

RESEARCH ARTICLE

Comparative Study of Serum Calcium in Preeclampsia and Normal Pregnancy at Government Medical College and Hospital, Aurangabad City, India

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ABSTRACT

Introduction: Preeclampsia, a pregnancy-specific disorder, is a global health problem. The major mineral calcium has been proposed to play an important role in the pathogenesis of preeclampsia. The present study was aimed to compare the level of serum calcium in normal pregnant women and in preeclampsia and determine the association of serum calcium with severity of the disease.

Study design: This study included 60 pregnant women diagnosed with preeclampsia as cases and 60 healthy pregnant women as controls in the third trimester of gestation. The concentration of total serum calcium was measured in both groups.

Results: Serum calcium level was significantly decreased in preeclamptic women than in normal pregnant women. Serum calcium showed significant negative correlation with systolic and diastolic blood pressure.

Conclusion: Hypocalcemia found in preeclamptic women in our study suggests that serum calcium may have a role in the etiopathogenesis of this disorder. Routine estimation of serum calcium may be useful as a diagnostic marker in preeclampsia.

Keywords: Hypocalcemia, Preeclampsia, Pregnancy, Serum calcium.

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INTRODUCTION

Preeclampsia is a progressive, multisystemic, and multifactorial pregnancy-specific disorder. It is characterized by the

new onset of hypertension (systolic/diastolic blood pressure $\geq 140/90$ mm Hg), proteinuria (≥ 300 mg/24 hours), and pathological edema after 20 weeks of gestation.¹ According to the World Health Organization report, it is the leading cause of maternal and fetal morbidity and mortality, particularly in developing countries.² Worldwide, preeclampsia affects 5 to 8% of all pregnancies.³ It is associated with various complications like disturbed autoregulation of cerebral circulation, visual disturbances, oliguria, pulmonary edema, and fetal growth restriction.⁴ The hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, a serious manifestation of preeclampsia, contributes to increased morbidity and mortality in this disorder. If untreated, preeclampsia progresses to eclampsia manifesting as convulsions, which may lead to confusion, coma, and death.

Despite considerable research, the etiology of preeclampsia is elusive and is still a mystery. It has attracted many schools of thoughts and, hence, was once called as "the disease of theories."⁵ The most plausible theory is the abnormal placentation. This states the inadequate invasion of maternal spiral arterioles by fetal cytotrophoblasts leading to insufficient maternal vascular remodeling and angiogenesis. These result in widespread vasospasm and decreased placental perfusion.⁶ Generalized systemic inflammatory response, increased productions of antiangiogenic factors, and endothelial injury are hallmarks of the disorder.⁷

While clinical symptoms of preeclampsia unveil themselves after 20th week of gestation, the predominant pathology, i.e., endothelial cell dysfunction actually sets in at the beginning of pregnancy.⁸ To overcome this "diagnostic delay," many tests have been endeavored to establish the diagnosis of preeclampsia as early as possible, before the patient presents with advanced complications.¹ Evidences have shown that alterations in the maternal serum levels of some minerals may be implicated in the pathogenesis of preeclampsia.⁵ Alterations in calcium homeostasis during pregnancy is more significant in this regard.⁷

Physiologically, calcium is an important macromineral. Intracellular calcium plays a key role in various cellular functions, such as muscle contraction, hormone secretions,

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neuronal activity as well as cellular death. Extracellular calcium is important for bone mineralization, blood coagulation, etc.⁵ Changes in plasma calcium levels have shown to alter the blood pressure.⁴ Approximately 200 mg/day of calcium is deposited in the fetal skeleton via placenta in the third trimester of pregnancy and maternal urinary calcium excretion is doubled during this period.⁷

Decreases in serum calcium level stimulate the release of rennin and parathyroid hormones. These hormones increase intracellular concentration of calcium in vascular smooth muscle cells. This leads to vasoconstriction and increased peripheral vascular resistance, culminating in raised blood pressure.⁶ Thus, abnormalities in calcium homeostasis may contribute to the abnormal vasculopathy that has been already manifested in preeclampsia.²

There are no well-established strategies for the prevention of preeclampsia. Some studies have shown that dietary calcium supplementation appeared to be effective in reducing the risk of developing preeclampsia.⁷

In view of the above findings, the present study was conducted to assess total serum calcium concentration in preeclampsia and to find the association between preeclampsia and calcium level.

MATERIALS AND METHODS

This case-control study included 120 pregnant women, who were primigravida, between 20 and 30 years of age, and in the third trimester of pregnancy. Study participants were matched for body mass index (BMI), maternal age, and gestational age. Pregnant women with renal disease, cardiovascular disease, thyroid and other endocrine disorders, liver disorder, smoking, alcoholism, and those on calcium supplementation were excluded from study.

