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Research Article

## Urinary calcium to creatinine ratio to predict preeclampsia and use of calcium supplementation to prevent preeclampsia

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### ABSTRACT

**Background:** Incidence of preeclampsia is around 5-10% of all pregnancies, and in developing countries around 4-18%. There is hypercalciuria during normal pregnancy, while pre-eclampsia is associated with hypocalciuria and low urinary calcium to creatinine ratio. Low calcium intake has been hypothesized to cause increase in blood pressure. The present study was carried out to investigate significance of urinary CCR in prediction of preeclampsia & role of calcium supplementation in reducing preeclampsia.

**Methods:** 100 pregnant patients were divided into two groups, 50 cases and 50 controls. A spot urine sample was collected for estimation of CCR at around gestational age of 20-24 weeks. Cases were given 2 gm of calcium supplementation. Controls were 1 gm calcium. Then at each visit both the groups, were evaluated for symptoms of preeclampsia. Urinary calcium to creatinine ratio was calculated and those with ratio  $\leq 0.04$  were considered test positive and those with ratio  $>0.04$  were considered test negative.

**Results:** The test (urinary CCR  $\leq 0.04$ ) was positive in 16 patients, 9 developed preeclampsia. The test was negative (urinary CCR  $>0.04$ ) in 84 patients and in those only 5 developed pre eclampsia. Urinary CCR had sensitivity of 63.63%, specificity of 94.87%. Out of 50 cases, only 3 developed preeclampsia. Out of 50 controls, 11 developed preeclampsia.

**Conclusions:** Urinary CCR between 20-24wks of gestation will be an effective screening method for impending pre-eclampsia. Calcium supplementation (2gms/day) can help in prevention of preeclampsia.

**Keywords:** Preeclampsia, Urinary calcium to creatinine ratio (CCR), Calcium supplementation

### INTRODUCTION

Around the world, an estimated 529,000 women die during pregnancy or childbirth.<sup>1</sup> Incidence of preeclampsia is around 5-10% of all pregnancies, and in developing countries around 4-18%.<sup>2-4</sup> It has been reported that, pre-eclampsia is a major cause of both maternal and fetal morbidity and mortality (Bringman et al., 2006).

Unfortunately, the pathophysiology of this multisystem disorder, characterized by abnormal vascular response to placentation, is still unclear.

Delivery is the only curative treatment for pre-eclampsia. Screening women at high risk and preventing recurrences are key issues in the management of pre-eclampsia.

There is hypercalciuria during normal pregnancy, while pre-eclampsia is associated with hypocalciuria and low urinary calcium to creatinine ratio. This phenomenon occurs early enough and persists throughout gestation, so it is useful for early identification of patients at risk.

The present study was carried out to investigate the significance of urinary calcium to creatinine ratio in prediction of preeclampsia and thus may identify

population at greater risk to be included in primary prevention programme.

An inverse relationship between calcium intake and hypertensive disorders of pregnancy was first described in 1980.<sup>5</sup> This was based on the observation that Mayan Indians in Guatemala, who traditionally soak their corn in lime before cooking, had a high calcium intake and a low incidence of pre-eclampsia and eclampsia. A very low prevalence of pre-eclampsia had been reported from Ethiopia where the diet, among other features, contained high levels of calcium.<sup>6</sup>

These observations were supported by other epidemiological and clinical studies and led to the hypothesis that an increase in calcium intake during pregnancy might reduce the incidence of high blood pressure and pre-eclampsia among women with low dietary calcium.

### **Aims of the study**

- To determine the predictive value of urinary calcium to creatinine ratio in a spot urine sample in asymptomatic pregnant female between 20-24 weeks of gestation, for preeclampsia.
- To determine the use of calcium supplementation (2 grams/day) in prevention of preeclampsia.

### **METHODS**

Out of women attending A.N.C. O.P.D. in tertiary care hospital, pregnant women who met the inclusion and exclusion criteria were selected. The study was initiated after seeking approval from ethics committee (CARE). Patients were enrolled for study after obtaining written informed consent from patient and husband or one of the relative.

