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Dr. Diwakr Naidu G
Associate Professors, Department of General Medicine, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

Dr. Balaji Prasad Naik
Associate Professors, Department of General Medicine, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

Corresponding Author:
Dr. Balaji Prasad Naik
Associate Professors, Department of General Medicine, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

A study on serum calcium in patients with essential hypertension: A cross sectional study

Dr. Diwakr Naidu G and Dr. Balaji Prasad Naik

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Abstract
Background and Objective: Serum calcium levels have been shown to be associated with cardiovascular disease (CVD); however, it is not clear whether serum calcium levels are related to hypertension, a risk factor for CVD.
In a country like India, people tend to have a diet rich in Sodium and poor in Potassium and Calcium. Studies have shown that a decreased intake of Sodium and increased Calcium intake or both together may be effective in prevention or even treatment of hypertension. So efforts were made to correlate the serum calcium levels with blood pressure.
Methodology: The present study attempts to focus the serum calcium and serum ionized calcium among essential hypertensives who were free from any other illness (or) under any medication and to correlate serum calcium and serum ionized calcium status with the blood pressure. Serum calcium and ionized calcium was estimated in fifty hypertensives (M= 26, F=24) & fifty healthy controls (M=28; F=22).
Results: Out of the 100 cases, mean serum calcium level was 8.1 ± 0.9 mg/dl whereas in 100 controls, it was 9.0 ± 0.8 mg/dl and the difference was significant with _p 'value of <0.001. Mean Serum ionized calcium level was 4.3 ± 0.4 mg/dl in cases and it was 4.8 ± 0.4 mg/dl in controls with _p 'value of <0.001. The blood pressure also correlated positively with body mass index and random blood sugar whereas negatively correlated with Serum Calcium and serum ionized calcium.
Conclusion: Serum calcium and serum ionized calcium was significantly less among hypertensives and correlated negatively with blood pressure. In view of the significant changes in Serum Calcium among Hypertensive population, community must be motivated to consume Calcium rich diet as a form of primary prevention for essential Hypertension. Body mass index correlated positively with blood pressure suggesting that people should be motivated for healthy life style and to maintain BMI in normal range.

Keywords: Hypertension, serum calcium, serum ionized calcium, body mass index, random blood sugar

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.
Hypertension is an emerging health problem in India. 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. Unfortunately even in developed countries like United States, 77.9 million people are found to have hypertension. Of these 78% are aware of their diagnosis, but only 68% are receiving treatment and only 64% are under control [2].
In addition to a primary increase in cardiac function propelled by overactive sympathetic nervous system, primary retention of salt and water by kidney, other factors contributing to hypertension are hereditary predisposition and high sodium and low potassium intake and excretion.

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

Objectives

1. To estimate serum total calcium and ionized calcium in patients with primary hypertension and compare it with that of the normotensive individuals.
2. To find the correlation of serum total calcium and serum ionized calcium with the systolic blood pressure and diastolic blood pressure in patients with essential hypertension.

Materials and methods

Source of data: Patients visiting Medicine out patient of, SIMS during the period of 1st June 2018 to 31st May 2019 were taken for our study considering the inclusion and exclusion criteria.

Method of collection of data: Information was collected through a pretested and structured preform for each patient. Qualifying patients will be undergoing detailed history, clinical examination and laboratory investigations.

Type of study: Cross Sectional study.

Inclusion criteria

- **Controls:** Normotensive healthy individuals within the age group of 18 to 60 years of both the sexes.
- **Cases:** Diagnosed essential hypertensive patients aged between 18 to 60 years of both the sexes and who fulfill the JNC-8 criteria of hypertension for the above mentioned age group, having diastolic blood pressure (DBP) ≥90 mmHg, or having systolic blood pressure (SBP) ≥140 mmHg.

Exclusion Criteria

1. Patients with secondary hypertension like chronic kidney disease, Pheochromocytoma etc.
2. Patients with any endocrine disorder.
3. Patients suffering from diseases of liver, and kidney, diabetes mellitus, ischemic heart disease and congestive heart failure.

Statistical analysis

i. Unpaired t 'test' was used to compare the values of serum total calcium and serum ionized calcium between cases and controls.
ii. Pearson correlation will be applied to correlate the parameters with SBP and DBP in patients with essential hypertension.

Consent

The study group thus identified by the above criteria (inclusion and exclusion criteria) was first instructed about the nature of the study. Willing participants were taken up after getting a written informed consent from them.

Details of the Study Subjects

All the patients were subjected to detailed history taking, careful physical examination.