Written informed consent was taken from all the participants. Institutional ethical committee approved the study protocol.

We obtained the information regarding demographic variables like education, occupation, income, and residence. Study participants in both groups were from the middle class strata. Family history of preeclampsia in mother or sister was recorded. Clinical history regarding preexisting hypertension, preexisting diabetes, previous history of convulsions was obtained. Participants were also asked about excessive weight gain, urinary tract infection, persistent headache, visual disturbances, nausea, vomiting, and epigastric pain.

Height was measured with each subject standing erect against wall without shoes with a wall-mounted ruler. Weight was measured using a standard weighing scale without shoes and subjects wearing light clothes. The BMI was calculated using the formula, weight (kg)/height (m²).

Blood pressure of each participant was taken by using mercury sphygmomanometer with appropriate sized cuff after 10 minutes of rest. Blood pressure was measured in the sitting position with the arm at the level of the heart. Clean-catch, mid-stream urine sample was obtained in a clean sterile container and tested with urinalysis strip for proteinuria. The test strip is dipped in the urine sample and color changes in specific reagent pads are noted and compared with the reference color chart on the testing strip container.

Preeclampsia was diagnosed according to the guidelines of American College of Obstetrics and Gynaecology,⁴ i.e., systolic blood pressure ≥ 140 mm Hg or a rise of 30 mm Hg and diastolic blood pressure ≥ 90 mm Hg or a rise of 15 mm Hg (manifested on at least two occasions 6 hours apart) and proteinuria ≥ 300 mg in 24-hour urine samples (manifested on at least two occasions 6 hours apart). Preeclampsia is of two degrees: Mild—blood pressure $\geq 140/90$ mm Hg, urinary albumin traces or +1; and severe—blood pressure $\geq 160/110$ mm Hg, urinary albumin +2.⁹

The subjects were divided into three groups. Group I included normal healthy pregnant women as controls (60), group II included women with mild preeclampsia (30), and group III included women with severe preeclampsia (30). Venous blood samples were collected and analyzed for serum calcium. Serum calcium was estimated by the O-cresolphthalein complexone method.

Sample size was calculated with the help of Open-epi software as 57 for cases and 57 for controls by the Fleiss method by taking the proportion of controls as 6.6 and cases as 25.91 with odds ratio as 4.95 with reference from study done by Sima Hashemipour et al.¹⁰

Statistical Analysis

The results were analyzed by GraphPad prism software, version 5. Differences in demographic characteristics and biochemical parameters were statistically analyzed using one-way analysis of variance test. Pearson's correlation was used to study the correlation among the study parameters. *p*-value < 0.05 was considered statistically significant.

RESULTS

A description of the demographic characteristics of the study and the control groups is shown in Table 1. The mean age, gestational age, and BMI did not show any significant difference between the two groups. The systolic and diastolic blood pressures were significantly increased (*p* < 0.05) in preeclamptic patients compared with normal pregnant women.

Table 1: Comparison of demographic characters in normal pregnancy, mild preeclampsia, and severe preeclampsia groups

Clinical parameters	Controls	Mild preeclampsia	Severe preeclampsia	p-value
Age (years)	25.50 ± 2.9	24.40 ± 3.8	25.0 ± 4.3	>0.05
BMI (kg/m ²)	25.45 ± 3.30	27.81 ± 2.05	24.91 ± 3.19	>0.05
Systolic BP (mm Hg)	108.13 ± 6.35	148.62 ± 7.2	172.69 ± 11.6	<0.05*
Diastolic BP (mm Hg)	74.8 ± 5.2	96.81 ± 4.8	120.53 ± 7.54	<0.05*
Gestational age (weeks)	31.69 ± 5.28	32.71 ± 4.30	33.15 ± 4.09	>0.05

BP: Blood pressure; *Significant (<0.05)

Table 2: Comparison of biochemical parameters in normal pregnancy, mild preeclampsia, and severe preeclampsia groups

Biochemical parameters	Controls	Mild preeclampsia	Severe preeclampsia	p-value
Sr. calcium (mg %)	9.96 ± 0.55	8.74 ± 0.56	7.81 ± 0.42	<0.001*

*Significant (<0.05)

Table 3: Correlation of serum calcium with systolic/diastolic blood pressure among mild preeclampsia and severe preeclampsia groups

Group	Biochemical parameters (r-value)			p-value
	Systolic BP	Diastolic BP		
Normal pregnancy	Ca 0.22	0.18	–	
Mild preeclampsia	Ca –0.52	–0.49		<0.01*
Severe preeclampsia	Ca –0.64	–0.56		<0.01*

BP: Blood pressure; *Significant (<0.05)

The preeclamptic patients had significantly decreased serum calcium levels compared with the healthy controls ($p < 0.05$). Also, serum calcium level was much lower in severe preeclampsia than in mild preeclampsia (Table 2).

