

Association of Serum Calcium and Serum Magnesium in Gestational Hypertension and Pre-Eclampsia: A Case-Control Study

Shashi Prabha Sinha¹, Amit Kumar Ambasta², Seema³, Sangeeta Singh⁴

¹Senior Resident, Department of Obstetrics and Gynaecology, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India

²Assistant Professor, Department of Pharmacology, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India

³Associate Professor and HOD, Department of Obstetrics and Gynaecology, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India

⁴Assistant Professor, Department of Obstetrics and Gynaecology, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India

Received: 17-08-2022 / Revised: 19-09-2022 / Accepted: 20-10-2022

Corresponding author: Dr. Shashi Prabha Sinha

Conflict of interest: Nil

Abstract:

Aim: The aim of the present study was to evaluate the association of serum calcium and serum magnesium in gestational hypertension and pre-eclampsia.

Methods: The study was conducted in the Department of Obstetrics and Gynecology, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India for 1 year. We conducted a prospective observational case control study. We enrolled 50 pregnant women in their third trimester in the age group of 18-35 years. 25 women were classified as cases based on the development of hypertension for the first-time during pregnancy and 25 were taken as normotensive controls. The serum calcium and magnesium level were estimated in each patient.

Results: The mean serum calcium level in the cases was 8.32 ± 0.58 mg/dl and 8.95 ± 0.45 mg/dl in the controls. Comparison of the serum calcium (mg/dL) between the two groups shows that serum calcium (mg/dL) is higher in control group with a t value of 4.450 and is statistically significant with a p value of <0.001 . The mean serum magnesium level in the cases was 1.66 ± 0.34 and in the controls was 1.80 ± 0.20 . Comparison of the serum magnesium (mg/dL) between the two groups shows that serum magnesium (mg/dL) is higher in Control group with a t value of 4.249 and is statistically significant with a p value of <0.001 . The correlation between the systolic blood pressure (mmHg) & serum calcium (mg/dL) shows a negative correlation, and is not significant with a t value -0.350 and with a p value of 0.050. The correlation between the systolic blood pressure (mmHg) & serum magnesium (mg/dL) shows a strong negative correlation, and is significant with a p value of 0.015.

Conclusion: Our study shows that both serum calcium and serum magnesium were significantly lower in pregnant women with hypertension when compared with normal pregnant women. Thus, intake of supplements of these trace elements may help in the reduction of incidence of hypertension in pregnancy especially in a population of the developing countries where the nutrition of the average woman is poor.

Keywords: Calcium, Magnesium, Nutrition, Pre-eclampsia

This is an Open Access article that uses a fund-ing model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Pre-eclampsia is one of the most common causes of maternal and fetal morbidity and mortality. [1] It is a systemic disease that affects about 5 – 7 % of all pregnancies and is the most common, yet least understood disorder of pregnancy. [2] It is a rapidly progressive condition characterized by high blood pressure, platelet aggregation, swelling of the lower extremities and protein in urine. [3] Sudden weight gain, headaches and changes in vision are important symptoms. Typically blood pressure elevations and pre-eclampsia occur in the late second trimester or third trimester [4]. The pathophysiological mechanism is characterized by a failure of the trophoblastic invasion of the spiral arteries which may be associated with an increased vascular resistance of the uterine artery and a decreased perfusion of the placenta.4 The incidence is about 6% in primigravid women. [5] Clinically pre-eclampsia is characterized by persistently elevated blood pressure of greater than 140/90 mmHg, proteinuria and oedema. [6] It may be associated with complications like visual disturbances, oliguria, eclampsia, hemolysis, elevated liver enzymes, thrombocytopenia, pulmonary oedema and fetal growth restriction. [7] Early detection and prompt management helps in reducing the complications of this condition. Despite its prevalence and severity, the patho physiology of this multisystem disorder is still poorly understood and its aetiology has not yet been fully elucidated. [8] Environmental and nutritional factors may play a role in the aetiology of pre-eclampsia.

