Research Article

# Evaluation of urinary calcium–creatinine ratio as a diagnostic tool in the management of preeclampsia

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**Abstract**

**Background:** Preeclampsia has a complex pathophysiology in which several studies have reported derangement in calcium metabolism. The decrease in urinary calcium and calcium–creatinine ratio (CCR) could be considered as a risk factor for development of preeclampsia. This ratio is easily measurable, most effective even with spot urine sample.

**Objective:** To study the levels of urinary CCR and to correlate with proteinuria in preeclamptic patients and to assess the role of CCR in urine as a diagnostic marker in preeclampsia.

**Materials and Methods:** This cross-sectional study was carried out in 30 cases of pregnant women diagnosed with preeclampsia and 30 age-matched controls in MS Ramaiah Teaching Hospital, Bangalore over a period of 2 months. Random urine samples were collected from the cases and controls, and urinary calcium, creatinine, and protein were measured using their corresponding methods. The urinary CCR was studied and correlated with proteinuria. All the quantitative variables were described in terms of mean and standard deviation. The differences in the mean values between cases and controls were tested through Student's *t*-test or oblique propriate nonparametric test of significance. To test for differences in the proportion between cases and controls, $\chi^2$ test of significance was employed.

**Result:** It was found that urinary calcium was significantly increased in cases compared with the controls, whereas there was no significant difference in CCR. The CCR had a sensitivity and specificity of 40% and 86.67%, respectively.

**Conclusion:** Although significant numbers of pregnant women with gestational hypertension and preeclampsia did not have decreased ratio, the urinary calcium levels had decreased in preeclamptic patients.

**KEY WORDS:** Calcium–creatinine ratio, proteinuria, preeclampsia, hypocalciuria

## Introduction

Preeclampsia is a clinical condition associated with hypertension and proteinuria, with or without pathological edema that occurs after 20 weeks of gestation and can present as late as 4–6 weeks postpartum. It is characterized by widespread vascular endothelial dysfunction and vasospasm.[1]

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Preeclampsia is also associated with complications such as visual disturbances, oliguria, eclampsia, hemolysis, elevated liver enzymes, thrombocytopenia, pulmonary edema, and fetal growth restriction.

In developing nations, the incidence of the disease is reported to be 4%–18%[1] and is the second most common obstetric cause of stillbirths and early neonatal deaths. Besides having increased maternal morbidity and mortality accounting for 40,000 maternal deaths annually.[2] In the Indian scenario, the incidence of preeclampsia is 5.47% in primigravida and 2.8% in multigravida. It accounts for 44.44% of all cases of hypertensive disorders of pregnancy.[3]

Despite its prevalence and severity, the pathophysiology of this multisystem disorder is still poorly understood. The exact etiology remains unclear even today. Preeclampsia is a multifactorial disease in which both placental and maternal

factors contribute. Different combinations of factors can then lead to differences in disease severity and time of onset. Renal function changes are seen in symptom free women in whom preeclampsia will eventually develop.[4] Methods to reduce the risk of hypertensive disorders in pregnancy have received considerable attention. Research is focusing on prevention rather than treatment.

The currently used diagnostic criteria are increased systolic blood pressure of ≥140 mm Hg or increased diastolic blood pressure of ≥90 mm Hg after 20 weeks of pregnancy in a woman with previously normal blood pressure and proteinuria of 0.3 g or more in 24-h urine sample corresponding with 1+ or greater on a urine dipstick test.[1] Although the 24-h urine protein is diagnostic, the process of sample collection is both cumbersome and inconvenient for the patient. The quick alternative method of the dipstick, although ideal for peripheral health center with limited facilities, is not accurate and therefore not reliable as a screening tool or diagnostic test.[5]

The other investigations such as liver function tests, lowered platelet count, and tests for pulmonary edema may be more expensive, nonspecific to preeclampsia, and only positive when the disease has advanced. The currently used screening or predictive tests include Doppler ultrasound, Doppler velocimetry in uterine artery or detection of the free fetal DNA in maternal serum, α-fetoprotein, cellular and total fibronectin, hemoglobin, hematocrit, human chorionic gonadotrophin, estriol, uric acid, and so on. These tests are expensive, require the proper equipment to perform, and may be nonspecific.[5]

