

Role of Urinary Calcium and Urinary Calcium to Creatinine Ratio (CCR) in Diagnosis of Hypertensive Disorders of Pregnancy

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Abstract

Context: Hypertensive disorders of pregnancy continue to be a major cause of maternal and perinatal morbidity and mortality worldwide. Several researchers have demonstrated the role of decreasing urinary calcium and urinary calcium to creatinine ratio in the prediction and detection of preeclampsia but no clear cutoff values have been provided, so this study was planned to determine the role of these tests planned in the early diagnosis and their feasibility as screening tools to identify women at risk of developing preeclampsia later in rural women of western U.P. *Aims:* To evaluate the role of urinary calcium and calcium to creatinine ratio (CCR) for early detection of Preeclampsia in spot urine sample. *Settings and Design:* Cross-sectional study in tertiary health care institute *Methods and Material:* A cross-sectional study was conducted in our department over a period of one year. Normotensive and hypertensive cases with singleton term pregnancy without other chronic medical disorder were enrolled as Group I, the controls (n=48) and Group II (n=129) respectively. After workup Mid-stream clean catch urine sample was collected for the estimation of calcium and creatinine. Data from all the groups were statistically analysed. *Statistical analysis used:* Independent T test. *Results:* Mean value of Urinary calcium and

urinary calcium to creatinine ratio in women with hypertensive disorder of pregnancy was found to be significantly lower (p value < .001) than in normotensive women. *Conclusion:* Estimation of calcium and creatinine in a spot urine sample is a simple test and easily performed. It has a good diagnostic accuracy, and thus it may be adopted as a diagnostic tool for preeclampsia.

Keywords: Preeclampsia; Urinary Calcium; Urinary Calcium to Creatinine Ratio (CCR).

Introduction

Hypertensive disorders are among the commonest medical disorders during pregnancy and continue to be a major cause of maternal and peri-natal morbidity and mortality worldwide, especially in developing countries like India. Hypertensive disorders complicate 5-10% of all pregnancies and together they form one important aspect of the deadly triad along with haemorrhage and infection [1].

Pre-eclampsia is generally regarded as a multisystem disorder specific to pregnant women, characterized by widespread endothelial damage [2]. This predominant pathology of pre-eclampsia i.e., endothelial dysfunction sets in early 8-20th weeks of gestation, but the signs and symptoms appears in late mid trimester or in the advanced stage of the disease [3]. If incipient pre-eclampsia can be diagnosed, intensive obstetrics can be utilized more effectively in patients who are at greater risk and this may improve maternal and fetal health respectively. Renal function changes are the first to appear even before clinical

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symptomatology in whom preeclampsia will eventually develop. Several researchers have reported that hypocalciuria was associated with preeclampsia and could be considered a risk factor for development of preeclampsia in pregnancy.^[4,5,6] Since then, several researchers have demonstrated the efficacy of decreasing urinary calcium and urinary calcium to creatinine ratio in the prediction of preeclampsia, whereas others have not found it as useful. Hence this study was conducted to determine the role of these tests in the early diagnosis and thereby their feasibility as screening tools to identify women at risk of developing preeclampsia.

Key Message

Estimation of calcium and creatinine in a spot urine sample is a simple test and easily performed. It has a good diagnostic accuracy, and thus it may be adopted as a diagnostic tool for preeclampsia

Materials and Method

This study was a cross-sectional study which was conducted in our department over a period of one year. Ethical clearance taken. Informed consent obtained from study subjects. Antenatal cases with singleton pregnancy having hypertensive disorder or pregnancy admitted in labour room were enrolled into Study group and categorized into pre-eclampsia, severe pre-eclampsia and eclampsia subgroup. Cases with blood pressure >140/90mmHg and 1+ proteinuria were defined as pre-eclampsia, those with 160/100mmHg and features of organ dysfunction defined as severe Pre-eclampsia and those with history of recent fits with raised BP into Eclampsia. Singleton normotensive cases admitted were taken as Control group. Pregnant women with other medical or obstetric complication were excluded from the study as- multiple pregnancy, molar pregnancy, diabetes mellitus, chronic renal disease, essential hypertension, urinary tract infection, epilepsy, severe anaemia. Normotensive and hypertensive cases with singleton term pregnancy without other chronic medical disorder were enrolled as Group I, the controls (n=48) and Group II (n=129) respectively.

