

# Serum calcium and magnesium in patients with Essential hypertension and their first degree relatives

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**Abstract** – Hypertension mostly essential is a major cardiovascular problem across the globe. Electrolytes like calcium and magnesium are linked with the pathophysiology of essential hypertension by various studies. Although a handful of studies are conducted worldwide including India, drawing their causative association with hypertension; but such a study was never conducted among the population of the north-east India. So, with this aim the pioneering study to verify the association of serum calcium and magnesium in essential hypertensives and their first degree relatives was conducted among 345 subjects of north east India. The study vividly draws significant results statistically ( $p < 0.001$ ), with serum calcium and magnesium levels being low in hypertensives when compared with normal subjects. The study also hints towards a genetic predisposition of hypertension; serum calcium levels were significantly low ( $p < 0.001$ ) among the first degree relatives of hypertensive patients, though serum magnesium did not show any such correlation. This study thus opens new avenue for the prevention as well as management of essential hypertension.

**Keywords** – essential hypertension, serum calcium, serum magnesium, first degree relatives

## 1. Introduction

Hypertension as a clinical entity is one of the most prevalent cardiovascular disorder with significant morbidity and mortality worldwide. An estimate shows that 26% of the adult population experiences hypertension and this is expected to rise to 29% by the year 2025 as estimated by Kearney et al [1]. Of all case of hypertension essential hypertension accounts for 90% of cases and is the 13<sup>th</sup> leading cause of death in the United States [2].

Calcium metabolism abnormalities have been suggested in essential hypertension by many researchers [3, 4]. Many researchers have hypothesized that abnormalities of calcium homeostasis at both organ and cellular level are a primary factor in the pathogenesis of human and experimental hypertension [5]. Zidek *et al* found an increase intracellular calcium activity in normotensive subjects with a familial hypertensive disposition in comparison with normotensives without family history of hypertension [3]. This is also supported by Sudhakar, Sujatha, Babu, Padmanathi and Reddy who found significantly decreased serum calcium levels in patients with essential hypertension and first degree relatives when compared with the controls [6]. Also, Coelho, Alves and Valle found that along with disturbance in sodium distribution, calcium and potassium alteration may play a role in regulating and sustaining essential hypertension [7]. While calcium is essential in the normal cycling of all cells, the cation's multiple functions have been best delineated in the vascular smooth muscle cell [3]. From observational studies, an inverse association between dietary calcium intake and blood pressure level has repeatedly been reported [8-11]. Some research has pointed to calcium supplementation as a means of relieving high blood pressure [8-12].

Disturbances of magnesium metabolism have a significant effect on vascular smooth muscle contractility as shown by extensive studies on experimental animal models [13]. Low magnesium states lead to insufficient production of prostaglandin E1, leading to vasoconstriction and increased

BP [14]. It is further suggested that diuretics like thiazides commonly prescribed for treatment of hypertension, induces a major change in the electrolyte balance of the body [15-18], and magnesium is suggested to influence the relation between extracellular and intracellular potassium [15,16]. A combination of factors like decrease of sodium, and the increase of potassium, calcium, and magnesium intakes, which are characteristic of the so-called Dietary Approaches to Stop Hypertension diets, has an excellent blood pressure lowering effect [19].

A significant heritable component to blood pressure levels in hypertension is documented by various adoption, twin, and family studies [20-22]. Estimates based on family studies, describes that the heritability of resting systolic and diastolic blood pressures, are generally in the range of 15% to 35%. In twin studies, heritability estimates of blood pressure are  $\approx 60\%$  for males and  $\approx 30\%$  to  $40\%$  for females [21]. Some investigations have suggested a genetic defect in handling of electrolyte in patient with hypertension and in their normotensive relatives [23]. A large proportion of the phenotypic variation in blood pressure appears to be inherited as a polygenic trait [24-26].

Thus, keeping in view the above context "a study of serum calcium and magnesium levels in patients with essential hypertension and their first degree relatives" was conducted, which is the first study of its kind in northeastern part of India.

## 2. Materials and Methods

The present study is conducted in the Department of Biochemistry in collaboration with the Out Patient Department of Cardiology of Gauhati Medical College and Hospital. The study is approved by the research and ethical committee of Gauhati Medical College and Hospital. A total of 345 individuals from north eastern region of India, irrespective of age and sex were selected. As per the plan of

the study, the target population was divided into three main groups as follows:

**Normal Control group:** comprising 115 normal healthy subjects between 20-50 yrs of age.

**Experimental or Test group:** comprising 115 patients between 20 and 50 yrs of age, who were recently diagnosed of having essential hypertension, not on medication, and free from any disease that might affect blood pressure or serum electrolyte level under study.

**First Degree Relative(FDR) group:** comprising 115 first degree relatives of the Test group, who were between 20-50 yrs of age.