Several researchers have reported that hypocalciuria is associated with preeclampsia due to derangement in calcium metabolism associated with this condition.[6] Also hypocalciuria could be preceded by the development of preeclampsia. Low serum calcium may cause high blood pressure by stimulating parathyroid hormone and renin release and also by inducing vasoconstriction by increasing its level in vascular smooth muscle. Calcium might also have an indirect effect on smooth muscle function by increasing magnesium levels.[7] Hence, the decrease in calcium–creatinine ratio (CCR) could be considered as a risk factor for the development of preeclampsia in pregnancy.[6]

This ratio is easily measurable, most effective even with spot urine sample compared with other methods that are expensive, time consuming, involving complex procedures, requiring specialized equipment, or inaccurate. Hence, we intended to study the role of CCR in urine as a diagnostic marker in preeclampsia.

## Materials and Methods

The study was carried out in patients diagnosed with preeclampsia attending the outpatient department and admitted for safe confinement to the labor ward of MS Ramaiah Teaching Hospital, Bangalore. Age-matched normal pregnant women were selected as controls. The ethical clearance was taken from the institute and informed consent was obtained from both the cases and controls.

It was a prospective cross-sectional study with a sample size of 30 in each group. The sample size was based on a study by Kazerooni and Hamze-Nejadi.[8] The patients diagnosed with preeclampsia based on urine analysis and blood pressure recording in the second and third trimester were included in the study. The women with history of chronic hypertension, diabetes mellitus, and kidney disease were excluded. Age-matched normal pregnant women were selected as controls. Random urine samples were collected from the cases and controls in a sterile collection bottle and transferred into a sterile plain glass tube and stored at 20°C. The following three parameters were measured from the urine sample using their corresponding methods: urinary calcium by o-cresolphthalein complex method,[9] urinary creatinine by modified Jaffe's method,[9] and urinary protein by turbidimetric method.[10]

### Statistical Analysis

All the quantitative variables such as urinary calcium, urinary creatinine, urinary protein, CCR, protein–creatinine ratio, proteinuria, and age were described in terms of mean, median, and standard deviation. Differences in the mean values between cases and controls were tested through oblique nonparametric test of significance. To test for differences in the proportion between cases and controls, Mann–Whitney test of significance for *p*-values was employed.

## Results

Among the 30 cases of preeclamptic women included in this study, the mean age was 26.1 and ranged between 19 and 39 years and in case of the controls, mean age of 24.5 years and ranged between 18 and 36 years of age.

Among the cases, the mean value of urinary calcium was found to be 3.16 mg/dL (0.45–6.32) while in controls it was 15.39 mg/dL (2.05–20.32) with a significant *p*-value of 0.001.

Among the cases, the mean value of urinary creatinine was found to be 41.65 mg/dL (17.3–69.32) while in controls it was 81.93 mg/dL (45.06–114.885) with a significant *p*-value of 0.001.

Among the cases, the mean value of urinary protein was found to be 23.75 mg/dL (19.55–145.175) while in controls it was 12.55 mg/dL (8.2–25.75) with a significant *p*-value of 0.021.

Among the cases, the mean value of urinary CCR was found to be 0.067 (0.0109–0.1868) while in controls it was 0.1222 (0.0652–0.2073) with a *p*-value of 0.072, which was not significant [Table 1].

A receiver-operating curve (ROC) was constructed [Figure 1] with the collected data and the cutoff ratio for CCR used was 0.0669. Using the ROC, the sensitivity was found to be 40% and specificity 86.67%. The positive predictive value was 59.09 and the negative predictive value was 75.04.

**Table 1:** Parameters assessed to calculate the calcium–creatinine ratio and its correlation with proteinuria along with *p*-values

| Parameter | Group | Mean | SD | *p* |
|---|---|---|---|---|
| Age | Cases | 26.4138 | 5.08160 | |
| | Controls | 24.5600 | 4.97561 | |
| Urinary calcium | Cases | 3.16 | 0.4525–6.3225 | 0.001 |
| | Controls | 15.3950 | 2.0575–20.3225 | |
| Urinary creatinine | Cases | 41.65 | 17.3050–69.3225 | 0.001 |
| | Controls | 81.93 | 45.0675–114.885 | |
| Urinary protein | Cases | 23.75 | 9.55–145.175 | 0.021 |
| | Controls | 12.55 | 8.2–25.875 | |
| Calcium–creatinine ratio | Cases | 0.0677 | 0.0109–0.1868 | 0.072 |
| | Controls | 0.1222 | 0.0652–0.2073 | |
| Protein–creatinine ratio | Cases | 0.6750 | 0.2666–3.6794 | |
| | Controls | 0.1828 | 0.1380–0.2597 | <0.001 |

