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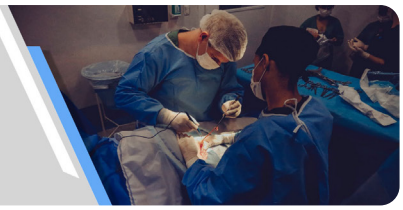

Urinary Calcium Creatinine Ratio and Association with Pre-Eclampsia

Lizwana Nusrat Lia[1*], Rezwan Sultana[2], Jasmin Ara Zaman[3], Fathima Sultana[4], Afreen Kabir Kheya[5]

Abstract

Background: Preeclampsia is a significant threat to the mother as well as the fetus. It forms deadly tried along with haemorrhage and infection and contributes significantly to maternal morbidity. Ra's complex pathophysiology remains unclear. An early prediction of preeclampsia with enabled accuracy is one of the essential prerequisites for its prevention.

Aim of the study: This study aimed to diagnose the urinary calcium creatinine ratio and its association with preeclampsia.

Methods: A case-control comparative study was conducted at the Department of Obstetrics & Gynecology in Mymensingh Medical College Hospital from October 2020 to September 2021. Pregnant women with preeclampsia were selected as cases, and women with normal pregnancies were selected as controls in their third trimester for the study. Singleton pregnancies with the same gestational age were matched in case and control. Urinary calcium, creatinine levels and calcium creatinine ratio were measured in a urine sample for all 140 subjects. Data were collected using a structured questionnaire and analyzed using the Statistical Package for Social Sciences (SPSS) version 26.0.

Result: 140 pregnant women in their third trimester were involved, whereas 70 with preeclampsia and 70 with normal pregnancy were selected for the study. A significant difference between preeclampsia and the norm group was observed in the case of urinary calcium concentration ($p<0.001$), but urinary creatinine concentration did not show any significant difference. Similarly, the urinary calcium to creatinine ratio was significantly lower in preeclampsia than in the standard group ($p<0.001$). Regarding assessment, decreased urinary calcium level (OR: 22.37, 95% CI: 3.96-24.7, p-value 0.001) and decreased urinary calcium creatinine ratio level (OR: 25.13, 95% CI: 4.58-27.9, p-value <0.0 were found as independent risk factors for preeclampsia.

Conclusion: The study revealed a decreased urinary calcium creatinine ratio in preeclampsia. So, the urinary calc creatinine ratio can be regarded as a predictor for preeclampsia

Keywords: Preeclampsia; Urinary Calcium Creatinine Ratio.

Introduction

Pre-eclampsia is an idiopathic multisystem disorder that causes maternal and fetal morbidity and mortality. It is one of the most common medical disorders obstetricians diagnose in clinical practice [1]. Pregnancy is a normal physiological condition, but its complications are the cause of maternal death of about 600000 every year worldwide [2]. Pre-eclampsia affects approximately 2-8% of pregnancies [3]; predisposing factors are

Affiliation:

[1]Medical Officer, Green Road Urban Dispensary, New market, Dhaka, Bangladesh.

[2]Medical Officer, Department of Hand & Microsurgery, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh.

[3]Medical Officer, Green Road Urban Dispensary, New market, Dhaka, Bangladesh

[4]Microbiologist, National Institute of Cardiovascular Disease (NICVD), Dhaka, Bangladesh.

[5]Medical Officer, Department of Pediatric Orthopedics, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh.

