sample Size:** 200 Subjects, 100- Cases and 100-Controls.

**Study Design:** CASE-CONTROL STUDY

**Sample Design:** Simple random sampling

**Duration of study:** Two years from November 2019 to October 2021

**Inclusion Criteria:**

- i. Patients with Newly diagnosed Essential hypertension
- ii. Patients whose age is above 18 years.

**Exclusion Criteria:**

- i. Patients who are below 18 years
- ii. Patients who are on Vitamin D and Calcium supplementation
- iii. Patients with Primary kidney disease/Chronic Kidney disease
- iv. Chronic Liver disease
- v. Secondary Hypertension
- vi. Pregnancy
- vii. Drugs influencing Calcium and Phosphorus metabolism

**RESULTS:**

The mean, median and standard deviation of the study population on various parameters are given below in the table.

**Table 1 : Mean, Median And Standard De**

PARAMETER	Median	Mean	SD	Minimum	Maximum
<b>BMI</b>	21.6	22.55	2.8	18	31
<b>AGE</b>	44	44.1	11.8	18	76
<b>Calcium (mg/dL)</b>	8.9	8.9	0.58	8	10
<b>Phosphorus (mg/dL)</b>	3.3	3.2	0.65	1.88	4.32
<b>CP Ratio</b>	2.7	2.78	0.63	2.14	4.6

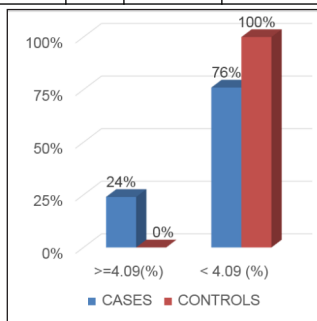
Out of all the participants, 62 % of the cases showed decreased serum calcium level while 24 % of the controls showed decreased serum calcium level with p value <0.001.

Only 38% of the cases had normal serum calcium level while 76 % of the controls had normal serum calcium level. (Pearson Chi-Square: 11.24, OR: 4.81; 95%: 1.78 – 12.9; p Value: <0.001)

Cutoff using lower limit of range

**Table 2: Serum Total Calcium Of The Patients**

SERUM CALCIUM	<8.70	<8.70 (%)	>=8.70	>=8.70(%)
<b>CASES</b>	62	62%	38	38%
<b>CONTROLS</b>	24	24%	76	76%
<b>TOTAL</b>	86	43%	114	57%



**FIG 1: Graph showing Calcium Phosphorous ratios in Cases and controls**

**Multivariate analysis by logistic regression**

**Table 3: Logistic Regression Model For Factors Associated With Hypertension**

Variable	MULTIVARIATE ANALYSIS						
	OR	95% C.I		Chi Sq.P-value	OR	95% C.I.	
		(unadjusted)	Lower			Upper	(adjusted)
<b>Female</b>	0.931	0.422	2.102	0.83	0.9	0.34	2.6
<b>Serum calcium &lt;8.70mg/dl</b>	4.78	2.01	11.24	<b>0.0031*</b>	4.81	1.78	12.9
<b>CP ratio &gt; 2.7</b>	4.61	1.98	10.51	<b>0.0022*</b>	5.31	1.9	14.8
<b>Smoker</b>	1.199	0.525	2.8	0.06	3.41	0.98	11.94
<b>BMI &gt;=25</b>	2.85	0.91	8.955	0.321	2.08	0.48	8.24
<b>Age &gt;=44yrs</b>	2.91	1.29	6.544	0.115	2.42	0.84	6.58

To adjust for potential confounders, selected variables from the Univariate analysis were analyzed. A logistic regression model was derived by entering the following variables: Sex, serum calcium <8.70 mg/dl, CP ratio >2.7, smoking history, BMI >=25 and Age >=44years. In this regression model Serum calcium <8.70 mg/dl [Adjusted OR 4.78 (95%CI 1.78-12.9)] and CP ratio >2.7

In other words the odds of a patient with hypertension is 4.78 times more likely to have a serum calcium level less than 8.70 mg/dl as compared to a non-hypertensive and the odds of a patient with hypertension to have a CP ratio >=2.7 is 4.61 more than that of a normotensive individual.

**DISCUSSION**

Using the multivariate analysis, we observed that participants with low serum total calcium are significantly associated with hypertension after adjusting for confounding factors. Several other investigators have reported positive associations between blood pressure levels and the concentrations of serum total calcium. On the other hand, some, but not all investigators have noted that, as compared to the normotensive subjects, the essential hypertensive subjects had lower serum ionised 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 ionised calcium suggests an abnormality in the protein binding of extracellular calcium.

It has been hypothesised that due to aberrant transmembrane calcium transport, lower serum ionised calcium levels in the hypertensive subjects may in fact reflect increased levels of intracellular ionised calcium, which would account for the arteriolar vasoconstriction in hypertension. Blaustein et al<sup>15</sup> hypothesised 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. 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.

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 stabilisation and the consequent relaxation of the vascular smooth muscles by increasing the extracellular levels of ionised calcium. 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. These views were further confirmed by studies in which calcium supplementations given to hypertensive patients were found to lower the blood pressure in those patients.

**Summary**

- i. Majority of our patients were in the age group of 40 – 55.
- ii. Males outnumbered Females slightly.
- iii. Most of the patients had normal body mass index.
- iv. Positive family history had only a slight association with Essential hypertension.
- v. Obesity may be an independent risk factor for low serum calcium.

- vi. Smoking and alcohol habits did not show any relationship with essential hypertension.
- vii. There was a significant association between serum total calcium, serum calcium / phosphorus ratio with essential hypertension.

## CONCLUSION

Hypertension is an emerging health problem in India. Hypertension significantly increases the risk of mortality and morbidity of cerebrovascular accidents (both ischaemic and haemorrhagic), Coronary artery disease, Congestive heart failure, Chronic kidney failure, and Peripheral vascular diseases. When majority of people come to know that they have hypertension they have already advanced into a stage with target organ damage - a fatal stroke or Myocardial infarction or Irreversible renal failure.

In addition to a primary increase in cardiac function propelled by increased activity in the sympathetic nervous system, primary retention of cations and water by kidney, other factors contributing to hypertension are genetic predisposition, low serum calcium level, high Sodium and low excretion, low Potassium and low calcium intake and increased excretion. Many recent studies have implicated serum calcium level in the role of development of hypertension and increasing evidence are emerging supporting this theory. This tendency has been observed even in pregnant women.

Thus, in addition to the routine dietary restriction salt in hypertensive individuals, estimation of serum calcium level and calcium / phosphorus ratio may be considered in patients with essential hypertension when planning for a treatment strategy and addition of oral calcium supplement in diet may offer a favorable outcome.

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