



COMPARATIVE STUDY OF SERUM CALCIUM AND MAGNESIUM LEVELS IN PRE-ECLAMPTIC AND NORMOTENSIVE PREGNANT WOMEN

FIRST AUTHOR-Dr. Penugonda Anveetha, Associate Professor, Department of Biochemistry, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram, India.

SECOND AUTHOR-Dr. Vamsi Krishna Chittimoju, Assistant Professor, Department of Biochemistry, Andhra Medical College, Visakhapatnam, India.

THIRD AUTHOR-Dr. Chaganti Sridevi, Associate Professor, Department of Biochemistry, Prathima Relief Institute of Medical Sciences, Warangal, India.

FOURTH AUTHOR & CORRESPONDING AUTHOR- Dr. Aleti Lakshmi Manohari, Professor, Department of Biochemistry, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram, India.

Corresponding email id- drnoha.manohari@gmail.com

Article History

Received: 12 March 2024

Accepted: 10 April 2024

Published: 16 May 2024

ABSTRACT

Background- Hypertensive disorders are major factors responsible for morbidity and mortality in pregnancy and Pre-eclampsia, a pregnancy specific disorder, is the leading cause. Despite of its prevalence and severity, the etiology of preeclampsia remains unknown, with poorly understood pathophysiology. Though the findings are heterogenous and inconsistent, several recent studies indicate that serum levels of calcium and magnesium may have a role in preeclampsia. Aim: The study is aimed to compare the levels of serum calcium and magnesium in pre-eclamptic women with that of normotensive pregnant women.

Materials & Methods: Total of 120 pregnant women, of which 60 are pre-eclamptic (cases group) and 60 are normotensive (controls group), with similar demographic data were included in the study. Serum calcium and magnesium levels were measured and analyzed. Data on BMI (Body Mass Index), maternal and gestational ages and blood pressure was collected and compared between the two groups. Data was expressed as Mean \pm S.D. Comparison of serum elements of both groups was performed by Independent t-test and chi square test. P value of < 0.05 was considered as statistically significant.

Results: The serum calcium and magnesium levels were significantly lower in pre-eclamptic cases compared to normotensive controls. The study also showed that pre-eclamptic women had higher BMI and systolic and diastolic blood pressure, when compared to normotensive pregnant women.

Conclusion: There was a significant reduction in serum calcium and magnesium levels in pre-eclamptic women when compared to normal pregnant women, suggesting the role of these nutrients in pre-eclampsia which needs further investigation.

Key words: serum calcium, magnesium, preeclampsia, nutrition, blood pressure

INTRODUCTION

Hypertensive disorders of pregnancy, including pre-eclampsia complicate 5 to 10% of all pregnancies worldwide.^[1,2,3] In a developing country like India, pre-eclampsia is a significant and one of the most common cause of maternal and fetal morbidity and mortality.^[4,5] Pre-eclampsia is a rapidly progressive, multisystemic and multifactorial disorder specific to human pregnancy. It is characterized by the new onset of hypertension (systolic/diastolic blood pressure $\geq 140/90$ mmHg), proteinuria (≥ 300 mg/24hrs) and pathological edema usually occurring after 20 weeks of gestation.^[6,7]

Despite decades of extensive research done worldwide, the etiology of preeclampsia is elusive and is still a mystery and it was once called as “the disease of theories”.^[8] Though the exact etiology of pre-eclampsia remains unclear, many theories suggest that abnormal placental implantation and abnormal trophoblastic invasion as possible causes of this disorder.^[9,10]

Pregnancy is a period associated with increasing metabolic demands compounded by requirements of a growing fetus.^[11] Both environmental and nutritional factors may play a role in etiology of pre-eclampsia. An inadequate dietary intake of nutrients might be harmful not only for mother but also for the growing fetus.^[11,12] Nowadays, nutritional deficiency is gaining prominence in pathogenesis of pre-eclampsia. It is assumed to be a predisposing factor in the development of pre-eclampsia because nutrients can modulate oxidative stress by increasing or decreasing free radicals or antioxidants and providing substrates for free radicals formation. Nutritional deficiencies are commonly found in pregnant women and it is well known that the pregnant women in developing countries consume diets deficient in essential minerals and vitamins.^[2,13,14] Pregnancy may induce hypertension in women who were apparently normotensive before becoming pregnant.^[15,16] Annually, hypertensive disorders of pregnancy account for 40,000 maternal deaths.^[17]