Hypertensive study group cases were further subclassified into mild preeclampsia(n=73), severe preeclampsia(n=36) and eclampsia(n=20). After obtaining consent, demographic details were noted and thorough history and examination was performed along with basic tests to confirm the hypertensive categorization and to rule out other medical disorders.

Mid-stream clean catch 10ml urine sample was collected in a sterile container without any preservative, irrespective of day time. Dipstick testing for protein and routine, microscopic examination was done immediately and rest of sample was stored at 2-8 degree celsius and collectively send to department of Biochemistry for the estimation of urinary calcium and creatinine, Calcium was determined by Ortho-cresolphthalein complexone method (OCPC) and creatinine by Max Jaffe's method (Jaffe's Reaction). Data was entered into SPSS and analysed using Independent T test.

Results

This study was conducted on 177 antenatal patients at term with singleton pregnancy. Mean age of patients in Group I was 27.18 ± 4.83 years and in Group II was 26.59 ± 4.93 years, which was comparable. Majority of patients in both the groups were primiparous, housewives and hindus. Many of the patients in both the groups had high risk factors. Significant difference in risk factors were found between Group- I and Group-II (P value 0.003) (Table 1).

Vaginal delivery was the main mode of delivery in both the groups, but Group II had higher caesarean rates (29.46% vs 20.91%). None of the patient in Group I had complications while few women of Group II had complications like, post partum haemorrhage (PPH), renal failure (ARF), coagulation failure and pulmonary edema etc. There were four maternal deaths in group II one each due to ARF, pulmonary edema, Cerebro vascular accident (CVA) and hemorrhagic shock. Group I had good perinatal outcome with no perinatal deaths whereas in Group II there were 14(10.85%) perinatal deaths (Table 2).

Group II was further subclassified into mild preeclampsia, severe preelampsia and eclampsia. Mean value of Urinary calcium was 8.915 ± 1.677 mg/dl in normotensives, 4.749 ± 1.310 in mild pre-eclampsia, 4.87 ± 1.55 and $4.52 \pm .68$ mg /dl in severe pre-eclampsia and eclampsia respectively. On statistical analysis using Independent sample "t" test, comparing values of normotensives to mild preeclampsia, normotensives to severe preeclampsia and normotensives to eclampsia, P value was found to be highly significant (.00001) which suggest that hypocalciurea (< 5 mg/dl) can be used for prediction or early diagnoses of Hypertensive Disorder of Pregnancy (HDP) (Table 3).

Mean value of CCR in normotensive patient was $0.0985 \pm .0207$, in mild pre eclampsia was 0.0399 ± 0.0167 , in severe preeclampsia was $0.0377 \pm .0211$

and in eclampsia was 0.0484 ± 0.0782 . All the subjects with hypertensive disorder of pregnancy had CCR values <0.05 . Statistical analysis was done using Independent sample "t" test, comparing values of CCR of normotensives to mild preeclampsia, normotensives to severe preeclampsia and normotensives to eclampsia, P value was found to be highly significant (.001) which suggest that with CCR decreased significantly in women with hypertensive disorder of pregnancy (Table 4).

In the present study, significant difference were found in the values of urinary calcium and calcium to creatinine ratio (CCR) between Group I and Group II. Hence a cut off value to evaluate the predictive efficacy of these variables was calculated by using

Receiver Operator Curve (ROC). Statistical analysis were done taking two different cutoff values 0.03 and 0.04 respectively. CCR with cut off ≤ 0.03 has diagnostic accuracy of 57.06%, high specificity of 97.91% and positive predictive value 98.18%, while sensitivity was found to be 41.80 % only. Taking CCR cut off value of ≤ 0.04 , test sensitivity increased to 84.5% maintaining high specificity of 95.83%. Thus CCR cut off 0.04 is best, as it has both high sensitivity as well as specificity (Table 5).