Hypertensive disorders account for 40,000 maternal deaths annually. [9] Due to this, methods to reduce the risk of hypertensive disorders in pregnancy have received

considerable attention. Research is focusing on prevention rather than treatment. There is evidence that indicates a role for micronutrients supplementation in preventing some pregnancy disorders. Among these, increasing calcium and magnesium intake can reduce the risk of pregnancy induced hypertensive disorders. [10]

Low serum calcium stimulates parathyroid hormone (PTH) production, which increases the intracellular calcium levels, this forms the physiological basis behind the hypothesis that hypocalcemia may lead to vasoconstriction and consequently a rise in BP. This leads to contraction of vascular smooth-muscle resulting in hypertension. [11] Magnesium is “nature’s physiological calcium blocker” and the effects of hypocalcemia are further augmented with decreased levels of serum magnesium. Hypomagnesemia opens the L type Ca²⁺ channel and blocks the Ca²⁺-ATPase present in sarcoplasmic reticulum and leads to increased intracellular calcium. [12] Low serum magnesium decreases prostacyclin production which in itself leads to vasoconstriction. Nutritional interventions to prevent pregnancy induced hypertension, if successful, would have considerable clinical and public health implications, especially in resource poor countries where dietary deficiencies are prevalent and access to optimal obstetric care is limited.

The aim of the present study was to evaluate the association of serum calcium and serum magnesium in gestational hypertension and pre-eclampsia.

Methods

The study was conducted in the Department of obstetrics and gynaecology, Darbhanga Medical College and Hospital,

Darbhanga, Bihar, India for 1 year. We conducted a prospective observational case control study. We enrolled 50 pregnant women in their third trimester in the age group of 18-35 years. 25 women were classified as cases based on the development of hypertension for the first time during pregnancy and 25 were taken as normotensive controls. The serum calcium and magnesium level was estimated in each patient.

Based on an article by Chaudhari R et al. mean serum calcium and magnesium was reported in the gestational hypertension/pre-eclamptic group was 8.69 ± 1.59 mg/dL and 1.91 ± 0.36 mg/dL versus 10.13 ± 0.66 mg/dL and 2.08 ± 0.12 mg/dL in the normotensive group. Taking this article as a reference the sample size was calculated by considering Serum calcium level as a variable [9].

In the study we enrolled a total of 50 patients with 25 participants in each group.

The inclusion and exclusion criteria were as follows:

a) Inclusion criteria

ACOG 2013 Guidelines were applied for recruitment of cases.

Study group

- Age: 18-35 years
- Singleton pregnancy
- Gestational age >28 weeks
- BP \geq 140/90 mmHg on two separate occasions 4 hours apart with or without proteinuria of more than \geq 1+ on dipstick.
- Control group
- Age: 18-35 years
- Singleton pregnancy
- Gestational age >28 weeks
- BP < 140/90 mmHg

b) Exclusion criteria

- Known case of chronic hypertension

- Known case of renal disease (acute kidney injury, chronic kidney disease)
- Known case of liver disease (hepatitis, cirrhosis, liver failure)
- Known case of cardiac disease (valvular heart lesions, cardiomyopathies, congenital heart disease, coronary artery disease)
- Known case of diabetes.
- Known case of seizure disorder

Biochemical analysis

Estimation of serum calcium was done by the NM-BAPTA method and reference range was 8.6-10.3 mg/dl.

Principle and method of the procedure used for estimation of serum magnesium was Colorimetric end point method (Xylidyl blue) and the reference range was 1.6-2.6 mg/dl

Statistical analysis

Data was collected by using a structured pre-format. Data was entered in MS excel sheet and analyzed by using SPSS 24.0 version IBM USA. Qualitative data was expressed in terms of percentages. Quantitative data was expressed in terms of mean and standard deviation (SD). Comparison of mean and SD between two groups was done by using unpaired t test to assess whether the mean difference between groups was significant or not. Descriptive statistics of each variable was presented in terms of mean, standard deviation and standard error of mean. Comparison of mean and SD between all groups was done by using one way ANOVA test. Logistic regression test was applied in order to assess the effect of independent risk factors on outcome. A p value of <0.05 was considered as statistically significant whereas a p value <0.001 was considered as highly significant.

