Comparison of Maternal Serum Calcium Level between Preeclamptic and Normotensive Pregnancies

Nurun Nahar Ruma[1*] Bonita Biswas[2] Sharmila Barua[3] Zeenat Rehena[2]
Syeda Yeasmin Akter[4] Afroza Bilkis[4] Abdullah Al Morshed[5]

Abstract

Background: The pathophysiology of preeclampsia remains poorly understood despite having many studies. The association of decreased calcium level Preeclampsia (PE) has been proposed for decades. This study aimed to compare serum total calcium levels between women with preeclampsia and normotensive pregnant women at a tertiary care teaching hospital in Bangladesh.

Materials and methods: One hundred pregnant women with a gestational age of more than 28 weeks and singleton pregnancy [50 preeclamptic (Cases) women and 50 normotensive pregnant women (Control)] were included in the selected case-control study from the Obstetrics & Gynecology Department of Chittagong Medical College Hospital. On admission, venous blood samples were collected before the commencement of treatment. Serum total calcium levels were estimated and compared between the two groups.

Results: Out of 50 cases, 23 (46%) had preeclampsia without severe features and 27 (54%) had preeclampsia with severe features. The mean (± standard deviation) serum level of calcium in the control group, PE patients without severe features and PE patients with severe features were 9.14±0.48 mg/dl, 8.31±0.59and 8.29±0.61mg/dl, respectively. The meanserum total calcium level was significantly lower in preeclamptic patients with severe features and preeclamptic patients without severe features than the normotensive women ($p<0.001$ for both). Hypocalcemia was found to have an incidence rate of 12% in controls and 58% among cases. The adjusted odds of having preeclampsia was almost eleven times higher among those participants with low total serum calcium level (Odds ratio 10.81, 95% confidence interval 2.98-39.16).

Conclusion: In conclusion, reducing serum calcium levels during pregnancy might contribute to the aetiology of preeclampsia, and supplementing these elements to the diet may be useful in preventing preeclampsia.

Key word: Normotensive; Preeclampsia; Serum calcium.

Introduction

Preeclampsia (PE) is a maternal health issue in worldwide and is responsible for maternal and neonatal severe morbidity and mortality.[1] PE and eclampsia-related mortality constitute a significant concern despite advances in reducing maternal and infant mortality in Bangladesh.[2] A recent study reported that in a maternity clinic of Dhaka, 44% of the 3rd trimester pregnant women were suffering from preeclampsia.[3] Therefore, interventions to alleviate these risks are urgently required and one of the ways is to address the modifiable risk factors of preeclampsia. Prevention of preeclampsia remains a cornerstone of therapeutic management because there is currently no curative treatment.[1]

Calcium is an essential element of cellular function. Most studies suggest that an imbalance of several nutrients, especially calcium harms pregnancy. Imbalanced low dietary intake of calcium during pregnancy is harmful for both for the mother and for the growing fetus.[4] The possible role of nutrients like calcium, copper and magnesium has been emphasized in PE.[5] Currently, for the management and prevention of PE calcium supplementation is of interest . This result agrees with the physiological role of calcium in humans. Serum calcium is very important for metabolism at the cellular level. It is vital for muscle contraction, cell death and neuronal activity, making it essential in pregnancy.[6]

One plausible explanation for this observation is that a reduction in serum calcium levels increased intracellular calcium levels, which subsequently caused smooth muscle constriction in blood vessels.

1. Registrar of Obstetrics and Gynecology
Chittagong Medical College Hospital, Chattogram.
2. Assistant Professor of Obstetrics and Gynecology
Chittagong Medical College, Chattogram.
3. Professor of Obstetrics and Gynecology (Retired)
Chittagong Medical College, Chattogram.
4. Junior Consultant of Obstetrics and Gynecology
Chittagong Medical College Hospital , Chattogram.
5. Registrar of Rheumatology
Chittagong Medical College Hospital, Chattogram.

