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Original Research Article

Calcium Creatinine Ratio: A Predictor of Preeclampsia

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Abstract:

Background: There is hypercalciuria during a normal pregnancy, while PIH isassociated with hypocalciuria and low urinary calcium-creatinine ratio. Since PIH represents a state of profound pathophysiological changes and, one of the important alteration is a change in urinary calcium creatinine ratio and microalbuminuria in patients of PIH, this test has emerged significantly as the early predictor for the development of PIH.

Material and Methods: The present study was carried on in Department of Obstetrics and Gynaecology, Nalanda medical college and hospital over a period of one year from November 2019 to September 2020.This study was done on 100 normotensive patients with gestational age of 20- 24 weeks attending routine antenatal clinic. The patients were divided in two groups: Study group – comprised of 50 normotensive patients who had either one or more risk factor for development of preeclampsia and Control group- comprised of 50 normotensive pregnant patients, who had no risk factors for development of preeclampsia. Urinary calcium is calculated from spot morning urine sample by Orthocresolpthalin method. Normal urinary excretion of calcium in healthy adult is 100 – 300 mg/day. Urinary creatinine is calculated by Jaffe's method. Normal urinary creatinine excretion in healthy adult is 1.5 – 3 gram/day. All collected data was reviewed and analyzed for relationship of urinary calcium creatinine ratio with development of preeclampsia in both study and control group.

Result: Maximum number of patients in the study group and in the control group belonged to 18 – 25 years of age group. 70% were primigravidae. Less urinary calcium levels seen in cases of preeclampsia**.** Parity does not have any significant effect over calcium excretion in both groups of patients. Inthe study group (n = 50), 10 (20%) had CCR ≤ 0.04 while in the control group (n =50), 5 (10%) had CCR ≤ 0.04. Out of total 100 patients, 15 had CCR ≤ 0.04 and outof these, 10 (66.67%) had developed preeclampsia later on. On the contrary, out of 85 patients with CCR> 0.04, only 5 (5.8%) had preeclampsia and remaining 80 patients did not have preeclampsia.

Conclusion: Measurement of urinary calcium creatinine ratio is a non-invasive, inexpensive and easy to carry out method. It can be used as early predictor to identify pregnant women having high risk of developingpreeclampsia and thereby help in initiating prompt education of the patients andtimely prophylactic interventions, thus minimizing the severity of preeclampsia.

Keywords: Preeclampsia, Urinary Calcium Creatinine Ratio, Pregnancy.

Introduction

Pregnancy Induced Hypertension is a common disorder of pregnancy and a major cause of maternal, fetal and neonatal morbidity and mortality and is unpredictable in its onset and progression.[1] This disorder is highly prevalent in our country. Preeclampsia and Gestational hypertension complicate approximately 2 – 8% of all pregnancies. [2]

Early identification of women at risk of developing preeclampsia/PIH followed by careful monitoring is importantto improve maternal and fetal outcome. [3] Pregnancy Induced Hypertension is diagnosed "whena woman with previously normal blood pressure shows a sustained rise of blood pressure to 140/90 mm Hg or more, on at least two occasions, 6 hours apart, after 20 weeks of gestation in absence of evidence of an underlying cause of hypertension, but in whom proteinuria has not developed". PIH is a multi-organ disease. Depending on the end organ effects it can be labelled as preeclampsia, when renal involvement leads to proteinuria, and eclampsia when CNS involvement leads to seizures and HELLP syndrome when there is hepatic involvement. [4,5]

Preeclampsia is a "pregnancy specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation, it is usually associated with proteinuria or edema or both". [6,7]

Preeclampsia is a multisystem disorder of unknown etiology characterized by development ofhypertension to the extent of 140/90 mmHg or more with