In every case, a careful history was taken and a thorough examination done. Also their contact details were properly taken so that diagnosis of essential hypertension (Hypertension defined as per JNC VII guidelines) could be confirmed on further visits to the hospital. Routine investigation like estimation of blood sugars, serum creatinine, blood urea, total protein and protein fraction, cholesterol and a complete blood count were done in every case to exclude any disease or factors known to cause hypertension.

All routine biochemical investigations were done using Vitros 350 Dry Chemistry system of Jhonson and Jhonson. Estimation of serum calcium and serum magnesium were also done using Vitros 350 Dry Chemistry system of Jhonson and Jhonson. Result values of test group and first degree relative group were compared with normal control group by "t" test and probability (p) is calculated by observing values of "t" at a particular degree of freedom (DF) [27].

### 3. Results

In the present study, majority of the essential hypertensive patients attended were in the age group of 35-45 years of age, of which 39 were female and 76 were males. In case of the first degree relative group, majority of the subjects were in the age group 20-40 years, of which 37 were females and 78 were males.

In the current study, Serum Calcium level of test group have a significantly lower values as compared to the control subjects ( $p < 0.001$ ). The control group comprising of 115 individuals have a mean serum Calcium level of  $9.26 \pm 0.44$  mg/dl, ranging from 8.4 mg/dl -10.1 mg/dl; while the test group has a mean value of  $8.23 \pm 0.49$  mg/dl, ranging from 7.6 mg/dl - 9.5 mg/dl. The First degree relative group has a mean serum Calcium level of  $8.27 \pm 0.61$  mg/dl, ranging from 7.6 mg/dl - 9.8 mg/dl, and it is statistically significant ( $P < 0.001$ ), when compared with the control group. In the present study, mean serum magnesium level is  $1.45 \pm 0.25$  mg/dl in the test group, ranging from 0.9 mg/dl – 2.1 mg/dl, while it is  $1.99 \pm 0.24$  mg/dl in the control group, ranging from 1.6 mg/dl – 2.5 mg/dl. Thus the present study draws a statistically significant ( $p < 0.001$ ) correlation between serum magnesium levels of hypertensive when compared with the normotensive controls. The present study however does not show any significance statistically ( $p = > 0.1$ ) when the mean serum magnesium level of the control and the first degree relatives of the hypertensive group are compared; the mean level being  $1.99 \pm 0.24$  mg/dl and  $1.90 \pm 0.31$  mg/dl respectively.

Table 1. Serum calcium (mg/dl)

	CONTROL	TEST	FDR
n†	115	115	115
AVAERAGE(MEAN)	9.26	8.23	8.27
SD±*	0.44	0.49	0.61
	DF ††	t VALUE	P VALUE
BETWEEN CONTROL & TEST	228	13.919	<0.001
BETWEEN CONTROL & FDR	228	14.143	<0.001

Table 2. Serum magnesium (mg/dl)

	CONTROL	TEST	FDR
n†	115	115	115
AVAERAGE(MEAN)	1.99	1.45	1.90
SD±*	0.24	0.25	0.31
	DF ††	t VALUE	P VALUE
BETWEEN CONTROL & TEST	228	16.875	<0.001
BETWEEN CONTROL & FDR	228	2.432	>0.001

Abbreviation used in the tables above: \* - standard deviation, † - total number of cases, †† - degree of freedom.

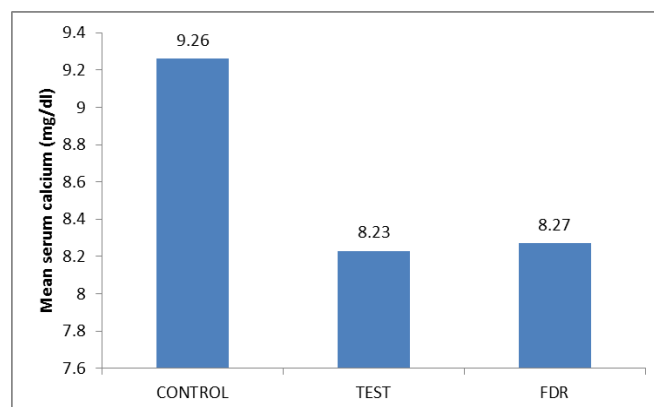


Figure 1. shows the means of serum calcium (mg/dl) in the three groups.

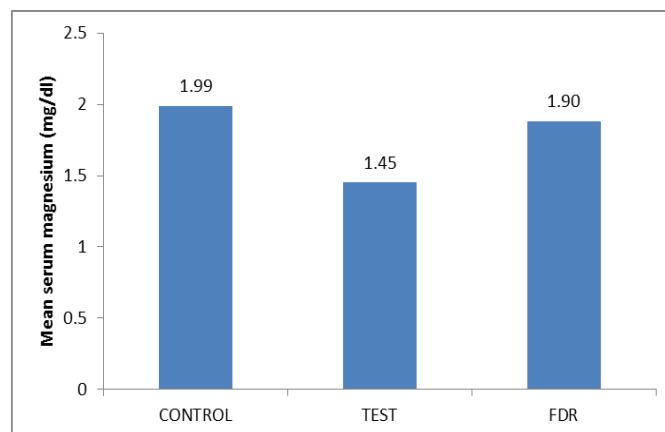


Figure 2. shows the means of serum magnesium (mg/dL) in the three groups.