***Correspondence:** **Dr. Nurun Nahar Ruma**
Cell : 01779 76 25 10
E-mail: nurunnaharruma1983@gmail.com

Submitted on : 08.05.2024
Accepted on : 25.05.2024

Consequently, this enhanced vascular resistance ultimately increased systolic and diastolic blood pressure. Moreover, prior studies indicate that elevated calcium excretion, which signifies a disruption in calcium homoeostasis, correlates with elevated blood pressure levels.[7] Low serum calcium levelsstimulating parathyroid hormone and renin release causes hypertension.[8,9]

Biochemical markers of bone turnover, like osteocalcin, bone-specific alkaline phosphatase and procollagen peptides, are higher in preeclampsia than in normal pregnancy, which further suggests that the supplementation of elemental calcium during pregnancies complicated with preeclampsia to preserve the maternal skeleton.[10] However, reports from clinical studies are inconsistent on the role of calcium in the aetiology and prevention of preeclampsia. Reports from different countries such as Bangladesh, India, Sudan, South Korea, Iran, and Ghana have shown significant relationships between low serum calcium levels and PE, whereas other studies from Nigeria, Ghana, and South Africa have shown no significant difference .[11-20]

As the serum calcium picture in preeclampsia remains uncertain, present study, sought to compare serum total calcium levels of preeclamptic and normotensive pregnant women at a tertiary care teaching hospital in Bangladesh. Study findings would contribute to understanding the relevance of early serum calcium screening and supplementation during pregnancy for PE prevention in a more evidence-based manner.

Materials and methods

A case-control study was conducted at the Department of Obstetrics & Gynecology, Chittagong Medical College Hospital from January 2021 to December 2021. Informed written consent was taken from each patient. Before obtaining consent, they have explained the aim and purpose of the research. Confidentiality and anonymity were maintained. The study protocol was approved by the Ethical Review Committee of Chittagong Medical College.

Fifty preeclamptic women with gestational age more than 28 weeks, with singleton pregnancy, were included as cases in this study, and an equal number of normotensive pregnant women with gestational age more than 28 weeks were included as a control group. Women with multiple pregnancies, chronic hypertension, diabetes mellitus, chronic kidney disease, autoimmune disease, and Thrombophilia were excluded.

Maximum patients (Normotensive) were more than 37 weeks they comes with labour pain, others 33-37 weeks they admitted with preterm labour false pain. 6 patients 28-32 weeks admitted with PROM.

Socio-demographic data like educational qualification, occupation, socioeconomic status, residence as well as para, gravida, gestational age, height, weight, and blood pressure were recorded in a structured proforma and two millilitres of venous blood was collected. Then serum total calcium level was measured. Serum calcium 8.5-10.5 mg/dl was considered as normal reference value.

Data were analyzed using a Statistical package for social science (IBM, SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). According to their distribution, quantitative data were expressed as mean (±standard deviation). Differences in mean values between the preeclamptic and normotensive pregnancy groups were tested using the independent sample t-test. Categorical data were expressed as frequency (Percentages) and compared between two groups either by Chi-square test or Fisher's exact test as appropriate. Independent effect of low serum total calcium level on preeclampsia risk was evaluated by multivariate regression analysis, and the results were expressed as an odds ratio with a 95% confidence interval. $p < 0.05$ was considered as statistical significance.

Results

The majority of the pre eclamptic women were in the age group of 20-29 years (62.0%). The majority of the preeclamptic women were multiparous (74.0%). More than half (58.0%) of the preeclamptic women had gestational age between 33-36 weeks. On the other hand 58% of the normotensive women had gestational age 37 weeks or more.The majority (64.0%) of the preeclamptic women reported that their pregnancies were unplanned. The mean BMI, was significantly higher in preeclamptic women compared to normotensive women (Table I). Out of 50 PE patients, 27(54.0%) had PE with severe features and other 23(46.0%) had PE without severe features.

Table I Demographic and obstetric characteristics of the participants

Variables	Preeclamptic (n=50)	Normotensive (n=50)	p value
Age group			
<20 years	5(10.0)	3(6.0)	0.540*
20-29 years	31(62.0)	36(72.0)	
30-39 years	14(28.0)	11(22.0)	
Parity			
0	13 (26.0)	19 (38.0)	0.137*
1	17 (34.0)	20 (40.0)	
≥2	20 (40.0)	11 (22.0)	
Gravida			
Primi	13 (26.0)	17 (34.0)	0.383*
Multi	37 (74.0)	33 (66.0)	
Gestational age			
28-32 weeks	11 (22.0)	6 (12.0)	0.001*
33-36 weeks	29 (58.0)	15 (30.0)	
≥37 weeks	10 (20.0)	29 (58.0)	
Planning of pregnancy			
Planned	18 (36.0)	30 (60.0)	0.016*
Unplanned	32 (64.0)	20 (40.0)	
Antenatal checkup			
Regualr	24 (48.0)	31 (62.0)	0.159*
Irregular	26 (52.0)	19 (38.0)	
BMI,kg/m^2	28.9±2.2	27.7±1.8	0.003†

Data were expressed as frequency (%) or Mean±SD, BMI: Body Mass Index, *Chi-square test or †independent sample t-test.