Patient's height and weight were measured. The body mass index was calculated using the formula weight / height.^{2} All the peripheral pulses were checked with special attention to carotid and the femoral to detect evidence for early atherosclerosis. An ocular fundus examination was done to detect hypertensive retinopathy.

Patients were informed to refrain from smoking or drinking tea or coffee for at least thirty minutes before measuring blood pressure.

Statistical Analysis

The data was entered in Microsoft Excel and analyzed using EpiData analysis software. The continuous variables like age, blood pressure, random blood glucose, serum albumin, BMI, serum calcium and ionic calcium were summarized as mean and standard deviation. The categorical variables such as age categories, gender, hypertension status, behavioral factors, stage of hypertension, family history of hypertension, fundus and ECG status were described as proportions. The difference between the age, blood pressure, calcium levels, random blood glucose, serum albumin, and BMI between the two groups was analyzed used students independent t test. The association between categorical variables such as age categories and gender between the two groups was identified using Chi square test. The correlation between serum calcium levels and blood pressure of the participants was found using Pearson correlation. P value <0.05 was considered for statistical significance.

Results

The total number of subjects included in this study was 200. Among these 200 subjects, 100 were cases (Hypertensive) and 100 were controls (Normotensives).

Analysis of cases and controls with respect to age

The age of the subjects in the study group ranged from thirty five to sixty years. The mean for the age of the cases and controls were 44.5 years and 46.5 years respectively. The study group and the control group did not differ from each other statistically with reference to age.

Table 1: Distribution of cases and control in relation to age groups

Age groups	Hypertensive patients N (%)	Non Hypertensive N (%)	Chi Square	Odds Ratio (95% CI)	P value
<45 years	28 (58.3)	20 (41.7)	1	1	
46-55 years	48 (49.0)	50 (51.0)	0.57	0.70 (0.27-1.85)	0.453
>55 years	24 (44.4)	30 (55.6)	0.99	0.58 (0.20-1.75)	0.323

Gender: Among the 100 cases studied, there were 52 males and 48 females. Among the 100 controls, there were 56 males and 44females (Table 2 and graph 3).

Table 2: Gender distribution of the study participants between the groups

Gender	Hypertensive Patients N (%)	Non Hypertensive N (%)	Chi Square	Odds Ratio (95% CI)	P value
Male	52 (48.1)	56 (51.9)	1	1	
Female	48 (50.0)	44 (50.0)	0.018	1.09 (0.37 – 3.25)	0.896

Family History: Among 100 cases there were 62patients (62%) with positive family history.

Table 3: Distribution of cases by family history

Family history of hypertension	Cases
Present	62
Absent	38

Symptoms: Among cases, there were 32 patients who did not have any symptoms, 26 patients with chest pain, 16 with giddiness, 18 with headache and 8 patient with palpitation were taken up for study.

Body Mass Index: Among cases 82 (82%) were found out to be in obese group (BMI ≥25 Kg/m^2) compared to 42 (42%) in controls. 10 cases (10%) were overweight (BMI 23 to 24.9 Kg/m^2) while 34(34%) controls were overweight.

Table 4: Distribution of cases and controls with respect to Body Mass Index (BMI)

BMI	Cases	%	Controls	%	Total
Underweight <18.5	0	0.0	0	0.0	0
Normal weight 18.5-22.9	6	6.0	24	24.0	30
Overweight 23-24.9	10	10.0	34	34.0	44
Obese > 25	84	84.0	42	42.0	126
Total	100	100.0	100	100.0	200

Significant difference was found in mean BMI of cases (27.3) compared to mean BMI of controls (24.9). Details given below shows that BMI of cases is significantly higher in cases than in controls.

Table 5: Body mass index of the participants in two groups

	Hypertensive patients Mean (SD)	Non Hypertensive Mean (SD)	T Test	P value
Body Mass Index	27.3 (2.83)	24.9 (2.4)	20.9	<0.001

Among cases males had the mean BMI of 27.4 and in females BMI was 27.2 which was significantly higher than controls where in males, mean BMI was 25.1 and in females it was 24.6.

Table 6: Mean BMI values of cases and controls based on gender

Gender	BMI of Hypertensive patients Mean (SD)	BMI of non-Hypertensive Patients Mean (SD)	T Test	P Value
Male	27.4 (2.3)	25.1(2.9)	10.6	0.002
Female	27.2 (3.5)	24.6 (1.9)	9.39	0.004

Among 14 grade 1 hypertensive 13 were obese and among 37 grade 2 hypertensive 29 were obese. This shows that hypertension was more seen in obese cases than in normal.

