



A STUDY OF SERUM TOTAL CALCIUM AND SERUM CALCIUM / PHOSPHORUS RATIO IN ESSENTIAL HYPERTENSION AND ITS CORRELATION WITH SEVERITY OF THE DISEASE

Raman Prabhakaran	Professor, Department of Internal Medicine, Madurai Medical College.
Syed Bahavudeen Hussaini	Assistant Professor, Department of Internal Medicine, Madurai Medical College.
Domeh	Junior Resident, Department of Internal Medicine, Madurai Medical College.
Vijayakumari Vrinda	Junior Resident, Department of Internal Medicine, Madurai Medical College.
Ahamed Kalil	Junior Resident, Department of Internal Medicine, Madurai Medical College.

ABSTRACT

CONTEXT Hypertension is an increasingly important medical and public health burden globally. In this study, we attempt to review the evidence that altered calcium metabolism, thereby change in serum calcium levels are implicated in primary hypertension. **AIM OF THE STUDY** To study the levels of serum Total Calcium and serum Calcium / Phosphorus ratio in patients with primary hypertension. To correlate the serum Total Calcium level and serum Calcium / Phosphorus ratio with blood pressure. **SETTINGS AND DESIGN** Analytical Case Control Study. **MATERIALS AND METHODS** This study is conducted among 50 ischemic stroke patients who were admitted at Government Rajaji Hospital, Madurai from December 2014 to June 2015. After taking detailed history and physical examination and investigations, MPV was determined for Ischemic stroke patients and Modified Rankin scale (MRS) at the time of admission was calculated. After 8 weeks of onset of stroke, all the patients were again followed up. Functional outcomes were determined by use of Modified Rankin Scale (MRS) 2,3. All patients were stratified using MRS 2,3 Scale [0-2, 3-4 and 5-6] into three groups. MPV level was correlated with MRS score at the time of admission and again at 8 weeks. Patients with MRS score of 5 and 6 were declared as very poor outcome & MRS of 3 and 4 as poor outcome. Patients with MRS 0, and 1 were considered as good outcome. **STATISTICAL ANALYSIS** Standard deviation, regression analysis, mean, median. **RESULTS** There is no statistically significant difference among the case and control groups with regard to the age or sex composition or smoking or alcoholism. MPV did not vary with diabetes or hypertension. There was a linear relation with MPV and severity of ischemic stroke i.e. as the MPV increases the severity (MRS) 2,3 of stroke increases. **CONCLUSIONS** There is significant elevation of Mean platelet volume in ischemic stroke patients compared to matched control group. Mean platelet volume can be used as a significant risk factor for acute ischemic stroke and other vascular events independent of other risk factor.

KEYWORDS : Calcium, calcium/phosphorous ratio, hypertension .

INTRODUCTION: Essential hypertension is associated with altered calcium metabolism. Changes in the regulation of intracellular free Calcium and disturbed extracellular calcium homeostasis are noted in patients diagnosed with primary hypertension. Extracellular calcium provides calcium ions for the maintenance of intracellular calcium levels, blood coagulation, bone mineralization and plasma membrane potential. It is widely accepted that the increase in peripheral vascular tone that characterises the established phase of hypertension is due to increased active tension in the smooth muscle cells. Calcium influx through receptor and voltage-gated calcium channels initiates vascular contraction and the fall in the intracellular free calcium concentration results in relaxation or vasodilatation.

MATERIALS AND METHODS:

Study Population: A total of 100 subjects, of which 50 cases of essential hypertension satisfying inclusion and exclusion criteria visiting medicine OPD and admitted in Government Rajaji hospital, Madurai and 50 age and sex matched normotensive controls from 1st June 2014 to 30th November 2014 will be taken up for study.