### 4. Discussion

The present study shows significant decrease in serum calcium levels of hypertensive and their first degree relatives when compare with normotensive controls, and the results are in close agreement with that of others who also found a significant decrease in serum Calcium in patients with essential hypertension [28, 29]. Though there are not enough study describing the relation of serum calcium in the first

degree relatives of hypertensive patients, but the findings of the present study are in agreement with that of Sudhakar, Sujatha, Babu, Padmanathi and Reddy [7].

The free intracellular calcium concentration determines the tension in vascular smooth muscle cells, thereby resulting in peripheral vascular resistance. Calcium has direct effect on peripheral vascular tone [30]. Calcium ions play a major role as an intracellular second messenger in excitation-contraction coupling in cardiac and smooth muscle cells. Calcium role in cell relaxation is correlated with a decrease in cytosolic calcium. The reduction of cytosolic calcium is achieved by the sarcoplasmic reticulum reuptake of calcium and the movement of the cation across the sarcolemmal membrane [31]. Sarcoplasmic reticulum reuptake is dependent on the calmodulin-calcium activation of Ca-ATPase. Both Ca-ATPase and the sodium-calcium exchange are important in the efflux of calcium across the sarcolemmal membrane [32-34]. In addition to these direct effects of calcium and calmodulin on the maintenance of lower cytosolic calcium concentrations, there is at least one other possibly important controlling point: the activation of adenylate cyclase by calcium and calmodulin [35]. Calcium by itself will inhibit adenylate cyclase and thereby cyclic AMP generation [35]. Cyclic AMP is thought to mediate vasodilation through its protein kinase-dependent phosphorylation of myosin light chain kinase [36]. It is thought that the alternations in intracellular calcium are involved in the common pathway mediating the secretion and action of many hormones, including the pressor action of catecholamines and angiotension II. Calcium regulating hormones like 1, 25 dihydroxy vitamin D, levels of plasma rennin activity, circulating ionized calcium contribute to the pathophysiology of essential hypertension [37, 38].

The present study also shows significant decrease in serum magnesium levels of hypertensive when compared with normotensive controls, and the results are in close agreement with that of others who also found a significant decrease in serum magnesium in patients with essential hypertension [19, 39]. The present study fails to draw any significant relation of serum magnesium between normotensive control and the first degree relatives of hypertensive patients, which is in contrast to study conducted by Sudhakar *et al* [40].

Magnesium is described to be involved in maintaining a balance between extracellular and intracellular potassium especially in patients receiving thiazide diuretics [15, 16]. Magnesium deficiency predisposes to potassium deficiency and may induce refractoriness to potassium repletion [16]. Furthermore, magnesium is described to have a direct effect on vascular smooth muscle [13]. Petersen *et al* found an inverse correlation between serum magnesium concentrations and blood pressure in hypertensives who were not on agents influencing magnesium metabolism [41]. Studies also described an inverse correlation between the concentration of magnesium in drinking water and the level of arterial blood pressure [42]. It is also found that hypertensives with hypomagnesemia require more antihypertensive medications than normal controls [43]. A recent study conducted by Sudhakar *et al* has described the heritable role of magnesium as a causative factor for essential hypertension [40].

Essential hypertension is regarded as a multifactorial

condition, the onset and severity of which are influenced by both genetic and environmental factors. The role of genetic factors in the aetiology of hypertension is supported by cross-sectional studies that document familial aggregation of the disorder despite different environmental factors. Twins and adoption studies have indicated a greater degree of trait concordance among identical compared with dizygotic twins and among natural compared with adoptive siblings respectively, which also stress the importance of genetic factors. The exact form of the underlying genetic mechanism remains unanswered. Estimates of genetic variance range from 20–50% [44-50].

## 5. Conclusion

The current study on calcium and magnesium on essential hypertensives and their first degree relatives was undertaken in an effort to draw an inference on any observed behavior in the proposed study, and if there is any scope for future utility. The study reveals a significant relation between essential hypertension and the states of hypocalcemia and hypomagnesemia. Further the study also reveals a state of hypocalcemia in the first degree relatives of hypertensives, which may infer the first degree relatives to be future hypertensives. The study thus hints towards a genetic predisposition of hypertension resulting in a state of electrolyte deficiency in genetically predisposed individuals. The study therefore opens avenues for prevention and treatment of hypertension by electrolyte estimation and their therapeutic supplementation.

Diagnosis and management of essential hypertension lays on the subject a lot of physical, mental and financial burden. So, if essential hypertension can be treated or managed or some prophylactic measures can be taken by supplementing electrolyte formulations in these subjects, then mankind can be saved from global problems of essential hypertension. With this idea this study proves to be very helpful.

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