Our study was randomized, prospective, interventional, case-control study. Randomization was done by means of computer generated randomization list (SAS 9.1 software package).

Inclusion criteria were pregnant women around 20-24 weeks of gestation. Exclusion criteria were history of chronic hypertension, diabetes, renal disease, urolithiasis, preeclampsia in previous pregnancy, family history of preeclampsia, patient who have proteinuria and those with a baseline blood pressure of more than or equal 140/90 mmHg at registration in A.N.C. O.P.D.

Then 100 normotensive patients were divided into two groups, 50 cases and 50 control by simple random method. Cases were 2 gm of calcium supplementation in the form of tablet calcium lactate 500mg four times a day. Controls were 1 gm calcium in the form of tablet calcium lactate 500 mg twice daily which was routine ANC dose. This routine ANC dose will eliminate the bias

due to low dietary calcium intake especially in developing country like ours.

A spot urine sample was collected for estimation of calcium and creatinine at around gestational age of 20-24 weeks of all patients. Urinary calcium was estimated by Ortho-Cresolphthalein Complexone (CPC) method, urinary creatinine was estimated by Jaffe's method.

Then at each visit both the groups, was evaluated by eliciting history for symptoms of preeclampsia and imminent eclampsia such as oedema, vomiting, epigastric pain, decreased urine output and visual disturbances. Blood pressure was measured and urine was tested for proteinuria.

According to the National High Blood Pressure Education Program Working Group (NHBPEP) and the American College of Obstetricians and Gynecologists (ACOG), hypertension in pregnancy is defined as diastolic blood pressure equal to or greater than 90 mmHg or systolic blood pressure level of 140mmHg or higher after 20 weeks of gestation in a woman with previously normal blood pressure, (NHBPEP,2000;ACOG,2002).

Voided urine was collected for the measurement of protein by dipstick. Proteinuria of >1+ (300 mg per liter in a 24 hour urine collection) was confirmed by testing a clean-catch, midstream sample.

Pre-eclampsia is hypertension associated with proteinuria, after 20 weeks of gestation, in previously normotensive and non proteinuric women. Based on these criteria the women studied were categorized as those who developed preeclampsia or those who remained normotensive.

Urinary calcium to creatinine ratio was calculated and those with ratio less than or equal to 0.04 were considered test positive and those with ratio of >0.04 were considered test negative.

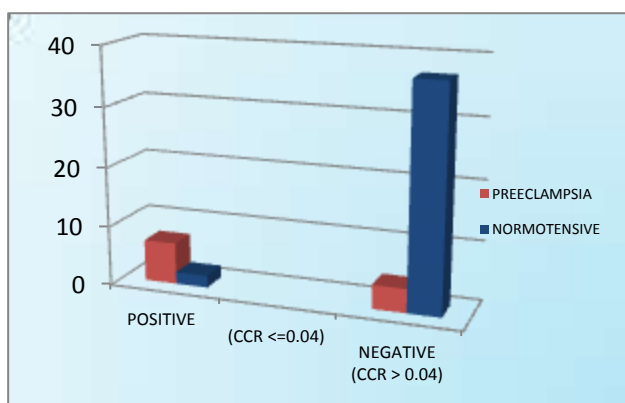
The predictive values of urinary calcium to creatinine ratio at less than or equal to 0.04, for pre-eclampsia, was determined by statistical analysis in control group and the use of supplemental calcium to prevent preeclampsia, was determined by statistical analysis in both the groups.

### **RESULTS**

In this table, all 100 patients are included, both cases & control, patients with and without calcium supplementation respectively. In patients with test (CCR) results positive, 9 developed preeclampsia and only 7 were normotensive. While in patient with test (CCR) results negative, only 5 developed preeclampsia & 79 were normotensive.