Inclusion Criteria: Patients with Newly diagnosed Essential hypertension Patients whose age is above 18 years are included Both sexes are included

Exclusion Criteria: Patients who are below 18 years
Patients who are on Vitamin D and Calcium supplementation
Patients with Primary kidney disease/Chronic Kidney disease
Chronic Liver disease
Secondary Hypertension
Pregnancy
Drugs influencing Calcium and Phosphorus metabolism

Ethical Committee Approval: Obtained.

Study Protocol: Patients with acute ischemic stroke admitted in the medicine department within 48 hrs. of onset of symptoms were enquired about presenting complaints, mode of onset of neurological deficit, past history of TIA, hypertension, diabetes mellitus in detail. Special enquiry about alcoholism, smoking, pregnancy or recent delivery and use of anticoagulants or oral contraceptives was made. Any similar illness in the family was asked. Complete general examination and neurological examination was done. Optic fundus was seen in all cases to identify papilloedema, diabetic retinopathy and hypertensive retinopathy. Other systems were examined in detail. Basic investigations such as Haemoglobin, blood cell count, urine for albumin, sugar deposit, blood sugar, urea, serum creatinine, and serum electrolytes, total cholesterol were estimated. Electrocardiography, echocardiography and CT scan of brain were done. Serum samples for MPV estimation were taken after confirming ischemic stroke & sent to the laboratory. MRI brain was also taken if the CT brain was normal and if the patient was

affordable. Other risk factors such as history of TIA, MI, SHT, DM and BMI & serum cholesterol were taken into account. Modified Rankin scale (MRS) at the time of admission were calculated. Standard treatment was given to all patients with ischemic stroke. After 8 weeks of onset of stroke, all the patients were again followed up. Functional outcomes were determined by use of Modified Rankin scale (MRS). All patients were stratified using MRS Scale [0-2, 3 and 5-6] into three groups. MPV level was correlated with MRS score at the time of admission and again at 8 weeks. Patients with MRS score of 5 and 6 were declared as very poor outcome & MRS of 3 and 4 as poor outcome. Patients with MRS 0, and 1 were considered as good outcome.

STATISTICAL ANALYSIS: The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done with the help of computer by using SPSS software and Sigma Stat 3.5 version (2012). Using this software, percentage, mean, standard deviation and 'p' value were calculated through one way ANOVA, Pearson correlation and Chi square test and P value of < 0.05 was taken as significant.

RESULTS:

The age distribution of the participants is given below in the table. 2. 36% of the participants were in the age group 18 – 39 years, 55% of the population was in the age group 40 – 59 years, while 9% of the population was in age group of 60 years and above.

The sex distribution of cases and control is given in the table 3 below. Among the cases, 24 participants were females while 26 participants were male which was statistically significant (p value 0.04). Among the controls, both the males and females were equal with 25 participants each. The median age of the study population was 44. 62% of the cases were less than the median, while 36% of the control were less than median. On the other hand, 38% of the cases and 64% of the control were above the median. Out of the total participants, 20 % of the cases were under “overweight” category and 4.40 % were under “obese” category, while 10.2 % of the controls were overweight and 2.1% were obese, the p value being 0.06. Out of all the participants, 60% of the cases showed decreased serum level while 24 % of the controls showed decreased serum calcium level with p value <0.001. Only 40% of the cases had normal serum calcium level while 76 % of the controls had normal serum calcium level. (Pearson Chi-Square: 13.3, OR:

4.75; 95%: 2.008 – 11.236; p Value: <0.001) 28% of the cases had a positive family history of hypertension while 72% did not have any family history. Among the control, only 12% had family history of hypertension while 88% of them did not have any positive family history. Although, the association of positive family history of hypertension was slightly stronger with cases, we did not find it statistically significant (p Value: 0.046) 36% of the cases were smokers and 64% were non smokers. On the other hand,