Results

Table 1: Mean Serum calcium and mean serum magnesium value (mg/dl) in cases and controls and their p value

Parameter	Control (n=25) Mean \pm SD	Cases (n=25) Mean \pm SD	t value	p Value
Serum Calcium (mg/dL)	8.95 \pm 0.45	8.32 \pm 0.58	4.450	<0.001
Serum Magnesium (mg/dL)	1.80 \pm 0.20	1.66 \pm 0.34	4.200	<0.001

The mean serum calcium level in the cases was 8.32 \pm 0.58 mg/dl and 8.95 \pm 0.45 mg/dl in the controls. Comparison of the serum calcium (mg/dL) between the two groups shows that serum calcium (mg/dL) is higher in control group with a t value of 4.450 and is statistically significant with a p value of <0.001. The mean serum magnesium level in the cases was

1.66 \pm 0.34 and in the controls was 1.80 \pm 0.20. Comparison of the serum magnesium (mg/dL) between the two groups shows that serum magnesium (mg/dL) is higher in Control group with a t value of 4.249 and is statistically significant with a p value of <0.001.

Table 2: Correlation between SBP and mean serum calcium and magnesium

Systolic BP (mmHg)	140-149mmHg	150-159mmHg	\geq 160mmHg	p Value
Mean serum calcium (mg/dl)	8.6	8.4	8.2	0.050
Mean serum magnesium (mg/dl)	1.7	1.7	1.4	0.015

The correlation between the systolic blood pressure (mmHg) & serum calcium (mg/dL) shows a negative correlation, and is not significant with a t value -0.350 and with a p value of 0.050. The correlation between the systolic blood pressure (mmHg) & serum magnesium (mg/dL) shows a strong negative correlation, and is significant with a p value of 0.015.

Table 3: Correlation between DBP and mean serum calcium and magnesium

Diastolic BP (mmHg)	90-99 mmHg	100-109mmHg	\geq 100mmHg	p Value
Mean serum calcium (mg/dl)	8.8	8.2	7.8	0.012
Mean serum magnesium (mg/dl)	1.7	1.6	1.5	0.058

The correlation between the diastolic blood pressure (mmHg) & serum calcium (mg/dL) shows a negative correlation, with a p value of 0.012 which is statistically significant. The correlation between diastolic blood pressure (mmHg) & serum magnesium (mg/dL) with a t value -0.368 and a p value of 0.058 which is not statistically significant.

Discussion

Pre-eclampsia has been considered as a disease of unknown pathophysiology. Numerous aetiologies have been put forward in light of this serious condition of pregnancy. [14-16] Altered concentration of various trace elements has been reported during pregnancy. [17,18] Serum Ca and Mg are two intracellular ions that are very

important for cellular metabolism such as muscles contractibility, secretion, neuronal activity as well as cellular death. [14] Changes in the levels of Ca, Mg and copper in all the trimesters of pregnancy and zinc during mid and late pregnancy and postpartum period have been reported. Moreover, reduction in serum Ca, Mg and zinc during pregnancy has been attributed as a possible contributor among the various aetiologies of PE, therefore supplementation of these elements in diet may be of high value to prevent this devastating condition. [17]

In this study, we observed a lower level of mean serum calcium among the cases as compared to the normotensive group (8.32 \pm 0.58 mg/dl versus 8.95 \pm 0.45 mg/dl).

It is a known fact that calcium homeostasis is altered during pregnancy to meet the needs of the growing foetus. [19] Previous reports such as that by Belizan JM et al. in 1988 have suggested that a decrease in serum calcium may be associated with hypertension in pregnancy. [20] Our findings are similar to the studies conducted by Sukonpan K et al. (2004), Punthumapol et al. (2008). [1,21]

Furthermore, we found a negative correlation between serum calcium and systolic BP with a p value of 0.064 and though we cannot conclude that it was statistically significant we can say that it is somewhat significant. We also found a statistically significant negative correlation between serum calcium and diastolic BP with a p value of 0.013. It simply means that the level of serum calcium decreased with an increase in systolic and diastolic BP among the subjects studied. This finding further corroborates the hypothesis that calcium may play an important role in the causation of hypertension in pregnancy. Our findings were similar to the studies conducted by Ephraim et al. (2014), Onyegbule O et al. (2014), Aghade S et al. (2017). [22-24]

