Int J Pharm Bio Sci 2013 July; 4(3): (B) 1021 - 1026

Research Article **BioChemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

ROLE OF URINARY CALCIUM CREATININE RATIO IN PREDICTION OF PREGNANCY INDUCED HYPERTENSION

DR. N.V. LAKSHMI MD , DR.P.KIRANMAI MD , DR.K.AMBIKA DEVI MD AND DR. J. RAMA RAO MD

Department of Biochemistry, Osmania Medical College, Hyderabad.

ABSTRACT

Background: Preeclampsia occurring in 6-8% of all pregnancies together with other hypertensive disorders of pregnancy is the 3rd most common cause of maternal mortality. The present study is intended to identify at risk patients. Methods**:** Serum calcium, creatinine and urinary calcium, creatinine were estimated in 25 controls and 100 study group women between 24-34 weeks of gestation. Calcium to creatinine ratio in urine was calculated. The patients were followed up for signs of development of Pregnancy Induced Hypertension (PIH) & its relation to low urinary calcium to creatinine ratio (CCR). Results: A calcium to creatinine ratio of 0.04 was considered as cut off for evaluation. Out of total 125 cases, 22 had CCR ≤ 0.04 and of these 68.18% developed PIH later (P<0.001). In remaining 103 patients with CCR >0.04 only 4.85% had PIH. The sensitivity of CCR in predicting PIH is 68.18% and specificity is 95.15%. Conclusion: The findings indicate that a low Ca/Cr ratio is an useful screening test to predict the PIH in patients free of symptoms.

KEY WORDS : Calcium Creatinine Ratio (CCR) , Pregnancy induced Hypertension (PIH)

DR.N.V.LAKSHMI
Assistant Professor,Department of Biochemistry,
Osmania Medical College, Hyderabad.

Corresponding author

INTRODUCTION

Hypertension, one of the commonest medical complications of pregnancy, is leading cause of maternal and perinatal morbidity and mortality. It accounts for more than 40% of pre-mature deliveries and associated complications of pre-maturity [1]. Prediction of Pregnancy induced hypertension in a patient is extremely essential so that early detection and timely intervention and treatment will prevent the complications of pregnancy-induced hypertension to occur.A variety of biochemical and biophysical markers, based primarily on rationales implicated in the pathology and pathophysiology of hypertensive disorders due to pregnancy have been proposed for the purpose of predicting the development of pre-eclampsia later in pregnancy.[2,3]Reduction in urinary calcium excretion was observed at 10-24 weeks of gestation in patients who later developed pre-eclampsia and persisted through out pregnancy [4] When used as a single test, the urinary Ca:Cr ratio is a better predictor of pre-eclampsia than the urinary microalbuminuria concentration[5,6,7,8] . The present study was to estimate the urinary calcium and creatinine ratio in prediction of pregnancy induced hypertension. It is a simple and an ideal screening test which is also cost effective.

MATERIALS AND METHODS

A prospective study was undertaken in the Department of obstetrics and gynaecology at Government Maternity Hospital, Nayapool, Hyderabad and Department of Biochemistry-Osmania General Hospital, Hyderabad in which 125 cases attending the antenatal outpatient unit between 24-34 weeks of gestation have been taken and divided into two groups viz Control (25 cases) and Study group (100 cases). These women were aged between 18-30 years with mean age of 24 years.The control group comprised of normotensive pregnant women with no risk factors for development of PIH like nulliparity, H/o twin pregnancy and previous history of PIH. Study group comprised of normotensive pregnant women who had either one or more high risk factors. Women with H/o chronic hypertension BP >140/90 mm of Hg, Diabetes mellitus, renal disease are excluded from the study. At the time of their first antenatal check up , after obtaining consent from the patient, clinical history regarding age, parity, socioeconomic status, past, family and personal history are taken. General examination is done for blood pressure, oedema, weight gain. None of the women received any antihypertensive medication until study samples were taken. In this study, a serial follow up of total 125 cases was undertaken during antenatal period. The first follow up started in between 24-28 weeks, then second follow up between 30-34 weeks, last followup of the patient at near term . On each follow up the following clinical data was elicited i.e weight of the patient, Blood pressure, pedal oedema, h/o headache and vomiting for the prediction of PIH. The presence of PIH was defined as the recorded blood pressure more than 140/90 mm of Hg or a rise of 30 mm of Hg in systolic pressure or of 15mm of Hg in diastolic pressure (measured twice 6 hrs apart at bed rest) associated with proteinuria or oedema or both.[9]