***Corresponding author:**
Lizwana Nusrat Lia, Green Road Urban Dispensary, New market, Dhaka, Bangladesh.

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nulliparity, black race, maternal age below 20 or over 35 years, low socioeconomic status, multiple gestation, hydatidiform mole, polyhydramnios, twins, obesity and underlying renal disease [4]. All over the world, pre-eclampsia is the third and seventh leading cause of maternal and perinatal mortality and morbidity, respectively [5]. In developing countries, the reason for maternal mortality for pre-eclampsia is 15-20% [6]. About 16% of maternal deaths are associated with pre-eclampsia in Bangladesh [7]. It is said that pre-eclampsia and eclampsia contribute to the death of a woman every 3 minutes worldwide [8]. Pre-eclampsia (PE) is a pregnancy-specific condition characterized by hypertension and proteinuria occurring after 20 weeks of gestation [5]. It is a serious complication of the second half of pregnancy [9]. Pre-eclampsia may cause maternal mortality and serious morbidity like stroke, convulsion, cerebral and pulmonary oedema, renal failure, hepatic failure, abruption of the placenta and disseminated intravascular coagulation. It also causes fetal complications such as intrauterine growth restriction, stillbirth and iatrogenic prematurity [10]. In severe disease, there is widespread organ dysfunction, especially kidneys, liver and brain. However, the chief target organ is the kidney, and proteinuria and hypertension are the predominant clinical features [11]. In healthy pregnant women, marked glomerular hyperfiltration is seen above normal non-gravid levels by 40 to 60%, primarily due to reduced plasma oncotic pressure (RPF) in glomerular capillaries and elevated renal plasma flow rate (RPF). However, there is a variable degree of renal insufficiency in pre-eclampsia, and GFR and RPF are significantly reduced [12]. One of the most important clinical problems is that complications appear suddenly in pregnant women, and unfortunately, as yet, no definite predictive factor is available [13]. Several potential predictive associated factors have been proposed for pre-eclampsia, ischides markers for liver and renal function, coagulation and fibrinolytic factor, colour Doppler USG, and Doppler velocimetry in the uterine artery. Angiotensin sensitivity test, calcium and calcium creatinine ratio [14]. As the pathogenesis is undefined, none of these methods has been proven ideal for predicting pre-eclampsia because of their complexity, high incidence of false positive results or subjective nature of results in interpretation [15]. Calcium metabolism in pregnancy is a complex process that changes during pregnancy [16]. It increases in all pregnant women, possibly because of increased intestinal absorption of calcium, increased renal filtered load of calcium and increased GFR of pregnancy [17]. Several abnormalities of calcium metabolism have been described in pre-eclampsia, the most important being hypocalciuria, i.e. reduced renal calcium excretion [18]. It is possibly due to reduced dietary intake of calcium, decreased absorption, increased uptake by fetus and placenta, reduced GFR, and increased glomerular calcium reabsorption [19]; women with established pre-eclampsia have been reported to have lower urinary calcium excretion, lower 1, 25 dihydroxycholecalciferol levels, ionized calcium levels, and higher PTH levels than normotensive controls [20]. The placenta contributes approximately 50% of circulating 1, 25 dihydroxycholecalciferol levels in pregnancy. it was postulated that in pre-eclampsia, the defective placenta is unable to produce sufficient levels of 1, 25 dihydroxycholecalciferols, resulting in inadequate gastrointestinal calcium absorption, low ionized calcium levels, and a secondary rise in PTH, which leads to increased intracellular calcium concentration in vascular smooth muscle cells and causes vasoconstriction and hypertension [21]. Low calcium levels may also contribute to hypertension by stimulating renin release from the kidney [22]. Creatinine is a product of muscle metabolism. It is produced nearly constantly and excreted in the urine [23]. Because of its constant production rate, the creatinine in the urine indirectly measures kidney function [24]. The physiologic increase in GFR and blood volume during pregnancy normally results in increased creatinine filtered out of blood and passed into the urine. If the kidneys are affected by pre-eclampsia, the creatinine clearance value decreases in urine because the kidneys filter less creatinine out of the blood [25]. The kidney damage can be estimated by the decrease in the creatinine clearance value [26]. Proteinuria is seen as a sign of many complications. It is used as a diagnostic parameter for several conditions, such as urinary tract infection, chronic kidney disease and pregnancy-related complications like pre-eclampsia [27]. However, the gold standard method for diagnosis of pre-eclampsia is 24-hour proteinuria detection. Measuring 24 hours' urine is time-consuming and has a chance of getting contaminated, causing errors in final estimation and diagnosis, which produces the need for a method which can provide a faster screening method with better accuracy and validity [28]. There is hypercalciuria during a normal pregnancy, while pre-eclampsia is associated with hypocalciuria and a low urinary calcium-creatinine ratio. This phenomenon occurs early enough and persists throughout gestation, so it is useful for the early identification of patients at risk [29]. Since pre-eclampsia represents a state of profound pathophysiological changes and one of the important alterations is a change in urinary calcium creatinine ratio, this test has emerged significantly as the early predictor for the development of pre-eclampsia in pregnant women who are free of symptoms [30]. Several studies implemented in different parts of the world revealed that spot urinary calcium creatinine ratio is a good indicator to detect pre-eclampsia [31]. So, the calcium creatinine ratio of a single voided urine specimen may have an important diagnostic role in managing pre-eclamptic women. Estimating urinary calcium creatinine ratio could be a simpler, quicker, more convenient and less expensive test to assess and predict pre-eclampsia. This study should evaluate the association between urinary calcium creatinine ratio and pre-eclampsia as it requires a specific, low-cost, easy, and quicker test to predict pre-eclampsia.