32% of the control were smokers and 68% did not have any history of smoking. Similarly, smoking has only a slightly stronger association with Cases but we did not find it statistically significant (p Value: 0.673). In our study population, 28% of both cases and control were alcoholics while 72% of them were non-alcoholics. The association of alcohol in cases and control was equal and statistically not significant. 28% of the participants who had BMI > 25 had serum calcium less than 8.07 mg/dl while only 9.10 % with normal serum calcium level had BMI more than 25. 71% of the participants who had BMI < 25 had decreased serum calcium while 90% of the participants with BMI less than 25 had normal serum calcium. (p Value: 0.015*). In the participants, we observed that a higher percentage of participants who are obese or overweight had lower calcium level rather than normal serum calcium which was statistically significant. In our study, 64.30% of the participants who were above 44 years had low serum calcium while 37.90% had normal serum calcium level. 35.70% of the participants who were below 44 years had low serum calcium and 62.10% of the participants in this

category had normal serum calcium. This shows that older people are more likely to have low serum total calcium as compared to younger age group. (p Value: 0.009*) In our study, 50% of the obese/overweight individuals had serum calcium phosphorus ratio more than 4.09 and 13.10% had serum calcium phosphorus ratio less than 4.09. 50% of the participants with normal weight had serum calcium phosphorus ratio more than 4.09 while 86% of the participants in this category had serum calcium phosphorus less than 4.09. This shows that subjects who are obese/overweight are more strongly associated with an increased C:P ratio as compared to subjects with normal body weight which was statistically significant. (p Value: 0.003*) 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 <8.07 mg/dl, CP ratio >2.7, smoking history. BMI>=25 and Age>=44years. In this regression model Serum calcium <8.07 mg/dl Adjusted OR 4.61 (95%CI 1.66-12.81 and CP ratio >2.7. Adjusted OR 5.26 (95%CI 1.89-14.7 are significantly associated with hypertension after adjusting for confounding factors.

In other words the odds of a patient with hypertension is 4.61 times more likely to have a serum calcium level less than 8.07 mg/dl as compared to a non hypertensive and the odds of a patient with hypertension to have a CP ratio>=2.7 is 5.26 more than that of a normotensive individual.

MRS	No. of Cases
Gr 0	5
Gr 1	14
Gr 2	9
Gr 3	11
Gr 4	9
Gr 5	2

Table 1: Severity of Ischemic Stroke

MRS vs. MPV	Mean	SD	p value
Gr 0, 1(19)	9.79	1.5	
Gr 2, 3(20)	10.09	1.73	
Gr 4, 5(11)	11.72	1.53	0.008 Sig

Table 2: MPV vs. severity of stroke (MRS)

DISCUSSION: In our study, the age distribution of the participants were grouped into three categories. 2. 36% of the study population was in the age group 18 – 39 years, 55% of the population was in the age group 40 – 59 years, while 9% of the population was in age group of 60 years and above. Among the three groups, age group 18-39 % had the lowest number of participants. This may be attributed to the fact that most hypertensive patients remain asymptomatic for many years and they seek medical attention only when complication sets in. As expected, participants from age group 40-59 were the highest as they began to develop hypertension related problems like end organ damage during this age.

The sex distribution of cases and control is given in the table 3 below. Among the cases, 24 participants were females while 26 participants were male which was statistically not significant (p value 0.04). Among the controls, both the males and females were equal with 25 participants each. In our study, we observed a slightly increased number of male participants but it was not significant. Therefore, our observation is that both males and females are almost equally affected, especially in the middle age.

The median age of the study population was 44.62% of the cases were less than the median, while 36% of the control were less than median. On the other hand, 38% of the cases and 64% of the control were above the median.

Out of the total participants, 20 % of the cases were under “overweight” category and 4.40 % were under “obese” category, while 10.2 % of the controls were overweight and 2.1% were obese, the p value being 0.06 which was statistically not significant in relation to

hypertension. However we observed that over weight/obese individuals tend to have decreased serum calcium level which was statistically significant. (p Value: 0.015*). Thus BMI may be an independent risk factor for low serum calcium.