**Table 1: Test results in all patients (including cases and control).**

Urinary calcium to creatinine ratio (test)	Preeclampsia	Normotensive	Total
Positive (ccr $\leq 0.04$ )	9	7	16
Negative (ccr $> 0.04$ )	5	79	84
Total	14	86	100

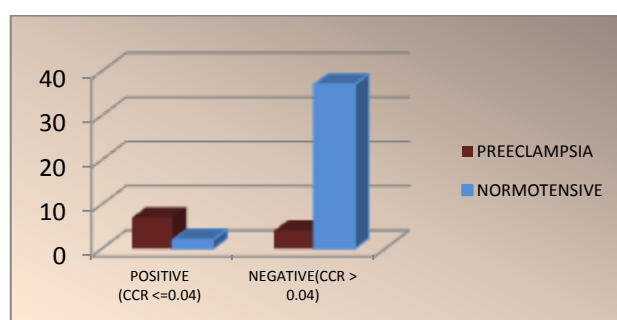


**Figure 1: Test results in all patients, (including cases and control).**

**Table 2: Test results in patients with preeclampsia and normotensive in control (without calcium supplementation).**

Urinary calcium to creatinine ratio(test)	Control		Total
	Preeclampsia	Normotensive	
Positive (ccr $\leq 0.04$ )	7	2	9
Negative (ccr $> 0.04$ )	4	37	41

By Fisher exact test, p value  $< 0.01$ , which is statistically significant, hence this test (urinary calcium to creatinine ratio) is useful in predicting preeclampsia.



**Figure 2: Test results in patients with preeclampsia and normotensive in control (without calcium supplementation).**

**Table 3: Sensitivity, specificity, PPV and NPV of test in control.**

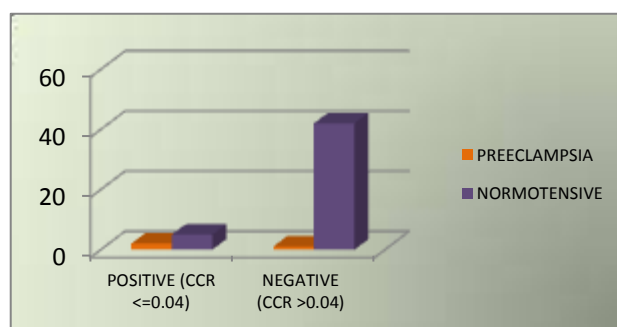
Urinary calcium to creatinine ratio	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Test	63.63%	94.87%	77.77%	90.2%

**Table 4: test results in patients with preeclampsia & normotensive in cases (with calcium supplementation).**

Urinary calcium to creatinine ratio (test)	Case		Total
	Preeclampsia	Normotensive	
Positive (ccr $\leq 0.04$ )	2	5	7
Negative (ccr $> 0.04$ )	1	42	43

By Fisher Exact test, p value = 0.048, which is still statistically significant.

These values are seen because this group has received calcium supplementation, which has shown to decrease the incidence of preeclampsia, according to many studies.



**Figure 3: Test results in patients with preeclampsia and normotensive in cases (with calcium supplementation).**

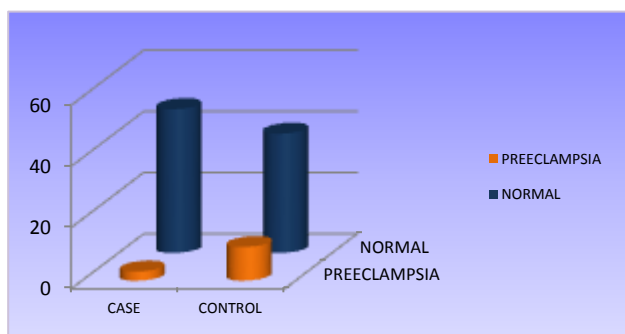
**Table 5: Preeclampsia and normotensive patients with and without calcium supplementation.**

Patients	Calcium supplementation		Total
	Case	Control	
Preeclampsia	3	11	14
Normal	47	39	86
Total	50	50	100

By Chi-square test, p value = 0.02 which is statically significant.