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Methodology & Materials

This case-control comparative study was conducted at the Department of Obstetrics & Gynecology in Mymensingh Medical College Hospital, Mymensingh, Bangladesh. Singleton pregnant women with pre-eclampsia in their third trimesters (29 weeks to 40 weeks) were selected as the case, whereas singleton normotensive pregnant women in their third trimesters (29 weeks to 40 weeks) with no medical or obstetrical disorders were the control group. The study duration was one year, from October 2020 to September 2021. There was no physical, psychological, social or legal risk during the patient history, physical examination and investigations. Proper safety measures were taken at every step of the study. Only the researcher was allowed to access the collected data. Ethical clearance was obtained from the Institutional Review Board (IRB) of MMCH to undertake the current study.

- **Inclusion criteria:**

➢ Gestational age 29 to 40 weeks.

➢ Normal pregnant women as a case.

➢ Pregnancy with pre-eclampsia as control.

- **Exclusion criteria:**

➢ Medical history includes previous history of pre-eclampsia, chronic hypertension, diabetes mellitus, renal diseases, chronic liver disease, and recurrent urinary tract infections.

➢ Subject who did not give consent.

Operational Definition

Pre-eclampsia: Pre-eclampsia is a hypertensive disorder in pregnancy which is characterized by the occurrence of a new set of persistent hypertensions with a new onset of proteinuria or, in the absence of proteinuria, the presence of new-onset end-organ damage, usually after 20 weeks of gestation [32]. Pre-eclampsia without severe feature: Raised blood pressure 2140/90 mm Hg plus 24-hour urine protein greater than or equal to 300mg/24 hour or urine dipstick +1 after 20 weeks of gestation in previously normotensive women. (ISSHP, 2018).

Pre-eclampsia with severe feature: Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time).

Data collection and analysis:

Data were collected using a structured questionnaire containing all the variables of interest. The questionnaire was finalized following pretesting. All data collection sheets were checked very carefully to identify any errors in collecting data. Data processing consisted of registering schedules, editing, coding, computerizing, preparing dummy tables, and analyzing and matching data. The researcher's matters included the technical matters of editing, code writing, and computerization. After collection, data were entered into a personal computer and then analyzed, plotted, and presented in graphs and tables. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26.0. P-values less than 0.05 (95% CI) were considered statistically significant.

Results

Distribution of maternal age was observed in the study. Maximum participants from both groups belonged to the age group of ≤30 years: 57(81.4%) from the pre-eclampsia group and 51(72.8%) from the normal pregnancy group (Figure 1). The distribution of sociodemographic characteristics among pre-eclampsia and normal pregnancy is shown in Table 1. Women live in urban and rural areas in pre-eclamptic groups 43(61.4%) and 27(38.6%), in regular pregnant groups 37(52.8%) and 33(47.2%). Most women completed secondary school education, 57(81.4%) from the pre-eclamptic group and 41 (58.6%) from the normal pregnant group. More than two-thirds were housewives in both groups, 57(81.4%) in the pre-eclamptic group and 56 (80.0%) in the normal pregnant group. Also, most belonged to low- and medium-income families, 36(51.4%) in the pre-eclamptic group and 31(44.3%) in the normal pregnancy group. Figure 2 represents the distribution of obstetric variables between pre-eclampsia and normal pregnancy. The maximum number of women from both groups were primigravida, which was 56(80.0%) in the pre-eclamptic group and 48(68.7%) in the normal pregnant group. Most women are multipara, 41(58.6%) from the pre-eclamptic group and 45(64.3%) from a normal pregnancy. Table 2, distribution of clinical variables between pre-eclampsia and normal pregnancy, shows that blood pressure was higher in pre-eclampsia without severe feature group 57(81.43%) than in normal pregnancy. Oedema was observed more in pre-eclamptic group 58(82.85%) than in normal pregnancy, and it showed statistically significant. No significant difference was observed concerning proteinuria. The study of urinary biochemical markers in Table 3 shows that a decreased level of urinary calcium was observed more in a pre-eclamptic group than in the normal pregnancy group, 59(84.3%) and 13(18.6%), respectively, which was statistically significant. An average urinary creatinine level was observed among most participants between the two groups. The study of urinary calcium creatinine ratio markers in Table 4 shows that decreased level of urinary calcium creatinine ratio was more found in pre-eclamptic group 57(81.4%) than in normal pregnancy group 10(14.3%), which was statistically significant. Table 5 shows urinary calcium (OR: 23.5, 95% CI: 9.74-56.7) and urinary calcium creatinine ratio (OR: 26.3, 95% CI: 10.6-64.7) are associated with the risk of occurring pre-eclampsia. Multivariate binary logistic regression of significant variables is presented in