Table 7: BMI with respect to grades in cases

BMI	Grade 1	%	Grade 2	%	Total
Underweight <18.5	0	0.00	0	0.00	0
Normal weight 18.5-22.9	0	0.00	6	100	6
Overweight 23-24.9	2	40	8	80	10
Obese > 25	26	62	58	69	84
Total	28	56	72	72	100

Comparison of cases and controls with SBP and DBP scores

The following table shows that SBP in cases (164±11.4 mm Hg) was significantly higher than in controls (119±8.3 mm Hg) and DBP was also high in cases (102±6.5 mmHg) than in controls (75± 6.4 mm Hg).

Table 8: Comparison of cases and controls with SBP and DBP scores by t test

Blood Pressure	Hypertensive Patients Mean (SD)	Non Hypertensive Mean (SD)	T Test	P Value
Systolic Blood pressure (mm/Hg)	165 (11.5)	120 (8.4)	519.8	<0.001
Diastolic Blood pressure (mm/Hg)	103 (6.5)	76 (6.4)	410.2	<0.001

Serum calcium value of the participants in two groups

Serum Calcium was significantly lower in Hypertensive than in normotensives with p value of <0.001 which is depicted in following table.

Table 9: Serum calcium value of the participants in two groups

	Hypertensive patients Mean (SD)	Non hypertensive Mean (SD)	T Test	P Value
Serum Calcium (mg/dl)	8.2 (0.9)	9.1 (0.8)	31.7	<0.001

Serum calcium level - overall between Genders

There was no statistically significant difference in serum calcium values in males and females in cases and controls combined.

Table 10: Serum calcium level - overall between Genders

	Male Mean (SD)	Female Mean (SD)	T Test	P Value
Serum Calcium (mg/dl)	8.7 (0.98)	8.6 (0.98)	0.12	0.738

Serum ionized calcium value of the participants in two groups

Serum ionized Calcium was significantly lower in Hypertensive than in normotensives with p value of <0.001 which is depicted in following table.

Table 11: Serum ionized calcium value of the participants in two groups

	Hypertensive Patients Mean (SD)	Non Hypertensive Mean (SD)	T Test	P Value
Serum Ionized Calcium (mg/dl)	4.4 (0.4)	4.9 (0.4)	27.0	<0.001

Serum ionized calcium values - overall between genders

There was no statistically significant difference in serum ionized calcium values in males and females in cases and controls combined with p value of 0.534.

Table 12: Serum ionized calcium values - overall between genders

	Male Mean (SD)	Female Mean (SD)	T Test	P Value
Serum ionized Calcium (mg/dl)	4.8 (0.44)	4.7 (0.46)	0.40	0.534

Table 13: Random blood sugar values of the participants in the two groups

	Hypertensive Patients Mean (SD)	Non Hypertensive Mean (SD)	T Test	P Value
Random blood sugar values (mg/dl)	140.0 (21.4)	116.8 (25.0)	24.8	<0.001

Serum albumin values of the participants in the two groups

There was no statically significant difference in serum albumin levels in cases and controls.

Table 14: Serum albumin values of the participants in the two groups

	Hypertensive Patients Mean (SD)	Non Hypertensive Mean (SD)	T Test	P Value
Serum albumin values (mg/dl)	4.7 (0.5)	4.66 (0.4)	0.00	0.951

Fundus examination

Among the hypertensive 60 (60%) had normal fundus examination, 26 (26%) had grade 1 hypertensive retinopathy and 14 (14%) had grade 2 hypertensive retinopathy.

ECG

Among th**e** hypertensive 56 (56%) had normal ECG findings and 44 (44%) had changes suggestive of left ventricular hypertrophy.

Risk Factors

Among the cases 56(56%) were non-smoker and non-alcoholic, 14(14%) were smokers, 12(12%) were alcoholics and 18(18%) had both the habits.

Discussion

Hypertension is one of the leading causes of death and disability among all over the world. Hypertension is the most common form of cardiovascular disease and is present nearly 25% of adults and increases in prevalence with age. It remains the major risk factor for coronary, central and peripheral vascular disease. Essential hypertension comprises more than 90% of hypertension [1]. Approximately 54% of all strokes and 47 % of all IHDs are attributed to hypertension [4].