By Fisher’s exact test, p value= 0.041

These tables showed that the preeclampsia is less likely to develop in cases compared to controls, as that group has received calcium supplementation.



**Figure 4: Graph showing preeclampsia and normotensive patients with and without calcium supplementation.**

**DISCUSSION**

Pre-eclampsia is a complex multisystem disorder. It causes changes in all organ systems, most notably the

**Table 6: Comparison of predictive value of calcium creatinine ratio in present study with other studies.**

Author	Year	No. of patients	Parity	Sensitivity%	Specificity%	PPV%	NPV%
Rodriguez et al <sup>8</sup>	1988	88	>0	70	95	64	96
Sanchez- Ramos et al <sup>11</sup>	1991	99	0	88	84	32	99
Ozcan et al <sup>14</sup>	1995	56	0	63	96	71	93
RituKamra et al <sup>15</sup>	1997	104	>0	71.4	95.5	71.4	95.5
J Kar et al <sup>17</sup>	1999	100	>0	75	94.38	64.23	96.51
Our study	2013-14	100	>0	63.63	94.87	77.77	90.2

In the study of Rodriguez et al<sup>8</sup> (1988), 83% patients with low CCR developed preeclampsia. In study of Kamra et al (1997) 71.4% with low CCR developed preeclampsia. In the study of J Kar (1999), 64.2% with low CCR developed preeclampsia.

The table shows five studies that have investigated the predictive value of low CCR in preeclampsia.

renal system. Some of these changes in renal function are present in other wise symptom-free patients in whom pre-eclampsia will eventually develop.

The involvement of the renal system in preeclampsia is in the form of endotheliosis and there is alteration in renal functions. It is found that urinary calcium excretion can be markedly decreased early in the course of preeclampsia, even before the clinical appearance of signs and symptom. This is the basis for using urinary calcium to creatinine ratio as a predictor of preeclampsia.<sup>16</sup>

The challenge of any screening test for preeclampsia is to differentiate between those who are and will remain normotensive versus those who appear normal but will develop preeclampsia.

The use of urinary calcium to creatinine ratio as early predictor of preeclampsia has been studied by various authors.

The present study was done on 100 normotensive patients between 20-38 weeks of gestation or upto delivery and were divided into cases and control depending on calcium supplementation given or not respectively. Urinary calcium to creatinine ratio was calculated from single spot urine sample at 20-24 weeks of gestation and then follow up of cases was done for signs of development of preeclampsia. This test showed a sensitivity of 63.63%, specificity of 94.87%, positive predictive value of 77.77%, negative predictive value of 90.2%.

Thus, the present study confirms that there is a definite relationship between low urinary calcium to creatinine ratio and development of preeclampsia.

In all the above studies it was found that patients who subsequently developed pre eclampsia had low urinary calcium excretion. Majority of the patient developed preeclampsia were found to have calcium creatinine ratio of less than 0.04.

**Calcium supplementation**

Preeclampsia is likely to be a multifactorial disease. However inadequate calcium intake represents a factor associated with an increased incidence of hypertensive disease.

Low calcium intake has been hypothesized to cause increase in blood pressure by stimulating the release of parathyroid hormone and/or renin which leads to increased intracellular calcium concentration in vascular smooth muscle cells and causes vasoconstriction.

Role of calcium supplementation in reducing hypertensive disorders in pregnancy can possibly be explained by reduction in parathyroid calcium release and intracellular calcium concentration, thereby reducing smooth muscle contractility and promoting vasodilatation. Calcium supplementation could also prevent preterm labor and delivery by reducing uterine smooth muscle contractility directly and indirectly by increasing magnesium levels.