Analytical methods

7ml of venous blood was collected under aseptic conditions, 2ml of which was placed in an oxalated bottle and 5ml in a sterile plain bottle. A simultaneous fasting sample of urine was collected into a sterile bottle. To that 1 drop of 6N Hcl is added as preservative. Serum and urinary calcium are estimated by OCPC (O-Cresolpthalein Comsplexone) method.[10,11] Creatinine is estimated by Jaffe's reaction[12]. The Urinary calcium concentration was divided by urinary creatinine concentration to derive the Ca/Cr ratio (CCR).

Statistical analysis

The results were expressed in terms of sensitivity and specificity. Comparitive study was done by using chi-square test.[13]

RESULTS

There is a significant decrease of mean serum calcium levels in study group (7.84mg%) when compared to control group on second follow up study.(9.97mg%) (p<0.01). There is a significant increase in serum creatinine levels in study group (0.83 mg%) when compared to control group (0.73mg%) on second follow up study (p<0.001). There was no significant change in serum calcium and serum creatinine levels between study and control groups at first follow up. Urinary Calcium and Urinary creatinine levels in control and study groups were measured at their first entrance into the study and CCR calculated. With the use of R.O.C (Receiver operator curve) a urine Ca: Cr ratio threshold value of 0.04 was taken as cut off for prediction of pre-eclampsia.[5] On follow up out of total 125 women 20 women developed PIH i.e. 16 women in study group and 4 women in control group developed PIH.The mean urinary calcium levels in cases with development of PIH (n=20) was 6.3mg%. The mean urinary calcium levels in cases without development of PIH (N=105) was 11.39mg/dl. There was significant lowering of urinary calcium level in cases with PIH (P< 0.001). The mean urinary creatinine levels in cases with development of P.I.H. (n=20) was 141.01 mg/dl and without development of P.I.H (n=105) was 142.81 mg/dl. There was no significant change in mean urinary creatinine values in cases with and without PIH (P>0.05).In study group, among 16 patients with PIH, 12 had CCR ≤ 0.04 and 4 had > 0.04 whereas in control group out of 4 cases who developed P.I.H, 3 had CCR ≤ 0.04 and one case had CCR > 0.04. In both study and control groups, 75% of patients who developed PIH had CCR ≤ 0.04. (Table-1) Fig-1

Table 1

shows distribution of patients with appearance of pregnancy induced hypertension in both study and control group with CCR.

Number of cases with PIH	CCR ≤ 0.04	CCR > 0.04
Study Group n=16	12 (75%)	4 (25%)
Control Group n=4	3 (75%)	1 (25%)
Total N=20	15	5