In our study, 86% of the participants with C:P ratio in normal range had normal BMI, while only 13.10% of the overweight/obese participants had C:P ratio in the normal range which was statistically significant. (p Value:0.003*) In the study population, 60 % of the cases showed decreased serum level while 24 % of the controls showed decreased serum calcium level with p value <0.001. Only 40% of the cases had normal serum calcium level while 76 % of the controls had normal serum calcium level. (Pearson Chi-Square: 13.3, OR: 4.75; 95%: 2.008 – 11.236; p Value: <0.001). This is in agreement with studies done various authors like Jha et al[7] where they concluded that serum total calcium is decreased in hypertensive subjects as compared to normotensives.

Touyz et al [2] also observed a significantly decreased level of serum calcium in hypertensive individuals along with decreased serum potassium and decreased serum magnesium. Yogesh et al [13] mentioned that serum ionised calcium was decreased in hypertension but no significant correlation exists between serum total calcium and hypertension. Our finding is also in accordance with studies done by Stern et al [5], Takale et al [3], Sharma et al[9], Sudhakar et al [4]. However, in a study done by Hazari and associates [10], they could not find any significant association of both serum calcium and serum ionized calcium with hypertension.

36% of the cases were smokers and 64% were non smokers. On the other hand, 32% of the control were smokers and 68% did not have any history of smoking. Similarly, smoking has only a slightly stronger association with Cases but we did not find it statistically significant (p Value: 0.673) In our study population, 28% of both cases and control were alcoholics while 72% of them were non-alcoholics. The association of alcohol in cases and control was equal and statistically not significant (p Value: 1). This is in contrast to the observations made by Danni and associates[29], Klatsy [30] who opined that alcohol may serve as an independent risk factor for hypertension.

28% of the cases had a positive family history of hypertension while 72% did not have any family history. Among the control, only 12% had family history of hypertension while 88% of them did not have any positive family history. Although, Sudhakar et al [4], and Sharma [18] concluded that serum calcium was decreased in the first degree relatives of hypertensive individuals as well, we observed that the association of positive family history of hypertension was only slightly stronger with cases, and we did not find it statistically significant (p Value: 0.046)

Using the multivariate analysis, we observed that participants with low serum total calcium are significantly associated with hypertension after adjusting for confounding factors.

In other words the odds of a patient with hypertension is 4.61 times more likely to have a serum calcium level less than 8.07 mg/dl as compared to a non hypertensive individual and the odds of a patient with hypertension to have a CP ratio >2.7 is 5.26 more than that of a normotensive individual.

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. 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 favourable outcome.

ACKNOWLEDGEMENTS: We express our sincere thanks and gratitude to the Dean, Government Rajaji Hospital and Madurai Medical College for permitting us to conduct this study.

We are extremely grateful to all our Assistant Professors and PG Residents of Department of Medicine for their constant source of cheer and encouragement throughout the study. We thank all our patients who have formed the backbone of my study, without them this work would not have been possible. We are also thankful to paramedical staff of all departments for their concern. There is no financial interest in this study.