proteinuria after the 20th week in a previously normotensive and non proteinuric women. Several well-defined risks have been described for development of PIH such as age, parity, socio-economic status, race, genetic predisposition, twin pregnancy, Hydatidiform mole,Polyhydraminos, diet, climate, obesity, chronic hypertension, chronic renal disease etc. [8,9] In patients with preeclampsia, there is increased cardiac output along with a propensity to vasospasm which is a major cause of most serious end organ effects. Plasma volume contraction is the most frequent haematological consequence of preeclampsia which results indecreased organ perfusion and the frequent haematological abnormality is thrombocytopenia.Kidney is very often affected and tubular necrosis is the commonest finding on renal biopsy.[10,11] The commonest sign of renal failure is oliguria due to reduced GFR , accompanied by rising serum creatinine, urea and uric acid. Several methods have been proposed for identifying pregnant women at risk of development of PIH/Preeclampsia.These include-Roll over test, Isometric hand grip exercise test, Second trimester mean arterial pressure test, Doppler velocimetry of uterine arteries, Urinary calciumcreatinine ratio, Detection of microalbuminuria, Uric acid test, Urinary kallikrien excretion, Fibronectin, Marker of oxidative stress, Immunological factor, Placental peptides,Angiotensin sensitivity test. As the pathogenesis is undefined, none of these methods have been proved as an ideal for prediction of preeclampsia either because of their complexity, high incidence of false positiveresults or subjective nature of result in interpretation. There is hypercalciuria during a normal pregnancy, while PIH is associated with hypocalciuria and low urinary calcium-creatinine ratio. [12,13] This phenomenon occurs early enough and persists throughout gestation, so it is useful for early identification of patients at risk. Since PIH represents a state of profound pathophysiological changes and, one of the important alteration is a change in urinary calcium creatinine ratio and microalbuminuria in patients of PIH, this test has emerged significantly as the early predictor for the developmentof PIH. Calcium metabolism in pregnancy is a complex process involving calcium, phosphorus,vitamin D, Parathyroid hormone and calcitonin. Calcium accumulation in pregnancy at term totals approximately 30 grams, almost all of which is present in fetus. Variability in maternal dietary intake of calcium has no effect on skeletal development in offspring. [14-18]

Henry and Skillman in 1971, suggested that Human Chorionic Somatotrophin, estrogen, and Parathormone were responsible for anticipatory adjustment of calcium. The Growth hormone like activity of HCS was responsible for increased estrogen level, causes decrease in bone resorption which leads to increase in PTH secretion. PTH enhances intestinal absorption of calcium. So, PTH antagonizes hypercalciuric effect of HCS and also counteracts the inhibition of bone resorption elicited by estrogen. As the fetal demand increases, PTH level rises further, resulting in bone resorption. [19-22]

Knapp in 1947, in a survey of 600 men, women and children noted the effect of age, sex and calcium intake on urinary excretion of calcium and found that Skeletal weight or quantity of bone as represented by total body weight was the factor responsible for difference in urinary calcium excretion with sex and increasing age. During period of calcium storage, urinary calcium does not reflect the amount of calcium absorption. When storage is complete, increased urinary excretion of calcium would be expected with increased absorption of this element. The quantity of urinary calcium is dependent on an endogenous factor, presumably endocrinological and on calcium intake per unit of body weight. [23-27]

The normal range of urinary excretion of calcium by adult on normal diet is approximately.

- 100 – 300 mg/day for men
- 100 – 250 mg/day for women

The urinary excretion of calcium is depressed if there is appreciable impairment of renal function Kleeman et al in 1973, demonstrated that the decrease in urinary calcium excretion in renal insufficiency depends on a number of factors-reduced glomerular filteration rate, decreased intestinal absorption of calcium, high circulation level of parathyroid hormone. [28,29]

Women with low calcium intake have an increase in mean blood pressure that predisposes to the development of PIH during the last trimester of gestation. Women with established preeclampsia have been reported to have lower urinary calcium excretion, lower 1,25 dihydroxycholecalciferol levels and ionized calcium levels and higher PTH levels than normotensive. Because the placenta contributes approximately 50% of the circulating 1,25 dihydroxycholecalciferol level in pregnancy, it is postulated that, in preeclampsia, the defective placenta is unable to produce sufficient levels of 1,25 dihydroxycholecalciferol, resulting in inadequate gastrointestinal calcium absorption, low ionized calcium levels and a secondary rise in PTH levels. How low circulating calcium levels and elevated PTH levels cause hypertension remains unclear. Although acute infusion of PTH is associated with a fall in Blood pressure, however chronic elevations have been reported to cause vasoconstriction and hypertension. An increase in circulating calcium produces vasodilatation and a decrease, causes vasoconstriction. [30,31] Calcium increase produces a stabilization of cellular membrane, raising its threshold for contractibility. Parathormone might be involved in this process,

Sinceprimary elevation of PTH is associated with a rise in Blood pressure values. An increase in ionized calcium within juxtaglomerular cells inhibit renin release, and all substances decreasing intracellular ionized calcium will cause increased renin activity. Plasma creatinine and urea concentration decrease during pregnancy and increase in 24 hourscreatinine clearance becomes apparent 4 weeks after conception. Renal function may deteriorate during pregnancy in women with preexisting renal disease or a history of preeclampsia in a previous pregnancy and hence monitoring of creatinine concentration is advisable.