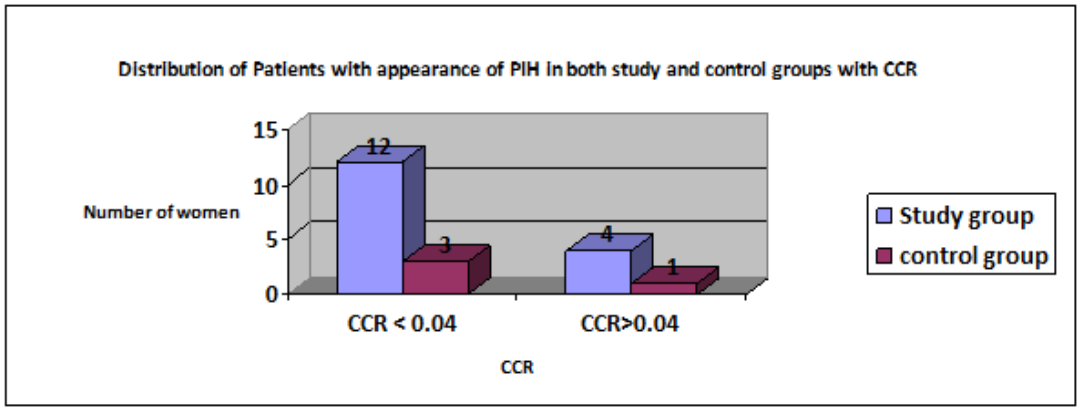


Figure1

Distribution of patients according to urinary calcium creatinine ratio was compared. In study group (n=100), 18(18%) had CCR ≤0.04 while in control group (n=25), 4 (16%) had CCR ≤ 0.04. (Table-2)

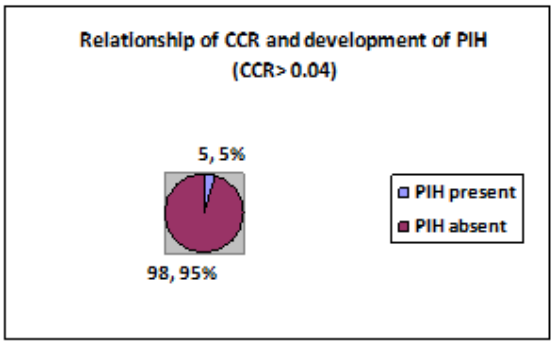
Table 2
shows distribution of patients according to urinary CCR.

Group	CCR ≤ 0.04	CCR > 0.04
Study Group n=100	18 (18%)	82 (82%)
Control Group n=25	4 (16%)	21 (84%)
Total N=125	22 (17.6%)	103 (82.4%)

Out of total 125 patients, 22 cases had CCR ≤ 0.04, of these 15 patients (68.18%) had developed pregnancy induced hypertension later on. On the contrary, out of 103 patients with CCR > 0.04, only 5 (4.85%) had pregnancy induced hypertension and remaining 98 (95.14%) did not have. When it was calculated statistically, (Chisquare test) there is significant development of PIH in cases with CCR ≤ 0.04 (P < 0.001). (Table-3) fig-2, fig-3

Table 3
shows relationship of calcium creatinine ratio and development of PIH. (**P<0.001)

Group	PIH present	PIH absent
CCR ≤0.04 n=22	15 (68.18%)**	7 (31.82%)
CCR > 0.04 n=103	5 (4.85%)	98 (95.15%)
Total N=125	20 (16%)	105 (84%)



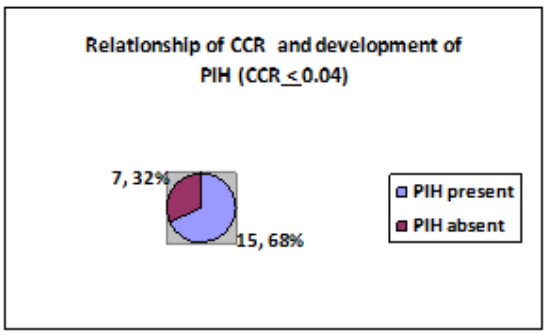


Figure 2 **Figure 3**

Out of 4 patients in control group with CCR ≤ 0.04, 3 patients developed PIH. Out of 18 patients in study group with CCR ≤ 0.04, 12 developed PIH. In patients with CCR > 0.04 in control group, out of 21 cases only one case developed PIH and in study group only 4 cases developed PIH.(Table-4)

Table-4
shows relationship of urinary CCR and development of pregnancy induced hypertension later on in control and study groups.