Several studies have reported that changes in serum levels of calcium and magnesium observed in pre-eclamptic patients may contribute to the pathogenesis of pre-eclampsia.^[15] Lowering of serum calcium level can cause high blood pressure in pre-eclamptic mothers by stimulating parathyroid hormone and renin release and also by inducing vasoconstriction by increasing its level in vascular smooth muscle.^[11]

Magnesium serves as an essential cofactor for many enzymes and plays an important role in nerve transmission and peripheral vasodilatation.^[18,19] Successful management of eclamptic seizures with magnesium therapy strongly suggest that pregnant women having magnesium deficiency might develop pre-eclampsia.^[15] It has been hypothesized by numerous studies that oscillations in the maternal serum ions may be the instigating cause of elevated blood pressures seen in preeclampsia.^[20] Many clinical studies showed the relationship between this hypertensive complication and changes in the serum levels of calcium and magnesium in pre-eclamptic women.^[18] However, the results from most of the studies are inconsistent and the role of calcium and magnesium in pregnant women remains uncertain and is still under discussion. Thus, the present study was done to measure and compare serum levels of calcium and magnesium of pre-eclamptic women with that of normotensive pregnant women.

MATERIALS AND METHODS

This case control study was conducted on total of 120 women. aged between 18 - 35 years , comprising 60 pregnant women diagnosed with preeclampsia (cases group) and 60 normotensive pregnant women (controls group) attending the antenatal clinic and admitted in the obstetric ward in the Department of Obstetrics & Gynaecology in Maharajah’s Institute of Medical Sciences, Nellimarla, Vizianagaram during period 2023 - 2024. All participants in the study were in the 3rd trimester of pregnancy with a gestational age of more than 24 weeks. Informed consent was obtained from all the study participants and the study was approved by Institutional Ethics committee.

Inclusion criteria for cases & controls:

For cases:

Preeclamptic pregnant women were selected based on the following criteria:

- New onset of hypertension after 20 weeks of gestation
- Systolic blood pressure (SBP) ≥ 140 mmHg and Diastolic blood pressure (DBP) ≥ 90 mmHg on 2 separate occasions 6 hours apart.
- Associated with proteinuria of more than 300mg/day or atleast 1+ on dipstick test.^[9,21]

For controls

Age and trimester matched pregnant women without hypertension (with BP $< 140/90$ mmHg with no increase in SBP up to 30 mmHg and DBP up to 15 mmHg due to pregnancy) and without evidence of proteinuria were selected.

Exclusion criteria:

Pregnant women with renal disease, diabetes, endocrine disorder, or any other systemic disease / with secondary causes of hypertension and on calcium supplementation were excluded from the study.

Height and weight of each subject were measured, in standing erect position against wall without shoes with a wall mounted

ruler and using a standard weighing scale without shoes and subjects wearing light clothes, respectively. BMI of each subject was calculated using the formula, weight (kg)/ height (m²). Blood pressure was measured with participants in a restful position using a mercury sphygmomanometer with appropriate sized cuff on atleast 2 occasions. Clean-catch, mid-stream urine sample was obtained in a clean sterile container from each participant and tested with urinalysis strip for proteinuria. Venous blood samples were collected and analyzed for serum calcium and magnesium. Serum calcium was estimated by O-cresolphthalein complexone method and magnesium was estimated by Xylidyl Blue method. Results obtained were tabulated, entered in MS Excel work sheet and analyzed using SPSS version 20. Numerical data was expressed as Mean \pm SD. Differences in demographic characteristics and biochemical parameters between the two groups were statistically analyzed using Independent t-test and Chi-square test. P-value of < 0.05 was considered as statistically significant.