Patients were studied on the basis of clinical parameters and simple Biochemical investigations. Serum calcium, serum albumin and serum ionized calcium were done for all the patients. In our study the mean serum calcium was estimated in the control and study groups. In cases, the mean serum calcium level was 8.2±1.0 mg/dl where in controls, it was 9.1±0.8 mg/dl and mean serum ionized calcium in hypertensive patients was 4.4±0.4 mg/dl and in non-hypertensive patients it was 4.9±0.4 mg/dl. Similar study was conducted by Kamlesh Jha, *et al.* (September 2011). In this study serum calcium levels were measured in 80 cases of essential hypertension which included 37 cases of grade I and 43 cases of grade II hypertension. The result showed that serum Calcium levels were significantly decreased in grade I ($p< 0.0001$) as well as grade II ($p< 0.0001$) hypertension cases when compared to age matched normotensive control.5 Kaushik, *et al.* found that mean ionized calcium in hypertensive patients was 4.6±0.108mg/dl and in non-hypertensive patients was 4.1±0.115mg/dl which matched with our study [6].

Takale LR, *et al.* conducted a study involving 40 healthy and 40 hypertensive subjects which showed reduced total free calcium levels in hypertensive subjects as compared to controls [7].

Devendra P. Singh *et al*. in their study of serum calcium and magnesium in hypertensive and normotensive subjects concluded that serum calcium is significantly lower in hypertensive compared to normotensives in age group <60 years [8].

Booloo Sharma, *et al.* who studied serum calcium and magnesium levels in hypertensive showed calcium levels to be low in hypertensives [9].

In Touyz RH, *et al.* study conducted in Johannesburg, South Africa states that the heterogeneous status of magnesium and calcium metabolism in hypertensive population may be related to the plasma renin activity (PRA). 39 normotensive (20 black, 19white) and 47 hypertensive (2 black, 22 white) subjects were studied. PRA and ionized calcium were significantly lower in black hypertensive as compared with the white hypertensive group (1.99±0.3 vs 5.6±1.02ng) ml/h for RA; 1.28±0.07 vs 1.42±0.01mmol/l for ionized calcium: black hypertensive as compared with white hypertensive group ($p< 0.05$). Ionized calcium was significantly decreased ($p< 0.05$) in white hypertensive patient as compared with the normotensive control (1.29±0.01 vs 1.45±0.04 mmol/l) [10].

In a study conducted by Sudhakar, *et al.* in 2004, Serum calcium levels were measured in 117 subjects with essential hypertension and 77 first-degree relatives. The results showed that serum calcium levels were significantly ($p< 0.01$) decreased in both males and females with essential hypertension and their first-degree relatives when compared with the normotensive controls [69]. The mean serum calcium levels in males and females were 2.53±0.26 and 2.51±0.21 (mmol/l) respectively in control group and the same were significantly ($p< 0.01$) decreased in males (2.27±0.36 mmol/l) and females (2.20±0.35mmol/l) in hypertensive group. The mean serum calcium level in control was 2.52±0.24 as against 2.23±0.36 in hypertensive. In the first-degree relatives also the calcium level was significantly decreased (2.42±0.24, $p< 0.01$) when compared with the controls (2.53±0.22).

In Lind L study states that a pattern of negative calcium balanced with lowered levels of serum ionized calcium (Ca2+) increased urinary excretion of calcium has been reported in hypertensive men. In a present study 10 untreated hypertensive subjects were salt loaded (20 gram Nacl) for one week after a week on a low salt diet (3g). The change in mean blood pressure at the end of the high compared with the low salt diet was called salt sensitivity and was related to index of mineral metabolism. It was found that salt sensitivity was significantly correlated with both plasma ionized ca+ and serum calcium concentration both r=0.64, $p< 0.05$ on different diet. Salt loading increased the urinary excretion of calcium by 95% and also induced reduction in Hb, serum albumin and serum calcium ($p< 0.0001$). In conclusion, low levels of plasma ionized calcium and serum calcium where mainly in support in hypertensive subjects with a low sensitivity to salt. The findings support the view that calcium metabolism is related to the regulation of BP [11].

The study concluded that calcium supplementation may lead to a small reduction in systolic but not diastolic blood pressure.

The results do not exclude a larger, important effect of calcium on blood pressure in subpopulations. In particular, further studies should address the hypothesis that inadequate calcium intake is associated with increased blood pressure that can be corrected with calcium supplementation. With respect to blood pressure, the clinical trial findings when calcium intake is increased are conflicting, but there is a trend toward a positive effect with calcium supplements of 1.0 g to 1.55 g per day.