Appearance PIH	CCR ≤ 0.04		CCR > 0.04	
	Control Group	Study Group	Control Group	Study Group
PIH present n=20	3 (25%)	12 (50%)	1 (8.33%)	4 (16.67)
PIH absent n=105	1 (1.58%)	6 (4.76%)	20 (31.74%)	78(61.90%)
Total: n=125	4 (3.2%)	18 (14.4%)	21 (16.8%)	82 (65.6%)

In this study sensitivity of CCR in predicting PIH when both control and study groups are considered together is 68.18%, Specificity-95.15%, Positive Predictive Value (PPV)-75% and Negative Predictive Value (NPV)-93.33% (Table-5).

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

S. No	Author	Year	No. of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1	Rodriguez et al[5]	1988	88	70.00	95.00	64.00	96.0
2	Sanchez Ramos et al[14]	1991	99	88.00	84.00	32.00	99.0
3	Ozcan et al[15]	1995	56	63.00	96.00	71.00	93.0
4	Ritu Kamra et al[16]	1997	104	71.40	95.50	71.40	95.5
5	Present study	2002	125	68.18	95.15	75.00	93.33

DISCUSSION

Pre-eclampsia can cause changes in virtually all organ systems, most notably the cardiovascular, renal, haematological and immunological systems. Early detection of PIH reduces the morbidity and mortality related to PIH. In this study an attempt was made to show the relationship between low urinary calcium creatinine ratio (CCR) and P.I.H. With the use of R.O.C (Receiver operator curve)[5] a urine Ca: Cr ratio threshold value of 0.04 was taken as cut off for prediction of pre-eclampsia.In this study, out of 125 patients, 20 developed PIH. So the incidence of P.I.H in this study was 16%. Out of these 20 patients who developed P.I.H, 15 (75%) patients showed Ca: Cr $\leq$ 0.04 and the remaining 5 (25%) had CCR > 0.04. It was also found that in spite of having Ca: Cr $\leq$ 0.04 at entrance into study, 7 of our patients did not develop P.I.H subsequently.The hypocalciuria in the women with pre-eclampsia may be due to decreased fractional excretion of calcium secondary to its increased tubular re-absorption.[17] Regardless of its mechanism and pathophysiologic importance, hypocalciuria may be a reliable sign distinguishing pre-eclampsia from the more benign forms of gestational hypertension.In normal pregnant woman, during late gestation, urinary calcium excretion has been reported in different studies both to increase and to decrease (Pitkin et al).[18] A recent large cross-sectional study (Howarth AT1 Morgan DB, Payne RB) showed urinary excretion of calcium in late pregnancy and its relation to creatinine clearance.[19] In preeclampsia there is reduced urinary calcium excretion due to increased calcium uptake by the foetoplacental unit (Pitkin et al)[37] and due to increased distal tubular reabsorption of calcium (Phyllis et al).[17]In this study, urinary CCR was $\leq$ 0.04 in 12 (75%) out of total 16 cases of study group who developed PIH. And in control group 3 (75%) out of 4 cases had CCR $\leq$ 0.04 who developed PIH. Percentage development of PIH in both control and study group is same . This shows CCR, as an independent test is more significant in prediction of PIH rather than other predisposing factors which were found in study group such as twin pregnancy and previous history of PIH.In this study, 68.18% patients with low CCR developed PIH (Table-3) which is in accordance with previous studies Rodriguez et al (1988)[5] who reported 83% incidence, Suzuki et al (1992)[20] showed 58% cases with low CCR developed PIH. In study of Kamra et al (1997)[16] 71.4% with low CCR developed pre-eclampsia. On statistical analysis it was found that when CCR is taken as high risk factor for prediction of PIH it was highly significant $p<0.01$, sensitivity 68.18%, Specificity- 95.15%, Positive Predictive Value (PPV)- 75%, and Negative Predictive Value (NPV)- 93.33%. These findings are coinciding with results of Ozcan et al 1995. [15]

SUMMARY AND CONCLUSIONS

The present study is undertaken to investigate the significance of urinary calcium creatinine ratio in prediction of pregnancy induced hypertension. In this study there is significant lowering of urinary excretion of calcium in cases who developed PIH. This may be due

to impaired renal reabsorption of calcium. There is also significant lowering of urinary creatinine in cases who developed PIH. (This may be due to altered creatinine clearance). PIH development was more in cases with CCR $\leq$ 0.04 in both control and study groups. This study concludes that a low Calcium and Creatinine ratio may be a useful screening tool between 24-34 weeks of gestation for predicting the development of pre eclampsia in patients who are free of symptoms.Therefore a single urinary CCR test may be an effective screening method for impending pre-eclampsia and may identify population at greatest risk. Hence the study suggests inclusion of this test in primary prevention programme in pregnant women .

