Original Article

Calcium-Creatinine Ratio and Microalbuminuria in Prediction of Preeclampsia

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Abstract

Objectives: To evaluate the predictive values of urinary calcium creatinine ratio (CCR) and microalbuminuria for preeclampsia. **Methods:** Urinary calcium creatinine ratio and microalbuminuria were determined in a spot urine sample in 200 asymptomatic pregnant women between 20-24 weeks of gestation, who attended the antenatal OPD at St John's Medical College and Hospital. The results were analyzed by Chi square test and Fisher Exact test to find the significant association of findings of preeclampsia and CCR and microalbuminuria. Area under Receiver Operator Curve (ROC) was used to find the predictive values of CCR at less than or equal to 0.04 and microalbuminuria for preeclampsia. **Results :** It was found that CCR had a sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of 69.2%, 98.2%, 85.7% and 95.8% respectively with a statistical accuracy of 87% and p value of <0.001 (strongly significant). It was found to be a good test for prediction of preeclampsia. Microalbuminuria had sensitivity, specificity, PPV and NPV of 53.6%, 86%, 36% and 95% and was found to be only a fair test for prediction of preeclampsia. **Conclusion:** CCR at 0.04 in spot urine sample being a good test for prediction of preeclampsia can be recommended as a screening test in all asymptomatic pregnant women, for preeclampsia. Microalbuminuria does not seem to be effective as a screening tool for preeclampsia at present.

Keywords: calcium creatinine ratio, microalbuminuria, prediction of preeclampsia

Introduction

Hypertensive disorders of pregnancy have been a challenge to obstetricians and researchers since many centuries and remain a major public health problem world wide. Preeclampsia and its complications are frequent causes for maternal and perinatal morbidity

and mortality, particularly in developing countries. Early diagnosis and treatment helps to reduce it to a minimum and therefore the importance of identifying the women at risk.

Though the exact etiology remains unclear even today, recent progress in understanding the disease process along with the availability of better research tools have led to the development of numerous tests to predict preeclampsia. Renal function changes are seen in symptom free women 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^{1,2,3}. Rodriguez et al⁴ evaluated the role of decreasing calcium creatinine ratio and microalbuminuria in prediction of preeclampsia as

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early as in 1988 and have concluded that these tests may be useful screening tools in prediction of preeclampsia. Since then, several researchers have demonstrated the efficacy of decreasing urinary calcium to creatinine ratio and microalbuminuria in the prediction of preeclampsia, whereas others have not found it as useful. Hence there is a need to determine the predictive values of these tests and thereby their feasibility as screening tools to identify women at risk of developing preeclampsia. This study is an attempt in this direction.

Aim of the study

To determine the predictive values of decreasing urinary calcium to creatinine ratio and microalbuminuria for preeclampsia, in a spot urine sample, in asymptomatic pregnant women between 20-24 weeks of gestation.

Material and Methods

Two hundred pregnant women who attended the St. John's Hospital OPD for routine antenatal care, over a period of one year, between 20-24 weeks of gestation were included in the study after obtaining informed consent. Women with history of chronic hypertension, diabetes and renal disease were excluded from the study. Women who had proteinuria by dipstick method at booking, as well as those with a baseline blood pressure of more than or equal to 140/90mmHg at booking were excluded from the study. All women were clinically evaluated at booking to rule out exclusion criteria.

Blood pressure was measured in the semi recumbent posture with a left lateral tilt, in the right arm and proteinuria was excluded by testing the spot sample for albumin by dipstick method.

A spot urine sample was collected for estimation of calcium, creatinine and microalbumin. Calcium was determined by O Cresolphthalein complex reaction and creatinine was estimated by Jaffes method. Microalbuminuria was detected by immunometric assay. All these women were followed up till delivery. At each visit they were evaluated by eliciting history of symptoms of preeclampsia and imminent eclampsia such as edema, nausea, vomiting, epigastric pain, decreased urine output and visual disturbances. Blood pressure was measured and urine was tested for protein

by the dipstick method.