The findings have been highly variable across studies and within studies but the largest study (TOHP). Trials and Hypertension Prevention Study found no significant blood pressure lowering at 600mg per day. Investigators have analyzed their data retrospectively and found sub group and calcium responders. These responders had a persistently lower blood pressure. An analysis to salt sensitivity has been made, but similar practical problem arises. There is no independent and prospective means of identifying those blood pressure will respond to calcium, just as there is no means of determining salt sensitivity before actually implementing therapy or experimental study. Hypertension has a complex etiology with multiple factors responsible for its development and maintenance. Thus it would be expected that certain subgroups of individuals might he responsive to an intervention while other would not.

Based on the data and experience available, calcium supplementation on increased dietary intake of calcium rich foods would be recommended for treatment of hypertension nonspecifically for prevention of hypertension. Some other studies are not supporting calcium therapy for treatment and prevention of hypertension, still calcium can be used because of the other benefits like prevention of osteoporosis. Therefore, a recommendation that calcium intake be maintained at 1.0 to 1.5gm per day through dietary intake on supplements on both can be made for adolescents and adults. This level should be sufficient to achieve a blood pressure lowering response in those who are responsive.

A DASH study (Dietary Approaches to Stop Hypertension) [13] was conducted by Frank M Sacks, *et al.* in 1999 concluded that The DASH diet may offer an alternative drug therapy in hypertensive and, as a population approach, may prevent hypertension. Two hypotheses were tested: (1) that high intake of fruits and vegetables lowers blood pressure, and (2) that an overall dietary pattern (known as the DASH diet, or DASH combination diet) that is high in fruits, vegetables, calcium, nuts, a low fat dairy products, emphasizes fish and chicken rather than red meat, and is low in saturated fat, cholesterol, sugar and refined carbohydrate lowers blood pressure. Participants were 459 adults with untreated systolic blood pressure 160 mmHg and diastolic blood pressure 80-95 mmHg. After a 3-week run in on a control diet typical of Americans, they were randomized to 8 weeks receiving either the control diet, or a diet rich in fruits and vegetables, or the DASH diet. The participants were given all of their food to eat, and body weight and sodium intake were held constant. Blood pressure was measured at the clinic and by 24-h ambulatory monitoring. The DASH diet lowered systolic blood pressure significantly in the total group by 533.0 mmHg, in African Americans by 6.9/3.7 mmHg, in Caucasians by 3.3/2.4 mmHg in hypertensive and by 11.6/5.3 mmHg in non - hypertensive.

BMI and Hypertension

In our study the mean BMI among the study group was 27.4± 2.83 and among the control group was 25.1±2.4. The p ‘value was <0.001. This shows that overweight and obesity also plays a role in the development of essential hypertension.

This was supported by a study conducted by Stamler [14]. They showed that the hypertension is about six times more common in obese than it is in lean subjects. The present study concurs with above observation.

Similarly a study conducted by Huang stated that even a small amount of weight gain is associated with a marked increase in the incidence of hypertension [15]. This study showed a positive correlation between BMI and blood pressure which supported our study.

Suman dua, *et al.* assessed SBP and DBP randomly and found that maximum percentage of overweight males had prehypertension. For SBP it was 72.9% and for DBP it was 54.2%. When only DBP is concerned, 25.2% of adult males had Stage I hypertension. Among females, prehypertension was maximum in overweight females when SBP (73.6%) as well as DBP (52.7%) were considered [15].

Hypertension with Impaired Glucose Tolerance

In our study, it was evident that, RBS was significantly high, in the range of Impaired Glucose Tolerance (IGT), in cases (140.0±21.4mg/dl) compared to controls (116.8±25.0 m/dl).

Zhonghua XinXue Guan Bing Za Zhi, *et al.* in 2009, studied the incidence of impaired glucose tolerance in hospitalized patients with essential hypertension without diabetes mellitus history and concluded that incidence of newly diagnosed disturbed glucometabolic status is common among patients with essential hypertension without DM history.[16] OGTT should be used as a routine procedure in these patients for the purpose of early intervention in hypertensive patients with abnormal glucometabolic status.

Conclusion

The following conclusions were derived from our study, Serum calcium and serum ionized calcium was significantly less among hypertensive and correlated negatively with both SBP and DBP. In view of the significant changes in Serum Calcium among Hypertensive population, community must be motivated to consume Calcium rich diet as a form of primary prevention for essential Hypertension. Body mass index correlated positively with blood pressure suggesting that people should be motivated for healthy life style and to maintain BMI in normal range.

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