A significant negative correlation was found between serum calcium and systolic/diastolic blood pressure (Table 3).

DISCUSSION

Preeclampsia, a complex, dynamic pregnancy disorder, is associated with increased maternal and fetal morbidity and mortality especially in developing countries. Although the precise factors that may cause preeclampsia are unknown, the most accepted mediator of this disorder is the remodeling of uteroplacental arteries and is considered as woman's immunological intolerance to the semiallogenic fetus and placenta. Ultimately, abnormal placentation leads to widespread vasospasm and endothelial injury in multiple organs.⁷

Pregnancy is an anabolic state associated with complex physiological adaptations in the maternal system. These changes are necessary to meet the metabolic demands of a growing fetus. Nutritional deficiencies are usual during this period, particularly in developing countries.⁴ Calcium homeostasis needs to be maintained adequately in pregnancy because its deficiency may lead to various complications.¹¹ A diet deficient in an essential mineral—calcium—during pregnancy has been implicated to be responsible for various gestational complications, such as preeclampsia, preterm birth, and intrauterine growth retardation.⁴

Calcium metabolism is remarkably altered in vascular smooth muscle cells in preeclampsia. During pregnancy, there is increase in intracellular calcium concentration. This effect is exaggerated in preeclampsia due to notable increase in membranous calcium content.

Our study found that the mean serum calcium level was significantly decreased in preeclamptic patients than in control group. Serum calcium can reduce blood pressure by various mechanisms. Calcium stimulates release of parathyroid hormone and renin from kidney. This increases intracellular calcium concentration, particularly in vascular smooth muscle cells, leading to vasoconstriction.¹² Low serum calcium influences the production of other vasoactive agents, such as nitric oxide, prostacyclins, and angiotensin.⁷ In addition, calcium can also modulates oxidative stress contributing to the pathology of preeclampsia.^{11,13} Abnormal placentation in preeclampsia leads to decreased activation, increased catabolism, and impaired placental uptake of vitamin D and is unable to produce sufficient levels of 1,25-(OH)₂ vitamin D. This results in inadequate calcium absorption, decreased serum calcium levels, and a secondary rise in parathyroid hormone.⁷

In preeclampsia, there is oxidative stress, inflammation, widespread vasospasm, ischemia, and cellular hypoxia leading to endothelial dysfunction. This cellular injury results in influx of calcium ions into the cell leading to increased intracellular ions and loss of calcium homeostasis.¹⁴ Thus, serum calcium appears to play an important role in the development of preeclampsia and it can evolve as a sensitive test for early detection of this disorder.¹⁵

In this study, we also found a negative correlation between serum calcium and systolic/diastolic blood pressure in preeclamptic women. This suggests a strong association between deficiency of this mineral and onset and progression of preeclampsia.¹³ Our findings are similar to many former studies by Onyegbule et al,⁵ Sultana et al,⁹ Sirajwala et al,¹¹ Akhtar et al,¹³ and Moholkar et al.¹⁵ In contrast, some researchers did not demonstrate significant

difference between the two groups.^{16,17} These contrasting findings may be due to differences in genetic pool of population, method of sample collection, storage and processing of sample, and method of analysis.⁷

So, from our study, we can deduce that hypocalcemia is significantly associated with preeclampsia and serum calcium may have a role in its etiology. This study may alert obstetrician and patients about the harmful effects of calcium deficiency on obstetric outcome. Calcium supplementation may be considered in women at high risk of this disorder; which is likely to prevent preeclampsia, consequently improving neonatal outcome. Further studies are needed to know the predictive ability of serum calcium for early diagnosis of this disorder.

CONCLUSION

In the present study, decreased serum calcium correlating with blood pressure has been observed among preeclamptic women. This supports the hypothesis that hypocalcemia may have a role in the etiology of preeclampsia and dietary interventions may reduce the disease risk. The estimation of serum calcium, which is relatively cheap and safe investigation, can be used as a cost-effective screening tool for early prediction of the disease. This will help to establish and enhance existing preventive strategies for this disorder.

LIMITATION

Dietary intake of calcium was not taken into consideration.

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