Creatinine levels in blood and urine may be used to calculate the creatinine clearance level,which reflects glomerular filteration rate. [32,33]

Normal urine creatinine levels are 1 -2 gm/day Normal plasma creatinine levels are 0.8 – 1 mg/dl

Detection of urinary calcium creatinine ratio in early stages of pregnancy could be goodpredictor of preeclampsia. [34,35]

The aim of this study is to know the value of urinary calcium-creatinine ratio in predicting subsequent development of preeclampsia in pregnant women who are free of symptoms, which will help in reducing the incidence of severe disease by early therapeutic interventions. [36]

Materials and Methods

The present study was done in Department of Obstetrics and Gynaecology, Nalanda medical college and hospital over a period of one year from November 2019 to September 2020. Thisstudy was done on 100 normotensive patients with gestational age of 20- 24 weeks attending routine antenatal clinic. The patients were divided in two groups: Study group – comprised of 50 normotensive patients who had either one or more risk factor for development of preeclampsia and Control group included 50 normotensive pregnant patients, who had no riskfactor for development of preeclampsia. Risk factors included primigravidae-young or elderly, BMI > 35kg/ m^2, History of Pregnancy Induced hypertension in past pregnancy, History of twin pregnancy in present or past pregnancy or in the family.

Exclusion Criteria: Past history of chronic hypertension, Diabetes Mellitus, Renal disease, Blood pressure ≥140/90 mmHg at the time of registration. Pretested semistructured questionnaire was used for the interview of the patients. Routine antenatal blood investiagations were done. Apart from these, Urinary calcium is calculated from spot morning urine sample by Orthocresolpthalin method. Normal urinary excretion of calcium in healthy adult is 100 – 300mg/day. Urinary creatinine is calculated by Jaffe's method. Normal urinary creatinine excretion in healthy adult is 1.5 – 3 gram/day All collected data was reviewed and analyzed for relationship of urinary calcium creatinine ratio with development of preeclampsia in both study and control group.

Observations

Table 1: Case distribution in study and control group

Group	No. of Cases	Percentage
Study	50	50%
Control	50	50%

Table 2: Showing age distribution in study and control group

Cases	Age Group	No. of Cases	Percentage
Study	18-25	30	60%
	26-35	15	30%
	>35	5	10%
Control	18-25	28	56%
	26-35	14	28%
	>35	8	16%

Maximum no. of patients were of age group18-25 years in both groups.

Table 3: Showing parity distribution in study and control group

Cases	Parity	No. of Cases	Percentage
Study	PrimiMulty	35 15	70% 30%
Control	Primi Multy	30 20	60% 40%

Maximum no. of patients were primigravidae in both groups.

Table 4: Showing urinary calcium in study and control groups

Cases	Urinary calcium(mg/dl)	MEAN±SD
Study	2.6-18.4	8.502±3.36
Control	5.2-24	10.702±3.99

Table shows that there is increased urinary calcium in control group.

Table 5: Showing urinary creatinine in study and control groups

Cases	Urinary creatinine(mg/dl)	MEAN±SD
Study	60-120	101.7±15.88
Control	80-160	117.6±19.96

Table shows that there is increased urinary creatinine in control group.

Table 6: Showing coefficient of correlation between urinary calcium and creatinine instudy and control groups

Cases	Urinary calcium mean(mg/dl)	Urinary creatinine mean(mg/dl)	coefficient of correlation
Study	8.502	101.7	0.76
Control	10.702	117.6	0.77

Table shows that there was highly significant correlation between urinary calcium and urinarycreatinine in both study and control group.

Table 7: Showing relationship between weight of the patients and urinary calciumand creatinine excretion in study group.

Weight (Kg)	Urinary calcium(mg/dl)	Urinary creatinine (mg/dl)
40-50	2.6-11	60-100
51-55	3.6-16.4	80-110
>56	5.2-18.4	86-120

Table 8 :Showing relationship between weight of the patients and urinary calciumand creatinine excretion in control group.

Weight (Kg)	Urinary calcium(mg/dl)	Urinary creatinine(mg/dl)
40-50	5.2-18.4	80-140
51-55	5.8-22.3	86-145
>56	7.4-24	90-160

Table 9: Showing effect of parity on urinary excretion of calcium in study and controlgroups

Cases groups	Parity	No. of cases	Urinary calcium(mg/dl)
Study	PRIMI MULTY	35 15	2.6-16.8 5.4-18.4
Control	PRIMI MULTY	30 20	5.6-18.8 7.6-24

Table shows that parity does not have effect on urinary excretion of calcium in both groups.

Table 10: Showing effect of parity on urinary excretion of creatinine in study andcontrol groups

Cases	Parity	No. of cases	Urinary creatinine(mg/dl)
Study	PRIMI MULTI	35 15	70-110 60-120
Control	PRIMI MULTI	30 20	90-140 80-160

Table shows that parity does not have effect on urinary creatinine in both groups.

Table 11: Showing distribution of pts according to urinary calcium creatinineratio(CCR)

Cases	CCR<0.04	CCR>0.04
Study N=50	10	40
Control N=50	5	45
Total=100	15	85

In study group, 10 pts had CCR<0.04, while in control group 5 pts had CCR<0.04.