Serum calcium level (Mean±SD) in the preeclamptic women was found to be significantly lower in than the normotensive women (Table II). Twenty nine (58%) of the preeclampsia cases and six (12%) of the normotensive women recorded low total serum calcium concentrations (Table II).

Table II Distribution of patients in preeclamptic group and normotensive according to serum calcium

Serum calcium	Preeclamptic (n=50)	Normotensive (n=50)	p value
Calcium level, mg/dl			
Mean ±SD	8.31±0.59	9.14±0.48	<0.001†
Range	6.90-9.40	8.50-10.20	
Calcium status			
Low	29 (58.0)	6 (12.0)	<0.001*
Normal	21 (42.0)	44 (88.0)	

Data were expressed as frequency (%) if not mentioned otherwise; *Chi-square test or †independent sample t-test.

The mean difference of total serum calcium level between PE without severe features and PE with severe features were not significant statistically (p=0.995) (Table III).

Table III Pair-wise comparison ofmean serum calcium level among threegroups

Pair wise comparison	Serumtotal calcium level, mean±SD, inmg/ml	p value*
Normotensive vs. PE with severe features	9.14±0.48 versus 8.29±0.61	<0.001
Normotensive vs. PE without severe features	9.14±0.48 versus 8.31±0.59	<0.001
PE without severe features vs. PE with severe features	8.31±0.59 versus 8.29±0.61	0.995

*Independent sample t test.

Multivariate regression was used to estimate the effect of low serum calcium level on preeclampsia risk after adjusting for other potential covariates like parity, gestational ageand BMI. The result was presented in Table IV. On multivariate analysis, the odd ofhaving preeclampsia was almost eleven times higher among those participants with low total serum calcium level (OR 7.94, 95% CI2.63-23.90).

Table IV Multivariate logistic regression for the factors associated with preeclampsia

Variables	OR	95% CI for OR		p Value
		Lower	Upper	
Parity				
Primiparous	Reference			
Multiparous	3.507	0.869	14.163	0.078
Gestational age				
37weeks	Reference			
33-36 weeks	1.682	0.323	8.753	0.537
28-32 weeks	1.844	0.484	7.024	0.370
BMI kg/m^2	0.963	0.684	1.356	0.829
Serum calcium				
Normal	Reference			
Low	10.805	2.982	39.155	<0.001
Planning of pregnancy				
Planned	Reference			
Unplanned	0.376	0.099	1.423	0.150
Antenatal checkup				
Regular	Reference			
Irregular	1.204	0.312	4.643	0.787

OR: Odds ratio; CI: Confidence Interval.

Discussion

Our study demonstrated the mean serum total calcium level was lower in the preeclamptic group than in normotensive pregnancies.

More than half (58%) of the subjects in the preeclamptic group had low serum total calcium level compared to only 12% of the normotensive pregnant group.

The age range was divided into three categories for the preeclamptic group and 10% respondents were below 20 years, 62% were 20 to 29 years and about 28% were in 30 years and above. This age distribution of the preeclamptic women had a similarity with arecent study from Bangladesh,[3] where the majority of the patients (75%) were below 30 years. The distribution of age of the cases in the present study was also comparable to the other studies conducted in and around our country.[12,21,22] The present study showed no statistically significant difference in maternal age between normotensive and pre-eclampsia.

In the present study the mean serum total calcium level was 8.31±0.59 mg/dl for the patient with PE and 9.14±0.48 mg/dl for those with normotensive pregnancy. The mean difference was found to be highly significant statistically. The finding of the present study was in line with the previous study findings from Bangladesh, [11,12,22,23] where serum calcium level was significantly low in preeclamptic group of women compared to normotensive pregnant group. The results of the present study was also found similar to and supported by the study findings of other investigators from different countries.[21,24] Most studies indicated that serum total calcium levels were significantly lower among the PE patients (Differences ranging from 0.30 to 1.95 mg/dL), though not necessarily reaching a state of low serum total calcium state. The exact serum total calcium levels of the case svary across studies, which is presumablyattributable to diverse food cultures, environmental factors or bioavailability.