**Table 7: Characteristics of other trials.**

Study ID	Methods	Participants	Interventions	Conclusion
Belizan <i>et al.</i> 1991 <sup>10</sup>	Multicentre, randomized trial. Of 593 women (calcium) vs 601 women (placebo)	Nulliparous women, < 20 weeks pregnant; blood pressure < 140/90 mmHg ; no present or past disease.	2 g calcium vs identical looking placebo tablets. Compliance was 84% (calcium) and 86% (placebo)	Pregnant women who receive calcium supplementation after the 20th week of pregnancy have a reduced risk of hypertensive disorders of pregnancy.
Sanchez-Ramos <i>et al.</i> 1994 <sup>12</sup>	Double-blind placebo-controlled trial.	Normotensive nulliparas; positive roll-over test (281/1065) and positive angiotensin II infusion test at 20–24 weeks of gestation (67/281)	Calcium supplementation with 2 g/day elemental calcium vs identical placebo tablets	Calcium supplementation given in pregnancy to high-risk nulliparas reduces the incidence of pregnancy-induced hypertension.
Purwar <i>et al.</i> 1996 <sup>13</sup>	Double-blind placebo-controlled trial.	Nulliparous women; normal single viable pregnancy; antenatal clinic before 20 weeks; normal glucose tolerance test; no hypertension; no underlying medical disorders.	Oral calcium containing 2 g elemental calcium daily, compared with identical placebo tablets, taken from 20 weeks	Calcium supplementation given in pregnancy to nulliparous women reduces the incidence of pregnancy induced hypertension.
WHO 2006 <sup>9</sup>	Double-blind placebo-controlled trial.	Populations with median daily calcium intake less than 600 mg; primiparous women less than 20 weeks pregnant. Exclusion criteria: renal disease or urolithiasis; parathyroid disease; blood pressure >140 mmHg systolic >90 mmHg diastolic	500 mg elemental calcium, three daily, or identical placebo tablets from enrolment till delivery	Calcium supplementation was associated with a non-statistically significant small reduction in preeclampsia (4.1% vs 4.5%) that was evident by 35 weeks of gestation (1.2% vs 2.8%; P = .04). Eclampsia (risk ratio, 0.68; 95% CI, 0.48-0.

The second explanation could be prevalent malnutrition in developing countries. It had been proposed that hormones involved in blood pressure control are altered during malnutrition and can lead to significant morbidity in malnourished pregnant women.

Calcium supplementation appears to reduce the risk of pre-eclampsia and to reduce the rare occurrence of the composite outcome 'maternal death or serious morbidity'. There were no other clear benefits or harms. (Hofmeyr, G., Duley, L. and Atallah, A. (2007), Dietary calcium supplementation for prevention of pre-eclampsia



and related problems: a systematic review and commentary. BJOG: An International journal of Obstetrics and Gynaecology.)

In this study, it was seen that out of 50 cases (i.e. with calcium supplementation 2 gm daily) only 3 developed preeclampsia and 47 were normotensive. Out of 50 control (i.e. without calcium supplementation) 11 developed preeclampsia and 39 were normotensive.

The difference between development of preeclampsia is statistically significant ( $p$  value = 0.002) between cases and control. Hence preeclampsia is less likely to develop in cases as compared to control as that group had received calcium supplementation. Thus calcium supplementation prevents preeclampsia.

### CONCLUSIONS

The triad of haemorrhage, hypertensive disorders and puerperal sepsis accounted for almost 53% of the maternal deaths, as stated in a study conducted by Indian Institute of health and family welfare. Our study is an attempt to predict and prevent one of significant cause of maternal mortality, preeclampsia.

This study suggests that an evaluation of urinary calcium to creatinine ratio after 20wks of gestation may be an effective screening method for impending pre-eclampsia and may identify population at risk, hence can be included in primary prevention programmes. And also this study suggests that simple intervention like calcium supplementation (2 gms/day) can help in prevention of preeclampsia in high risk population. Hence this study is an attempt to predict and prevent preeclampsia and reduce maternal mortality.

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*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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