Pearson's correlation coefficient (r) was used to see the relationship between urinary calcium and CCR. Positive correlation were seen between urinary calcium and calcium to creatinine ratio (CCR). As the concentration of urinary calcium decreases in women

Table 1: Demographic details of enrolled cases

Demographic variables	Group I(n=48) Control group	Group II (n=129) HDP study group
Mean Age(in years)	27.183 ± 4.83	26.592 ±4.93
Parity		
P0	23(47.9%)	58(44.9%)
P1	18(37.5%)	43(33.3%)
P2	6(12.5%)	23(17.8%)
P3	1(2.1%)	4(3.2%)
P4 or more	None	1(0.8%)
Religion		
Hindu	42(87.5%)	105(81.39%)
Muslim	5(10.41%)	19(14.72%)
Others	1(2.08%)	5(3.8%)
Occupation		
Housewife	36(75%)	97(75.19%)
Working women	12(25%)	32(24.81%)
Risk factors		
PIH in previous pregnancy	2(4.16%)	32(24.8%)
Family History of HDP	10(20.8%)	27(20.9%)
Obesity	5(10.41%)	27(20.9%)
Age >35	3(6.9%)	8(6.2%)
Mean Systolic BP (mm Hg)	126.54 ± 6.41	154 ± 8.69
Mean Diastolic BP (mm Hg)	81.5 ± 2.8	112.74 ± 4.83

Table 2: Feto-maternal outcome in the study subjects

Parameters	Group I (n=48)	Group II (n=129)
Mode of delivery		
Vaginal	32(66.66%)	78(60.47%)
Assisted vaginal	5(10.41%)	13(10.07%)
Caesarean section	11(22.91%)	38(29.46%)
Maternal complications		
Shock	None	4(3.1%)
ARF	none	12(9.3%)
PPH	none	16(12.4%)
DIC	none	14(10.85%)
Pulmonary edema	none	11(8.5%)
Intracranial hemorrhage	none	1(0.7%)
Coma	none	1(0.7%)
Death	none	4(3.1%)
Neonatal outcome		
Alive & healthy	47(97.9%)	90(69.76%)
Still birth/IUD	0	8 (6.2 0%)
NICU admission	1(2.1%)	13(10.07%)
Early neonatal death	0	6 (4.65%)

Table 3: Comparison of urinary calcium & CCR values between different groups and their statistical significance

Parameters	Group	N	Mean	Std. Deviation	Std. Error Mean	P value
Urinary Calcium (mg/dl)	Mild preeclampsia	73	4.7495	1.31046	.15338	0.000001
	Normotensives	48	8.9157	1.67759	.24214	
Urinary Calcium (mg/dl)	Severe preeclampsia	36	4.8706	1.55027	.25838	0.000001
	Normotensives	48	8.9157	1.67759	.24214	
Urinary Calcium (mg/dl)	Eclampsia	20	4.5280	.68007	.15207	0.000001
	Normotensives	48	8.9157	1.67759	.24214	
CCR Values	Mild preeclampsia	73	.03990	.016797	.001966	0.000001
	Normotensives	48	.09856	.020747	.002995	
CCR Values	Severe preeclampsia	36	.03770	.021155	.003526	0.00001
	Normotensives	48	.09856	.020747	.002995	
CCR Values	Eclampsia	20	.04845	.078256	.017499	0.00034
	Normotensives	48	.09856	.020747	.002995	

Table 4: Comparison of diagnostic validity of calcium to creatinine ratio (CCR) cut off ≤ 0.03 vs. ≤ 0.04

Statistical Significance	Urinary CCR cut- off	
	≤ 0.03	≤ 0.04
Sensitivity	41.83%	84.50%
Specificity	97.91%	95.83%
PPV	98.18%	98.20%
NPV	38.52%	69.70%
Diagnostic accuracy	57.0621%	87.5706%
P Value	0.0001	0.00001
X ² Value	28.483	94.116

Table 5: Comparison of predictive value of CCR in present study with other studies.