RESULTS

The present study enrolled 120 pregnant women, aged 18-35 years, of which 60 women with preeclampsia were considered as cases and another 60 normotensive women as controls.

Table 1 depicts the clinical and demographic characteristics of Cases and Control groups. The mean age did not show any significant difference between the 2 groups. The body mass index (BMI) is higher in preeclamptic cases when compared to normotensive controls which is statistically significant (29.34 ± 2.88 kg/m² vs 23.72 ± 2.26 kg/m², p value < 0.001). The period of gestation (weeks) was significantly lesser in pre-eclamptic cases compared to normotensives (36.70 ± 0.80 vs 38.26 ± 0.92 , p value < 0.001). The systolic and diastolic blood pressures were significantly higher in cases compared to controls (SBP - 154.40 ± 11.84 vs 109.60 ± 5.80 , p value < 0.001 , DBP - 99.20 ± 8.74 vs 72.40 ± 5.28 , p value < 0.001).

Table 1: Clinical & Demographic Characteristics of Cases & Controls

| General Characteristics | Cases (n = 60) | Controls (n = 60) | p-value |
|-------------------------|--------------------|-------------------|---------------------|
| Age (years) | 28.42 ± 4.34 | 26.74 ± 3.16 | 0.246 ^{NS} |
| BMI(Kg/m ²) | 29.34 ± 2.88 | 23.72 ± 2.26 | < 0.001 |
| Gestational Age(weeks) | 36.70 ± 0.80 | 38.26 ± 0.92 | < 0.001 |
| Systolic BP(mmHg) | 154.40 ± 11.84 | 109.60 ± 5.80 | < 0.001 |
| Diastolic BP(mmHg) | 99.20 ± 8.74 | 72.40 ± 5.28 | < 0.001 |

Values are expressed as mean \pm SD (standard deviation), p value < 0.05 - Statistically Significant

BMI - Body Mass Index, BP - Blood Pressure, NS – Not Significant

Table 2 depicts the comparison of levels of serum calcium and magnesium (biochemical parameters) between the 2 groups. The serum calcium concentration was significantly lower in the pre-eclamptic cases compared to the normotensive controls (7.62 ± 0.74 mg/dl vs 9.23 ± 0.67 mg/dl, p value < 0.001). The serum magnesium concentration was also significantly lower in the pre-eclamptic cases compared to the normotensive controls (1.28 ± 0.46 mg/dl vs 2.07 ± 0.31 mg/dl, p value < 0.001).

Table 2: Comparison of Biochemical Parameters in Cases & Controls

| Parameter | Cases (n = 60) | Controls (n = 60) | p-value |
|-------------------|-----------------|-------------------|-----------|
| Calcium (mg/dl) | 7.62 ± 0.74 | 9.23 ± 0.67 | < 0.001 |
| Magnesium (mg/dl) | 1.28 ± 0.46 | 2.07 ± 0.31 | < 0.001 |

Values are expressed as mean \pm SD (standard deviation), p value < 0.05 - Statistically Significant

DISCUSSION

Pre-eclampsia, a complex, dynamic pregnancy specific complication, is associated with increased maternal and fetal morbidity and mortality especially in developing countries.^[6,22] Despite considerable research for several years, the exact etiology of this disorder still remains unknown, although contributory factors include obesity, diabetes, calcium deficiency, old maternal age and job stress.^[23]

Pregnancy is an anabolic state associated with complex physiological adaptations occurring in the maternal system and these changes are necessary to meet the requirements of a growing fetus.^[24] Nutritional deficiencies are common during this period and studies show that pregnant women in developing countries consume diets that are low in essential minerals and vitamins.^[14] Dietary deficiencies of minerals like calcium and magnesium during pregnancy have been implicated to be responsible for various gestational complications, such as pre-eclampsia, eclampsia, preterm birth and intrauterine growth retardation.^[12]

Several studies have reported that alteration in levels of serum calcium and magnesium observed in pre-eclamptic patients could be responsible in pathophysiology of pre-eclampsia.^[25,26] Since both these elements have significant role in blood pressure regulation, the present study was conducted to compare serum levels of calcium and magnesium of pre-

eclamptic women with that of normotensive pregnant women.