Preeclampsia was defined as hypertension - blood pressure of more than or equal to 140/90 mmHg by using Korotkoff 5th sound for diastolic BP associated with proteinuria.

Based on these criteria the women studied were categorized as those who developed preeclampsia and those who remained normotensives. Calcium to creatinine ratio (CCR) was calculated and those with a ratio of less than or equal to 0.04 were considered as test positive. Those with a ratio of >0.04 were considered as test negative. Women with urinary albumin levels between 30-300 mg/L were considered to be positive for microalbuminuria and therefore as test positive. Those with level <30 mg/L were considered negative for microalbuminuria and hence test negative. The predictive values of calcium to creatinine ratio at ≤ 0.04 and microalbuminuria were determined by statistical analysis.

Statistical methods

Chi square test / Fisher Exact test has been used to find the significant association of findings of preeclampsia and CCR and microalbuminuria. A p value of ≤ 0.01 being strongly significant, 0.01-0.05 moderately significant and 0.05-0.1 being suggestively significant. Area under ROC (Receiver operator curve) has been used to find the predictive values of CCR at ≤ 0.04 and microalbuminuria for preeclampsia, 0.9-1 indicating an excellent test, 0.8-0.9 a good test, 0.7-0.8 a fair test and 0.6-0.7 a poor test.

Results

In this prospective clinical study comprising of 200 women between 20-24 weeks of gestation, majority (79%), were in the age group of 21-30 years, 10% were below 21 and 11% more than 30 years of age; mean age being 25.62 ± 3.87 . Incidence of preeclampsia in the study group was 13% of which 11% had mild, 1.5% severe disease and 0.5% eclampsia. Mean gestational age at which preeclampsia developed was 37.49 ± 2.48 . Among those who developed preeclampsia, 61.5% were in the age group of 21-30 years, 27% more than 31 years and 11.5% less than 21 years. Sixty five percent were primigravida and the rest were multigravida.

Of the 200 women studied, 21(11%) were test positive

Table 1.
No of Test Positive Women

Test Parameter	Test Positive (n (%))	Test negative n (%)	Total
CCR	21 (10.5%)	179 (89.5%)	200 (100%)
Microalbuminuria	38 (17%)	162 (83%)	200 (100%)

Table 2.

Association of calcium creatinine ratio with preeclampsia

CCR	Preeclampsia (n%)	Normotensives (n%)	Total (n%)
Test positive ≤0.04	18 (9%) (True positive)	3 (1.5%) (False positive)	21 (10.5%)
Test negative >0.04	8 (4%) (False negative)	171 (85.5%) (True negative)	179 (89.5%)
Total	26 (13%)	174 (87%)	200 (100%)

Table 3.

Association of microalbuminuria with preeclampsia

Microalbuminuria	Preeclampsia present (n%)	Normotensives (n%)	Total (n%)
Test Positive 30-300 mg/L	14(7%) (True positive)	24(12%) (False positive)	38 (19%)
Test negative <30 mg/L	12 (6%) (False negative)	150 (75%) (True negative)	162 (81%)
Total	26 (13%)	174 (87%)	200 (100%)

Table 4.

Results of statistical analysis

	Sensitivity	Specificity	PPV	NPV	Statistical accuracy	P Value
CCR	69.2%	98.2%	85.7%	95.5%	87%	<0.001**
Microalbuminuria	53.8%	86%	36%	95%	73.6%	<0.001**

** Strongly Significant

Table 5.