SN.	Author (Year)	Cut off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1.	Aherwar Ret al. (2013) ^[19]	0.04	83	96	75	98
2.	Vahadat M et al. (2012) ^[18]	0.07	77	78	-	-
3.	Sheela CN et al. (2011) ^[20]	0.04	69.2	98.2	85.7	95.8
4.	Kazemi AFN et al. (2010) ^[16]	0.068	35	93	24	96
5.	Present study	0.03	41.83	97.91	98.18	38.52
		0.04	84.50%	95.83%	98.20%	69.70%

with hypertensive disorders of pregnancy (HDP), the urinary calcium to creatinine ratio (CCR) also decreases thus suggesting that this correlation is statistically significant (P value < 0.001).

Discussion

The study subjects were divided into two groups - group I, the controls (n=48) included the antenatal women admitted in labour who were normotensives and group II, the cases (n=129) included the antenatal women admitted with the diagnosis of hypertensive disorder of pregnancy.

Mean age of Group-I subjects was 27.183 ± 4.83

years and Group-II subjects was 26.592 ± 4.93 years. No significant difference was found between the mean age of both the groups Hypertensive disorders of pregnancy are more likely to occur at both extremes of reproductive age, but more common in women aged less than 25. Similar findings noted by Sajith M. et al [7], and Nadkarni J. et al [8], but Owiredu WK et al. [9] Duckit K. et al. [10] found in their studies that hypertensive disorders of pregnancy were more common in older women of age between 30-35 years.

Pre-eclampsia has long been believed to be a disease of primigravida. Majority of the patients in group II were primigravida.

In accordance with our study, Hernandez-Diaz S et al. [11], and Conde-Agudelo A et al. [12], also found

in their studies that incidence of pre-eclampsia is higher in primigravida women than multigravida.

Both LSCS and operative vaginal delivery rates were found higher in Group-II than Group-I women. This is supported by study of Singhal RS et al [13].

Adverse perinatal outcomes were higher in babies born to Group-II women than in Group-I women which was in accordance to study done by Sachan R et al [14].

Both maternal complications and mortality were higher in Group-II women than Group-I. Difference was significant between women of both the Groups (P value < 0.001). Singhal RS et al. [13], also found in their study, that maternal complications were higher in women with hypertensive disorders of pregnancy and maternal mortality rate was also higher in women with HDP (8.89%).

We found that the mean urinary calcium level was significantly lower in Group II than in Group I concluding that hypocalciurea can be used as a predictor of hypertensive disorders of pregnancy (HDP). Mittal S et al.[15], in their study also found significantly lower mean urinary calcium level in pre-eclamptic women, Kazemi AFN et al.[16], Dasgupta M et al.[17], also found hypocalciurea in pre-eclamptic than normotensive women.

Mean spot urinary calcium /creatinine ratio (CCR) were found to be significantly lower in women with hypertensive disorder of pregnancy than in normotensive.

These findings were in accordance with the studies of Vahadat M et al.[18], Dasgupta M et al.[17], Kazerooni T et al.[19], Rodriguez MH et al [20], Ozcan T et al. [21] but the cut off values of their studies were different, these differences in results may be due to differences in sample size, period of gestation at which cases have been taken, prevalence of pre-eclampsia, and ethnicity in the populations studied (Table-6).

Conclusion

It can be concluded from our study that, spot urinary calcium to creatinine ratio (CCR) at cut off value ≤ 0.04 is a simple, easy and rapid test and can be used for the prediction of hypertensive disorders of pregnancy (HDP) as a screening tool.

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