In the present study, both serum calcium and magnesium levels are significantly reduced in pre-eclamptic pregnant women when compared to normal pregnant women. These findings are in accordance with other studies and confirmed the hypothesis that hypocalcemia and hypomagnesemia may be the etiological factors in the development of pre-eclampsia.^[18,23]

In pregnancy, the increase in plasma volume leads to concomitant hemodilution state which results in dilution of all the constituents of plasma including calcium and magnesium.^[25] Calcium physiologically plays a vital role in muscle contraction and regulation of water balance in cells. Changes in plasma calcium levels lead to alteration of blood pressure.^[27] Maternal hypocalcemia during pregnancy has been known for many years. Over the course of pregnancy, total serum calcium tends to decrease in normal women and decreased significantly during preeclampsia.^[15] Furthermore, with advancement of pregnancy, there is more pronounced hypercalciuria due to enhanced renal plasma flow and glomerular filtration rate. Hence, in response to this hypocalcemic effect, there is increased synthesis of parathyroid hormone which in turn raises intracellular calcium concentration in vascular smooth muscles and have vasoconstriction effect. This process leads to increased vascular resistance of arteries and arterioles that might result in hypertension in pre-eclamptic mothers.^[25]

Like hypocalcemia, reduced magnesium concentration in blood is often seen during pregnancy. Magnesium levels may have profound effects on cardiac muscle excitability and on vascular tone, contractility and reactivity.^[15] Magnesium acts as a cofactor for many enzymes and plays a significant role in neurochemical transmission and peripheral vasodilatation. It also promotes vascular muscle relaxation.^[11] Hypomagnesemia observed in most pregnant women could be due to decreased dietary intake, increased renal clearance, haemodilution due to expansion of the extracellular space and increased consumption of minerals by the growing fetus. Reduced level of extracellular magnesium causes partial membrane depolarization and decreased repolarization along with opening of calcium membrane channels, leading to an intracellular calcium shift.

Further, the already existing increased fetal calcium demand may also block resorption of calcium from a bone with concurrent intracellular pull. This phenomenon results in vasoconstriction together with an increase in blood pressure in pre-eclamptic women.^[2] Increased blood pressure may also be due to decreased vasodilating action of serum magnesium. Reduced concentrations of these maternal serum ions, calcium and magnesium, induce constriction of vascular smooth muscles and increase vascular resistance and thus cause elevation in blood pressure.^[27]

In the present study, we observed that levels of serum calcium and magnesium were decreased significantly in pre-eclamptic women compared to normotensive pregnant women. Similar to the findings in other studies,^[9,15,28] our study showed no significant difference in the maternal ages of pregnant women with pre-eclampsia (cases) and those who are normotensive (controls). In this study, we also found that BMI, SBP and DBP of preeclamptic women were significantly higher when compared to normotensive pregnant women. Our results are consistent with findings of other studies.^[1,2,11,15,23] Women with a greater BMI in pregnancy are more likely to become hypertensive than those having a lower BMI.^[29] Maternal obesity predisposes a woman to develop pre-eclampsia, and a relationship between increasing BMI and the risk of developing pre-eclampsia during pregnancy is well established.^[21] Gestational age was significantly lesser in pre-eclamptic cases than that of normotensive controls. Studies done by Chaurasia et al, Deepa VK et al and Vanaja D et al also showed similar findings.^[11,23,30] Based on the results obtained in the present study, we support the hypothesis that decreased levels of serum calcium and magnesium may contribute for generation of oxidative stress, increased vascular resistance and high blood pressure observed in pre-eclamptic women. Hence, measurement of these elements may be used in early diagnosis of pre-eclampsia in pregnancy. Further, pregnant women especially in developing countries should also be encouraged to consume diets rich in calcium and magnesium.