Predictive values of CCR and microalbuminuria

	AUC	SE	95%CI	Remarks
CCR	0.8803	0.0412	0.79-0.96	Good test
Microalbuminuria	0.7985	0.042	0.72-0.88	95%

AUC – Area Under Curve

SE – Standard Error

CI – Confidence Interval

(CCR $\leq$ 0.04) and 179(89%) were test negative (CCR $>$ 0.04). Thirty eight (17%) were test positive for microalbuminuria (30-300mg/L) and 162(83%) were test negative ($<$ 30mg/L). Table 1 shows the number of test positive women. Association of CCR and microalbuminuria with preeclampsia was determined and is shown in Table 2 and 3 respectively.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were arrived at after the statistical analysis of the results and are shown in Table 3. CCR at $\leq$ 0.04 had a sensitivity of 69.2%, specificity of 98.2%, PPV of 85.7% and NPV of 87% with a statistical accuracy of 87%, p value of $<$ 0.001 which is strongly significant. Microalbuminuria was comparatively less accurate with a sensitivity of 53.8%, specificity of 86%, PPV of 36% and NPV of 95% with a statistical accuracy of 73.6% and p value of $<$ 0.001. Predictive values of CCR and microalbuminuria for preeclampsia were calculated using Area Under Curve of ROC and it was found that CCR at $\leq$ 0.04 was a good test whereas microalbuminuria was only a fair test for prediction of preeclampsia.

Discussion

In our study comprising of 200 asymptomatic pregnant women between 20-24 weeks of gestation, the calcium to creatinine ratio (CCR) at less than or equal to 0.04 in a spot urine sample had a sensitivity of 69%, specificity of 98% with a good PPV and NPV of 85.6% and 95.5% respectively and was found to be a good test for prediction of preeclampsia. Ozcan et al⁵ who investigated the predictive value of decreasing calcium to creatinine ratio in a spot urine sample as early as in 1995 reported that it might be an effective marker for

preeclampsia. Saudan⁶, have reported a sensitivity of only 68% and specificity of 70% and Izumi et al⁷ found that it had limited value in prediction of preeclampsia, but the threshold value used was 0.10 by the former and Izumi et al carried out the test in early pregnancy, at less than or equal to 12 weeks of gestation. Kazerooni⁸ evaluating between 20-24 weeks of gestation and Kar et al⁹ evaluating the predictive value of CCR at less than or equal to 0.04 between 20-34 weeks of gestation (similar to our study), have reported that it was a satisfactory test for prediction of preeclampsia and could be an effective method for screening asymptomatic women for preeclampsia.

Estimation of calcium and creatinine in a spot urine sample is a simple test, easily performed and hence assures patient compliance. It has a good predictive value and hence justifies the cost and is suited to be adopted as a screening tool for preeclampsia. It can therefore be recommended as a screening test for preeclampsia and could be offered to all asymptomatic pregnant women between 20-24 weeks of gestation during their routine antenatal visit.

Microalbuminuria, on the other hand, was found to be only a fair test in predicting preeclampsia with sensitivity, specificity, PPV and NPV of 53.8%, 86%, 36% and 95% respectively. Salako et al¹⁰ has reported that a single estimation of microalbuminuria at booking had a high sensitivity (88.9%) but a low PPV (22%). Shaarawy¹¹ who have evaluated the clinical value of microtransferrinuria and microalbuminuria in prediction of preeclampsia in asymptomatic women have concluded that microtransferrinuria was a more sensitive marker than microalbuminuria. However, Chhabra¹² have found that estimation of microalbuminuria around 18 weeks of gestation seemed

useful, especially in primigravida. It is clear that more trials are needed to establish the usefulness of microalbuminuria in prediction of preeclampsia before it can be adapted as a screening tool. It therefore cannot be recommended as a screening test for preeclampsia at present.

Preeclampsia is a major cause for concern world wide and there has been a constant search to find means for prediction and prevention. An availability of a good screening test would initiate more research in this direction and would ultimately pave the way for implementation of measures for primary prevention.

Conclusion

A single estimation of calcium to creatinine ratio at less than or equal to 0.04, in a spot urine sample, in asymptomatic pregnant women between 20-24 weeks of gestation is a good predictor of future development of preeclampsia and therefore can be recommended as a screening test for all pregnant women as it justifies the cost. Microalbuminuria, when used alone is only a fair test for prediction of preeclampsia and cannot be recommended as a screening test as present.

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