In the present study, the relation between severity of PE and serum total calcium level was assessed and failed to demonstrate a significant mean difference of serum total calcium level between PE patients with severe features than the PE patients without severe features. Incontrast, Parveen et al. found the mean serum calcium was significantly lower in PE with severe feature compared to PE with mild feature and normal pregnantwomen.[23] This difference between studies could be explained by the small sample size ofboth studies.

In our study, 58% of pregnancy with PE was associated with low serum calcium, whereas it was just 12% among the normal pregnancy. Similarly, in the study of Parveen et al. it was described that 53.7% of pregnant women with PE was associated with hypocalcemia, where as it was just 12.5% among the normal pregnancy.[23] It was found that, both the preeclamptic and normotensive groups were similar interms of the sociodemographic and clinical characteristics and thus eliminating most of the effect of covariates and confounding factors on serum total calcium level. However, the effect of serum total calcium level on PE was further adjusted for other potential confounders like gestational age and BMI. Finally, it was revealed that the odd of having PE was almost eleven times higher among those participants with low total serum calcium level (OR:7.94, 95% CI: 2.63-23.90) compared to the participants with normal serum total calcium. It was in agreement with the findings of Gebreyohannes et al. where on multivariate analysis, the odds of having PE was almost eight times higher among those participants with lowionized calcium level (OR7.5,95% CI2. 388–23.608) and three times higher in those with low total serum calcium level (OR3.0, 95% CI1.024–9.370).[25]

The findings mentioned above in the present study and similar studies confirmed a significant relationship between serum calcium levels and the risk of developing PE. The data supported calcium deficiency could be a cause of PE. In contrast, some other investigators from Bangladesh as well as from other countries found that serum calciumin preeclamptic group did not differ significantly from the normal pregnant group.[18-20] It is possible that the differences in the findings may be attributed to not only differences in the methodof assay of serum calcium but also dietary habits and socio-economic status would be influencial. The dietary history of the participants in this study was, however, notelucidated. Additionally, differences in sample size may also account for the observed differences in findings

Limitations

The present study had few limitations. As the samples were selected conveniently from a single tertiary-level hospital, the results might not be generalized to the whole population. Another limitation was the late gestation age at sampling across the two groups in most cases. Information regarding dietary intake was absent. The serum total calcium status of the participants was

measured at the same time as the PE status. So, the temporal association between these two variables needed to be explained by future prospective studies.

Conclusions

This study demonstrated an association of low serum total calcium levels and preeclampsia. So, serum total calcium level may have an role in the pathogenesis of PE.

Recommendations

Early identification of hypocalcaemia and supplementation of calcium to pregnant women may help reduce the incidence and complications of PE.

Acknowledgement

Thankful to participants of the study and Department of Obstetrics and Gynecology of CMCH.

Contribution of authors

NNR-Conception, acquition of data, drafting & final approval.

BB-Acquitation of data, data analysis, drafting & final approval.

SB-Design, interpretation of data, critical revision & final approval.

ZR-Acquitation of data, drafting & final approval.

SYA-Data analysis, interpretation of data, drafting & final approval.

AB-Acquitation of data, drafting & final approval.

AAM-Data analysis, critical revision & final approval.

Disclosure

All the authors declared no competing interest.

References

1. Karrar SA, Hong PL. Preeclampsia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2022. https://www.ncbi.nlm.nih.gov/books/NBK570611/.

2. National Institute of Population Research and Training (NIPORT). 2012, 'Bangladesh Maternal Mortality and Health Care Survey. 2010. https://www.icddrb.org/images/stories/WhatWeDo/HealthProgramme/PopulationScience/bmms.

3. Akter K, Khanum H. Prevalance of pre-eclampsia and factors responsible among third trimester pregnant women in hospital of dhaka. Biomedical Journal of Scientific & Technical Research. 2021;33(4):26089-26097.

4. Pathak P, Kapil U. Role of trace elements zinc, copper and magnesium during pregnancy and its outcome. The Indian Journal of Pediatrics. 2004;71:1003-1005.

5. 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;133:162-170.

6. Sandip S, Asha K, Paulin G, Hiren S, Gagandeep S, Amit V. A comparative study of serum uric acid, calcium and magnesium in preeclampsia and normal pregnancy. J Adv Res Biol Sci. 2013;5:55-58.