CONCLUSION

In the present study, decreased serum calcium and magnesium levels and elevated blood pressure have been observed in the pre-eclamptic women compared to normal pregnant women. Results obtained in our study support the earlier hypothesis that hypocalcemia and hypomagnesemia may have a role in the etiology of pre-eclampsia during pregnancy. Estimation of these elements, which are relatively economical and safe, can be used as a cost effective screening tool for prediction of pre-eclampsia in early stages of pregnancy. Dietary interventions by increasing intake of calcium and magnesium may reduce the disease risk in pregnant women.

REFERENCES

1. Poonia L, Kochar A, Chaudhary S, Gaur P, Solankim K.A cross sectional study to evaluate serum calcium levels among pregnant women and its association with preeclampsia and delivery outcomes at tertiary care hospital Bikaner, Rajasthan. *Int J Reprod Contracept Obstet Gynecol* 2021;10:2026-30.
2. Sethi S, Chaudhary A, Sonkhya P, Mital P, Arora A, Kasana VK, Agarwal I.A comparative study of serum calcium and magnesium levels in women with pre-eclampsia and normotensive women. *Int J Reprod Contracept Obstet Gynecol* 2021;10:2420-26.

3. Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hoffman BL, Casey BM, Sponge CY. Hypertensive disorder in pregnancy. Textbook of Williams Obstetrics. 25th ed. New York: McGraw-Hill. 2014;1566-677.
4. Chaitra Ramachandra, Rekha. N, Roopa.N.K, Shankaregowda, Nirupama.Y.S. Comparative study of the serum calcium level in normal pregnancy and pre-eclamptic women in a tertiary centre in India. *Int J Med Res Rev* 2016;4(5):834-838.
5. Sukonpan K, Phupong V. Serum calcium and serum magnesium in normal and preeclamptic pregnancy. *Arch Gynecol Obstet Archives of Gynecology and Obstetrics*. 2004Jul;273(1):12-6.
6. Aghade SM, Bavikar JS. Comparative Study of Serum Calcium in Preeclampsia and Normal Pregnancy at Government Medical College and Hospital, Aurangabad City, India. *Indian J Med Biochem* 2017;21(2):147-150.
7. Koley A, Das S, Sarkar S, Char D, Saha TK. Association of serum calcium and uric acid level with hypertensive disorders of pregnancy [preeclampsia and eclampsia] and their correlation with disease severity. *IOSR J Dent Med Sci* 2013 Sep-Oct;9(5):32-35.
8. Onyegbule OA, Meludu SC, Dioka CE, Udigwe GO, Udo JN, Ezidigboh AN, Atuegbu CC, Osakue N. 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* 2014 May;2(2):404-408.
9. Owusu Darkwa E, Charles A, Robert D, Christian O, Samuel O,† Daniel S. Serum magnesium and calcium in preeclampsia: a comparative study at the Korle-Bu Teaching Hospital, Ghana. *Integrated Blood Pressure Control* 2017;10 9-15.
10. Smith RA, Kenny LC. Current thoughts on the pathogenesis of pre eclampsia. *Obstet Gynaecol*. 2006;8(1):7-13.
11. Kanagal DV, Rajesh A, Rao K, Harshini DU, Shetty H, Kumari S [11] et al. Levels of Serum Calcium and Magnesium in Pre-eclamptic and Normal Pregnancy: A Study from Coastal India. *J Clin Diagn Res*. 2014; 8(7):OC01-OC04.
12. 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;133:162-70.
13. Sarwar MS, Ahmed S, Ullah MS, Kabir H, Rahman GKMM, Hasnat A, et al. Comparative Study of Serum Zinc, Copper, Manganese and Iron in Pre-eclamptic Pregnant Women. *Biol Trace Elem Res*. 2013;154:14-20.