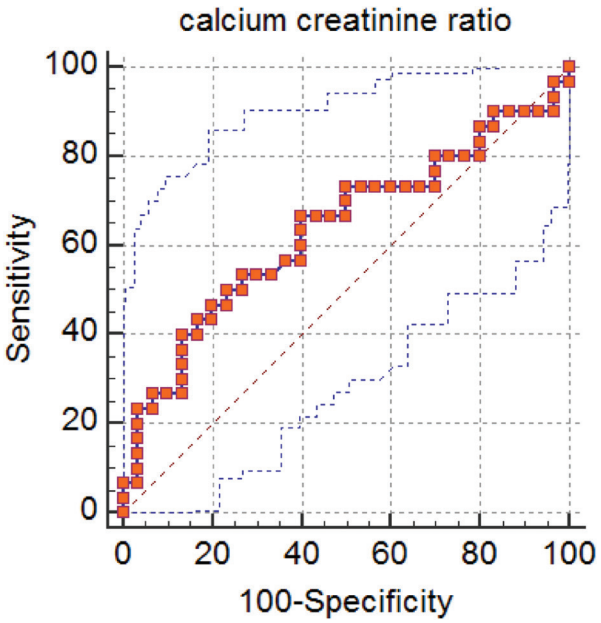


**Figure 1:** Receiver-operating curve indicating sensitivity and specificity.

## Discussion

Preeclampsia has a complex pathophysiology, the primary cause being abnormal placentation. Defective invasion of the spiral arteries by cytotrophoblast cells is observed during preeclampsia.[11] Renal tubular function is also affected leading to the manifestation of hypocalciuria.[12] The 24-h urine protein excretion measurement has been the gold standard for diagnosis of preeclampsia, but it is an inconvenient and time-consuming test.[13]

Parameters assessed in our study were based on previous studies[16] in which urinary calcium, creatinine, protein, and the CCR were determined in a spot urine sample. From our results we have found that the urinary CCR was not significantly altered among cases and controls. It had a sensitivity of 40% and a specificity of 86.67% in agreement with the other studies. However, significant hypocalcuria was seen in cases compared with controls.

The etiology of hypocalciuria in preeclamptics remains obscure, but the study by Taufield et al.[14] proposed the hypothesis that it is because of increased tubular reabsorption, independent of sodium reabsorption, and because of reduced fractional excretion of calcium. Another study by Seely et al.[15] suggested an alternate hypothesis of rise in parathyroid hormone secondary to suboptimal intestinal absorption of calcium leading to increased reabsorption from kidneys.

In addition, there are mixed results on whether CCR is sensitivity to be used as a screening test for the emergence of preeclampsia. Meads et al.[5] conducted an extensive review of current diagnostic modalities in use/under consideration for preeclampsia, including CCR. They concluded that the accuracy of test was generally poor, and while some tests appeared to have high specificity, it was at the expense of compromised sensitivity. The advantages of this method are cost-effectiveness and ease of performance.

However, previous studies by Sanchez–Ramos[16] and Rodriguez et al.[17] have yielded conflicting results, who gave a very high sensitivity of 75% and 80%, respectively, and also a high specificity of 95% and 91%, respectively. These conflicting results highlighted the difference due to sample size, ethnicity of population, and age of gestation when the study was conducted.

In our study, hypocalciuria is significantly increased in pregnant women with preeclampsia although CCR is not significant. This can be due to small sample size and may be due to complex pathophysiology of preeclampsia.

## Conclusion

From our study we can conclude that hypocalciuria precedes an emerging preeclampsia both in gestational hypertensive and normal women. Further research into the cause of hypocalciuria would help understanding the general pathophysiology of the disorder, and to prevent and treat the condition better with probable better screening modalities.

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