Magnesium sulphate is the drug of choice and is highly effective for the treatment of severe pre-eclampsia and eclampsia. Magnesium plays an important role in the neurochemical transmission and has an important role in peripheral vasodilation. It is also an essential cofactor for many enzyme systems. [25,26]

Comparison of the serum magnesium (mg/dL) between the two groups shows that serum magnesium (mg/dL) is significantly lower in the cases. We also observed a strong negative correlation of serum magnesium with systolic BP with a p value of 0.015 which was statistically significant and a negative correlation of magnesium with diastolic BP. Since the p value of this comparison was 0.050, we cannot call it statistically significant. However, an association of serum level of

magnesium, or more importantly, hypomagnesemia with hypertensive disorders of pregnancy cannot be denied. Our finding is similar to that of Sukonpan K et al. (2004), Jain S et al. (2009). [1,27] The causal relationship between hypomagnesaemia and hypertensive disorders of pregnancy can also be explained by the hypothesis that magnesium deficiency may be responsible for spasm of umbilical and placental vasculature. [28] Thus hypomagnesaemia may be one of the important factors for the pathophysiological changes of pregnancy induced hypertension. [29]

Conclusion

Our study shows that both serum calcium and serum magnesium were significantly lower in pregnant women with hypertension when compared with normal pregnant women. Thus, intake of supplements of these trace elements may help in the reduction of incidence of hypertension in pregnancy especially in a population of the developing countries where the nutrition of the average woman is poor. The results of this study may help us better understand the pathophysiological process behind the development of hypertension in pregnancy, more so its association with trace elements, and assist us to establish and boost existing preventive strategies for the condition. Adequate dietary mineral supplementation during the antenatal period, at least in susceptible women, may influence significantly, the occurrence of hypertensive disorders in pregnancy and could provide us with a simple and cost-effective preventive measure.

References

1. Sukonpan K, Phupong V. Serum calcium and serum magnesium in normal and preeclamptic pregnancy. Archives of gynecology and obstetrics. 2005 Nov;273(1):12-6.
2. Ziaei S, Ranjkesh F, Faghihzadeh S. Evaluation of 24-hour urine copper in

- preeclamptic vs. normotensive pregnant and non-pregnant women.
- Sarsam DS, Shamden M, Al Wazan R. Expectant versus aggressive management in severe preeclampsia remote from term. *Singapore medical journal*. 2008 Sep 1;49(9):698.
 - Akinloye O, Oyewale OJ, Oguntibeju OO. Evaluation of trace elements in pregnant women with pre-eclampsia. *Afr J Biotechnol*. 2010;9(32):5196-5202.
 - Kumru S, Aydin S, Simsek M, Sahin K, Yaman M, Ay G. Comparison of serum copper, zinc, calcium, and magnesium levels in preeclamptic and healthy pregnant women. *Biological trace element research*. 2003 Aug; 94(2):105-12.
 - American College of Obstetrics and Gynaecology (ACOG) Practice bulletin. Diagnosis and management of pre-eclampsia and eclampsia. *Obstet Gynaecol*. 2002; 99:159-67.
 - Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Dashe JS. *Williams obstetrics*, 24e. New York, NY, USA: Mcgraw-hill; 2014.
 - Bringman J, Gibbs C, Ahokas R, Syamal B, Ramsey R, Egerman R. Differences in serum calcium and magnesium between gravidas with severe preeclampsia and normotensive controls. *American Journal of Obstetrics & Gynecology*. 2006 Dec 1; 195(6):S148.
 - Hofmeyr GJ, Duley L, Atallah A. Dietary calcium supplementation for prevention of pre-eclampsia and related problems: a systematic review and commentary. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2007 Aug;114(8):933-43.
 - Cetin I, Berti C and Calabrese S. Role of micronutrients in the periconceptional period. *Human Reprod Update*. 2010;16(1):80-95.
 - Villa-Etchegoyen C, Lombarte M, Matamoros N, Belizán JM, Cormick G. Mechanisms Involved in the Relationship between Low Calcium Intake and High Blood Pressure. *Nutrients* [Internet]. 2019 May, 18;11(5):1112.
 - Iseri LT, French JH. Magnesium: Nature's physiologic calcium blocker. *Am Heart J*. 1984 Jul;108(1):188-93.
 - Naik SM, Sehra R, Bansal M. Association of serum calcium and serum magnesium in gestational hypertension and pre-eclampsia.
 - Atamer Y, Koçyigit Y, Yokus B, Atamer A, Erden AC. Lipid peroxidation, antioxidant defense, status of trace metals and leptin levels in preeclampsia. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2005 Mar 1;119(1):60-6.
 - Serdar Z, Gür E, Develioğlu O, Çolakoğulları M, Dirican M. Placental and decidual lipid peroxidation and antioxidant defenses in preeclampsia: lipid peroxidation in preeclampsia. *Pathophysiology*. 2002 Oct 1;9(1):21-5.
 - Liu J, Yang H, Shi H, Shen C, Zhou W, Dai Q, Jiang Y. Blood, copper, zinc, calcium, and magnesium levels during different duration of pregnancy in Chinese. *Biol Trace Elem Res*. 2010;135(1-3):31-37.
 - Jain S, Sharma P, Kulshreshtha S, Mohan G, Singh S. The role of calcium, magnesium, and zinc in pre-eclampsia. *Biological trace element research*. 2010 Feb;133(2):162-70.
 - Ingec M, Nazik H, Kadanali S. Urinary calcium excretion in severe preeclampsia and eclampsia. *Clin Chem Lab Med*. 2006;44(1):51-53.
 - Kovacs CS, Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, et al. Calcium and Phosphate Metabolism and Related Disorders During Pregnancy and Lactation[Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000.