Table 12: Showing relationship of CCR and development of preeclampsia

Group of patents having	Preeclampsia present		Preeclampsia absent	
	Number	%	Number	%
CCR<0.04	10	66.67	5	33.33
CCR>0.04	5	5.8	80	94.12
Total-100	15		85	

Out of 100 patients studied,15 had CCR < 0.04 and out of these, 10 patients had developed preeclampsia later on. On the contrary out of 85 patients with CCR>0.04, only 5 had preeclampsia. When it was calculated statistically, it was found that CCR can be taken as a predictor of preeclampsia. It was highly

significant i.e. p value<0.0001, sensitivity 66.67%, specify 95%.

Discussion

The present study was carried out over a period of one year from November 2019 to September 2020 in the Department of Obstetrics and Gynaecology of Nalanda Medical College Hospital, Patna. A total number of 100 normotensive patients with gestational age between 20 – 24 weeks attending the antenatal clinic of Nalanda Medical College and Hospital were studied. 50 patients were included in the study group and 50 patients were in the control group (Table l). The maximum number of patients in the study group (60%) and in the control group (56%) belonged to 18 – 25 years of age group (Table ll). My study compared with the observations of Kar J et al (2002). [37] They estimated that the maximum patients in the study group i.e. 88% and in the control group i.e. 62% belonged to 16 – 25 years. In this study, maximum number of patients i.e.70% were primigravidae. This corresponded with the result of Sanchez et al (1991), in which maximum patients included inthe study group were primigravidae (Table lll). The range of calcium excretion (42±29 mg/day) in women with preeclampsia in the study by Taufield (1987) corresponded with theobservations of present study, which also showed less urinary calcium levels in cases of preeclampsia(Table lV & V). This observations also corresponded with the results of Anai et al (1991) and Sanchez et al (1991) who estimated that calcium excretion was significantly lower in preeclampsia than in normal pregnant women. Table Vll &Vlll, showed relationship between the weight of patients with urinary calcium excretion in both study and control groups which corresponded with the study by Knapp (1947). He founded that skeletal weight or quantity of bone represented by total body weight was the factor responsible for difference in urinary calcium excretion. In the present study, table lX and X showed that parity does not have any significant effect over calcium and creatinine excretion in both groups of patients**.** In the present study, CCR ≤ 0.04 was taken as a cut off level for the development of preeclampsia. In the study group (n = 50), 10 (20%) had CCR ≤ 0.04 while in the control group (n = 50), 5 (10%) had CCR ≤ 0.04. as shown in Table Xl. [38]

These findings corresponded with the results of Rodriquez et al (1988), who estimated the mean calcium to creatinine ratio and founded it to be significantly lower in preeclamptic group compared to the normal healthy pregnant group. They had taken cut off level of 0.04 for the CCR with sensitivity of 70%, specificity of 95%, positive predictive value of 64% andnegative predictive value of 96%. [39]

In the present study, out of total 100 patients, 15 had CCR ≤ 0.04 and out of these, 10 (66.67%) had developed preeclampsia later on. On the contrary, out of 85 patients with CCR> 0.04, only 5 (5.8%) had preeclampsia and remaining 80 patients did not have preeclampsia. When it was calculated statistically, it was found that when CCR alone was taken as a high-risk factor for prediction of preeclampsia, it was highly significant with p value < 0.001, sensitivity 66.67%, specificity 95%, positive predictive value 66.67% and negative predictive value 95%. So, out of total 100 normotensives, 15 developed preeclampsia (Table Xl & Xll) [40]

The observations of this study also correlated with the study of J. Kar et al (2002), where CCR was taken as a high-risk factor for prediction of Pregnancy Induced Hypertension. [41-44]

My study corresponded with the study of Suzuki et al (1992) and Ozcan et al (1995), in which 58% and 83% of the patients with low calcium creatinine ratio developed preeclampsia. [45,46]

Conclusion

The present study showed a close relationship between urinary calcium creatinine ratio in patients with preeclampsia. This study observed that the levels of urinary calcium were significantly decreased in preeclamptic patients when compared to normotensive women.

There is hypocalciuria in gestational hypertensive patients. As these patients are at risk of developing preeclampsia, these tests can be used as a screening tool between 20 – 24 weeks of gestation for predicting the development of preeclampsia in patients who are symptom free. Measurement of urinary calcium creatinine ratio is a non-invasive, inexpensive and is an easy to carry out method. They can be used as early predictors to identify pregnant women having high risk of developing preeclampsia and thereby help in initiating prompt education of the patients and timely prophylactic interventions, thus minimizing the severity ofpreeclampsia.

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