REFERENCES

1. Williams text book of obstetrics (22nd edition) Section VII ,Pg 761-808.
2. Gant NF, Chand S, Worley RJ, Whalley PJ, Crosly UD, Mac Donald P.A Clinical test useful for predicting the development of acute hypertension in pregnancy. Am J . Obst @ Gynec 1974 : 120 : 1-7.
3. Progress in Obstetrics and Gynaecology Vol 10; edited by John Studd-Screening tests for Pregnancy induced Hypertension; pp 69-86.
4. Friedmann EA, Neff RK : Pregnancy outcome as related to hypertension oedema, and proteinuria. In Lindheimer MD, Katz AL, Zuspan FP (eds). Hypertension in pregnancy- New York, Wiley 1976 p13.
5. Rodriguez MH, Masaki DJ, Mestman J, Kumar D, Rude Ratio of Calcium/creatinine ration and Micro albuminuria in the prediction of pre-eclampsia. American Journal of Obstetrics and Gynaecology 1988; 1591 1452-55.
6. Dekker Ga, Sibai BM, Early detection of pre-eclampsia, American Journal of Obstetrics and Gynaecology, 105, 160172.
7. Role of urinary CCR in prediction of PIH ,J.Kar, K.Srivastava, R.K.Mishra, N.Sharma,O.N.Pandey, Shalini gupta, J.ofObst & Gyn of India, Vol 52, No.2, March/April 2002, Pg 39-42.
8. William F.O' Brien; the prediction of pre-eclampsia COG, Vol.35, No.2; June 1992.
9. Mudaliar and Menon's clinical Obstetrics (9th edition) pg 133-154
10. Serum Direct colorimetric determination of serum calcium with o-cresolpthalein complexon . Leo G Morin, PHD A.J.C.P-vol 61 1974 Pg 114
11. Urine OCPC method- Giletman HJ 1967 Anal Biochemistry 18:52, clinical Acta 46:46.
12. Harold Varley 4th edition –practical clinical biochemistry Page No: 197-203 (Jaffe's method).
13. Mahajans book of statistics for medical students and research workers, B.K.Mahajan, 6th edition , Chapter 11, Pg 168-185.
14. .Sanchez-Ramas L, Jones DC, Cullen MT: Urinary calcium as an early marker for pre-eclampsia Obstet Gynecol 77 : 685, 1991.
15. Ozcan T,Kaleli B, Ozeren M, Turan C, Zorlu G, : Urinary CCR for predicting preeclampsia, Am Journal of Perinatalogy, 12 (5) : Pg 349-351(1995)
16. Kamra Ritu, Gupta H.P. Das K , Natu S.M. J Obstet Gyn Ind Vol. 47,353,1997
17. Phyllis A. Taufield MD, et al hypocalciuria in pre-eclampsia. NewEngland Journal of Medicine Vol.316 no 12 1987
18. Calcium metabolism in pregnancy and the perinatal period : A review, Roy M Pitkin , MD American Journal of Obstetrics Gynaecol 1985
19. Howarth, Morgan et al (Urinary excretion of calcium in late pregnancy and its relation to creatinine clearance AMJ Obstetrics Gynaecol 129: 499, 1977.
20. Sujuki Y, Hayashi Y, Murakarani I , Yamaguchi K , Yagami Y, Nippon sanaka Fujinka Gakkai Zasshi 44: 14211, (1992).