20. Belizán J, Villar J, Repke J. The relationship between calcium intake and pregnancy-induced hypertension: up-to-date evidence. *American journal of obstetrics and gynecology*. 1988 Apr 1;158(4):898-902.
21. Punthumapol C, Kittichotpanich B. Serum calcium, magnesium and uric acid in preeclampsia and normal pregnancy. *J Med Assoc Thai Chotmaihet Thangphaet*. 2008 Jul;91(7):968-73.
22. Ephraim RK, Osakunor DN, Denkyira SW, Eshun H, Amoah S, Anto EO. Serum calcium and magnesium levels in women presenting with pre-eclampsia and pregnancy-induced hypertension: a case-control study in the Cape Coast metropolis, Ghana. *BMC pregnancy and childbirth*. 2014 Dec;14(1):1-8.
23. Onyegbule OA, Meludu SC, Dioka CE, Udigwe GO, Udo JN, Ezidigboh AN, et al. Comparison of serum levels of calcium and magnesium among preeclamptic and normotensive pregnant women at Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria. *Int J Res Med Sci*. 2017 Jan, 23;2(2):404-8.
24. Aghade S, Bavikar J. Comparative Study of Serum Calcium in Preeclampsia and Normal Pregnancy at Government Medical College and Hospital, Aurangabad City, India. *Indian J Med Biochem*. 2017 Dec; 21(2):147-50.
25. Euser AG, Cipolla MJ. Magnesium sulfate treatment for the prevention of eclampsia: A brief review. *Stroke J Cereb Circ*. 2009 Apr;40(4):1169-75.
26. Walker JJ. Magnesium Sulfate is the Drug of Choice for the Treatment of Eclampsia. *Hypertens Pregnancy*. 1996 Jan;15(1):1-6.
27. Jain S, Sharma P, Kulshreshtha S, Mohan G, Singh S. The role of calcium, magnesium, and zinc in pre-eclampsia. *Biol Trace Elem Res*. 2010 Feb;133(2):162-70.
28. Altura BM, Altura BT, Carella A. Magnesium deficiency-induced spasms of umbilical vessels: relation to preeclampsia, hypertension, growth retardation. *Science*. 1983 Jul; 22: 221 (4608): 376-8.
29. Diane S., Baldé A. K., Camara F., & Diane, M. H. Problématique du traitement de limbo-conjonctivite et endémique des tropiques. *Journal of Medical Research and Health Sciences*. 2022; 5(9): 2244-2249.