REFERENCES

1. Aaron R.Folsom, Charles L.Smith, Ronald J. Prineas, and Richard H Grimm,Jr. Serum Calcium Fractions in Essential Hypertensive and Matched Normotensive subjects. *Hypertension* 1986;8: 11-15.
2. Touyz RM, Milne FJ, Seftel HC, Reinach SG.Magnesium, calcium, sodium and potassium status in normotensive and hypertensive Johannesburg residents. *S Afr Med J*. 1987 Sep 19; 72(6):377-81.
3. Takale LR, More UK ,Sontakke AN ,Tilak MA. Serum Total and Free Calcium in Hypertension, *Indian Journal of Basic & Applied Medical Research*; June 2013; Issue-7, Vol.-2, P.716-720.
4. Sudhakar K, Sujatha M, Babu SR, Padmavathi P, Reddy PP.Serum calcium levels in patients with essential hypertension and their first degree relatives. *Indian J Clin Biochem*. 2004; 19(1):21-3.
5. McCarron DA. Low serum concentrations of ionized calcium in patients with hypertension. *N Engl J Med* 1982 Jul 22;307:226-8.
6. Zidek,W., Vetter, H., Dorst, K.G., Zunkley, H. and Loose, H. (1982). Intracellular Na and Ca =⁺ activities in essential hypertension. *Clinical Science*. 63, 41S –43S.
7. Kamlesh Jha, Poonam Kumari.Serum calcium in essential hypertension and its correlation with severity of the disease. *Advanced studies in Biology*2011; vol.3 no.7:319-25
8. Resnick LM, Laragh JH, Sealey JE, Alderman MH. Divalent cations in essential hypertension. Relations between serum ionized calcium, magnesium, and plasma renin activity. *N Engl J Med* 1983 Oct 13;309(15):888-91
9. Booloo Sharma, Devajit Sarmah.Serum calcium and magnesium in patients with essential hypertension and their first degree relatives. *International Journal of Basic Medical Sciences and Pharmacy* Dec 2012;vol.2 no.2:66-9.
10. Hazari M A, Arifuddin M S, Muzzakar S, Reddy V D. Serum calcium level in hypertension. *N Am J Med Sci* 2012 Nov;4(11):569-72
11. Fu Y, Wang S, Lu Z, Li H, Li S. Erythrocyte and plasma Ca²⁺, Mg²⁺ and cell membrane adenosine triphosphatase activity in patients with essential hypertension. *Chin Med J (Engl)* 1998;111:147
12. Christina Martinez.Calcium and Hypertension.Nutrition Bytes 1998;
13. Vol. 4 Issue 2, Article 4.
14. Abdelmarouf H. Mohieldein, Asma A. Dokem, Yousif H M. Osman, Hamza M. A Idris, Serum calcium level as a marker of pregnancyinduced hypertension. *Sudan JMS* Vol. 2, No.4, Dec. 2007
15. Reichel H, Liebethal R, Hense HW, Schmidt Gayke H, Ritz E. Disturbed calcium metabolism in subjects with elevated diastolic blood pressure. *Clin Investig* 1992;70:748-51.
16. Saeed Behradmanesh, Hamid Nasri, Association of serum calcium with level of blood pressure in type 2 diabetic patients, *J Nephropathology*. 2013; 2(4): 254-257
17. Azin Alavi, Keramat allah Jahanshahi, Samie Karimia, Nasim Arabzadea, Soghra Fallahi, Comparison of serum calcium, total protein and uric acid levels between hypertensive and healthy pregnant women in an Iranian population. *Life Sci J* 2012;9(4):485-488 [ISSN:1097-8135]. <http://www.lifesciencesite.com>.
18. Cutler JA, Brittain E. Calcium and blood pressure. An epidemiologic perspective. *Am J Hypertens*. 1990 Aug;3(8 Pt 2):137S-146S. Arpita B. Patel, N. Haridas, Hitesh Shah. "Serum Total Calcium, Serum
19. Ionized Calcium and Serum Albumin Levels in patients with Essential Hypertension and their First Degree Relatives". *Journal of Evolution of Medical and Dental Sciences* 2014; Vol. 3, Issue 06, February 10; Page: 1354-1360. DOI: 10.14260/jemds/2014/1991
20. H Kesteloot and J V Joossens, Relationship of serum sodium, potassium, calcium, and phosphorus with blood pressure. *Belgian Interuniversity Research on Nutrition and Health. Hypertension* 1988; 12: 589 - 593, <http://hyper.ahajournals.org/content/12/6/589>
21. Aviv A. The links between cellular Ca²⁺ and Na⁺ /H⁺ exchange in the pathophysiology of essential hypertension. *Am J Hypertens* 1996; 9: 703-
22. Haller H, Philipp T; *Klin. Wochenschr, J. of Hyper.*, 1988 May 16;66(10):455-61