14. Akinloye O, Oyewale OJ, Oguntibeju OO. Evaluation of trace elements in pregnant women with pre eclampsia. *Afr J Biotechnol*. 2010;9:5196-202.
15. Chaudhary RK, Niraula A, Bataju M, Baranwal KJ, Khan SA, Bhatt RD et al. Serum Calcium and Magnesium levels in Pre-eclampsia. *National Journal of Laboratory Medicine*. 2018;7(4):BO01-06.
16. Conde-Agudelo A, Belizan J.M. Risk factors for preeclampsia in a large cohort of Latin American and Caribbean women. *BJOG*. 2000;107(1):75-83.
17. Hofmeyr GJ, Duley L, Atallah A. Dietary calcium supplementation for prevention of pre-eclampsia and related problems: a systematic review and commentary. *BJOG*. 2007;114: 933-43.
18. Moholkar AP, Bankar MP, Pujari KN, Jadkar SP. SERUM CALCIUM AND MAGNESIUM LEVELS IN PREECLAMPSIA. *Int J Pharm Bio Sci*. Volume 4| Issue 3 |JUL-SEPT|2014|42-45.
19. Sandip S, Asha K, Paulin G, Hirens S, Gagandeep S, Amit V. A Comparative Study of Serum Uric Acid, Calcium and Magnesium In Preeclampsia and Normal Pregnancy. *JARBS*, 2013; 5(1): 55-58.
20. Gamal Mohammed El-Maghraby, M., Mohammed Zakarya, A. E., Abd EL-Latif Hashish, M., Aly El-Boghdady, A. COMPARATIVE STUDY BETWEEN SERUM CALCIUM AND MAGNESIUM LEVELS IN PRE ECLAMPSIA VERSUS NORMAL PREGNANCY. *Al-Azhar Medical Journal*, 2022; 51(2): 999-1014.
21. Ugwuja EI, Famurewa AC, Ikaroha CI. Comparison of Serum Calcium and Magnesium Between Preeclamptic and Normotensive Pregnant Nigerian Women in Abakaliki, Nigeria. *Ann Med Health Sci Res*. 2016 Jan-Feb;6(1):33-7.
22. Ositadinma OL, Ezike OV, Azubuike ON, Nwosu OB, Atha nasius OO. Evaluation of serum calcium level in pregnant normotensive and pre-eclamptic/eclamptic women in Nnewi, Nigeria: a case control study. *Savant J Med Med Sci* 2015 Sep;1(4):60-64.
23. Chaurasia PP, Jadav PA, Jasani JH. Changes in serum calcium and serum magnesium level in preeclamptic vs normal pregnancy. *Int J Biomed Adv Res*.2012;3:511-513.
24. Baruah K, Choudhury B (Dutta), Borgohain MK, Choudhury NH. A comparative study of the serum calcium level in normal pregnant and pre-eclamptic women attending Gauhati Medical College and Hospital. *Int J Biomed Adv Res* 2015;6(11):776-779.
25. Aslam F, Hayat I, Zakir FA, Haider SS, Shams Un Nisa, Sadaf Un Nisa. Comparative analysis of serum calcium and magnesium as a better predictor in cases of mild and severe pre-eclampsia. *Professional Med J* 2020; 27(8):1722-1727.
26. 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. 2006; 19(6): S148
27. Al-Jameil N, Tabassum H, Ali MN, Qadeer MA, Khan FA, Al-Rashed M. Correlation between serum trace elements and risk of preeclampsia: A case controlled study in Riyadh, Saudi Arabia. *Saudi J Biol Sci*. 2017 Sep;24(6):1142-1148.
28. Agu CT, Okeudo C. A Comparative Study of Serum Calcium Levels between Pre-eclamptic and Normotensive

- Singleton Pregnancies in Federal Medical Centre, Owerri. *J Adv Med Medical Res.* 2018;27(11):1-8.
29. Pipkin FB. Risk Factors for Pre-eclampsia. *N Engl J Med.* 2001;344:925-6
 30. Vanaja D, Shaila C, Banu R. Association of serum calcium and magnesium levels in pre-eclampsia: A case control study. *Int J of Clin Obstet and Gynaecol* 2021; 5(1): 77-79.