7. Kesteloot H, Tzoulaki I, Brown IJ, Chan Q, Wijeyesekera A, Ueshima H,et al. Relation of urinary calcium and magnesium excretion to blood pressure: the international study of macro-and micro-nutrients and blood pressure and the international cooperative study on salt, other factors, and blood pressure. American journal of epidemiology. 2011;174(1):44-51.

8. Kumar A, Kaur S. Calcium: a nutrient in pregnancy. The Journal of Obstetrics and Gynecology of India. 2017;67:313-318.

9. Indumati V, Kodliwadmath MV, Sheela MK. The role of serum electrolytes in pregnancy induced hypertension. J Clin Diagnostic Res. 2011;5(1):66-69.

10. Kumar A, Devi SG, Prasad S, Kapoor S, Sharma S. Bone turnover in preeclampsia complicated pregnancy in North Indian women. Journal of Obstetrics and Gynaecology Research. 2012;38(1):172-179.

11. Akhtar S, Begum S, Ferdousi S. Calcium and zinc deficiency in preeclamptic women. Journal of Bangladesh Society of Physiologist. 2011;6(2):94-99.

12. Bhowmick R, Bhowmik J, Chowdhury S, Nur AN, Begum F. Serum Calcium Level in Patients with Pre Eclampsia: A Case Control Study. Chattagram Maa-O-Shishu Hospital Medical College Journal. 2021;20(1):33-36.

13. Elmugabil A, Hamdan HZ, Elsheikh AE, Rayis DA, Adam I, Gasim GI. Serum calcium, magnesium, zinc and copper levels in sudanese women with preeclampsia. PloS one. 2016;11(12):e0167495.

14. Kanagal DV, Rajesh A, Rao K, Devi UH, Shetty H, Kumari S, et al. Levels of serum calcium and magnesium in pre-eclamptic and normal pregnancy: A study from Coastal India. Journal of clinical and diagnostic research. 2014;8(7):OC01.

15. Kim J, Kim YJ, Lee R, Moon JH, Jo I. Serum levels of zinc, calcium, and iron are associated with the risk of preeclampsia in pregnant women. Nutrition research. 2012;32(10):764-769.

16. Farzin L, Sajadi F. Comparison of serum trace element levels in patients with or without pre-eclampsia. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2012;17(10):938.

17. 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;14(1):1-8.

18. Darkwa OE, Antwi-Boasiako C, Djagbletey R, Owoo C, Obed S, Sottie D. Serum magnesium and calcium in preeclampsia: A comparative study at the Korle-Bu Teaching Hospital, Ghana. Integrated blood pressure control. 2017:9-15.

19. Ugwuja EI, Famurewa AC, Ikaraoha CI. Comparison of serum calcium and magnesium between preeclamptic and normotensive pregnant Nigerian women in Abakaliki, Nigeria. Annals of medical and health sciences research. 2016;6(1):33-37.

20. Richards DG, Lindow SW, Carrara H, Knight R, Haswell SJ, Van der Spuy ZM. A comparison of maternal calcium and magnesium levels in pre eclamptic and normotensive pregnancies: An observational case–control study. BJOG: An International Journal of Obstetrics & Gynaecology. 2014;121(3):327-336.

21. Kumar N, Singh AK. Maternal serum uric acid and calcium as predictors of hypertensive disorder of pregnancy: A case control study. Taiwanese Journal of Obstetrics and Gynecology. 2019;58(2):244-250.

22. Rashid B, Richard MM. Low Serum Calcium Levels in Pre-eclampsia. Journal of South Asian Federation of Obstetrics and Gynaecology. 2017;7(3):126-129.

23. Parvin S, Chowdhury SB, Nahar KN, Hoque MM. Serum calcium and its association with preeclampsia. Bangladesh Journal of Medical Science. 2021;20(2):379.

24. Jafrin W, Paul SK, Sultana S, Rabeya S, Hoque MR, Muttalib MA. Serum calcium level among normal pregnant and pre-eclamptic women in a sub urban area of Bangladesh. Mymensingh Medical Journal. 2013;22(3):418-422.

25. Gebreyohannes RD, Abdella A, Ayele W, Eke AC. Association of dietary calcium intake, total and ionized serum calcium levels with preeclampsia in Ethiopia. BMC pregnancy and childbirth. 2021;21(1):1-7.