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Table 4.6, which shows decreased urinary calcium level (OR: 22.37, 95% CI: 3.96-24.7, p-value 0.001). Decreased urinary calcium creatinine ratio levels (OR: 25.13, 95% CI: 4.58-27.9, p-value <0.001) are independent risk factors for pre-eclampsia (Table 6).

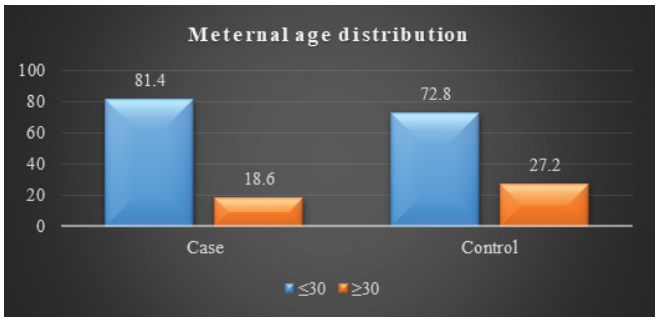

Figure 1: Distribution of maternal age among cases & control.

Table 1: Demographical characteristics based on pre-eclampsia & normal pregnancy.

Variables	Pre-eclampsia (n=70)		Normal Pregnancy (n=70)		P Value
	n	%	n	%	
Residence					
Urban	43	61.4	37	52.8	0.305
Rural	27	38.6	33	47.2	
Educational status					
No formal Education	2	2.8	3	4.3	0.03
Primary	7	10	17	24.3	
Secondary	57	81.4	41	58.6	
Graduate and above	4	5.8	9	12.8	
Occupation					
Housewife	57	81.4	56	80	0.397
Service Holder	5	7.2	9	12.9	
Student	8	11.4	5	7.1	
Economic status					
Below medium	25	35.7	23	32.8	0.292
Low medium	36	51.4	31	44.3	
Upper medium	4	5.8	11	15.8	
Upper status	5	7.1	5	7.1	

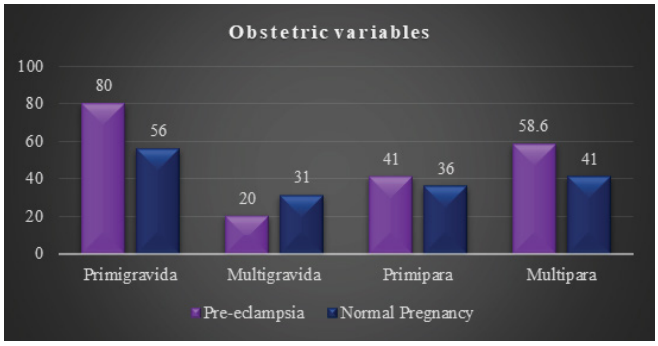

Figure 2: Distribution of obstetric variables between pre-eclampsia and normal pregnancy.

Table 2: Distribution of clinical variables among pre-eclampsia & normal pregnancy.

	Pre-eclampsia (n=70)		Normal Pregnancy (n=70)		P Value
	n	%	n	%	
Blood pressure					
Normotensive	0	0	70	100	0.061
Pre-eclampsia without severe feature	57	81.43	0	0	
Pre-eclampsia with severe feature	13	18.57	0	0	
Oedema					
Present	58	82.85	6	8.58	0.0001
Absent	12	17.15	64	91.42	
Proteinuria					
Negative	0	0	67	95.72	0.082
Trace	22	31.43	3	4.28	
+	20	28.58	0	0	
++	19	27.14	0	0	
+++	9	12.85	0	0	

Table 3: Distribution of urinary biomarkers between pre-eclampsia (n=70) and normal pregnancy (n-70).

Variables	Pre-eclampsia (n=70)		Normal Pregnancy (n=70)		P Value
	n	%	n	%	
Urinary Calcium					
Normal	11	15.7	57	81.4	<0.001
Decreased	59	84.3	13	18.6	
Urinary Creatinine					
Normal	47	67.2	58	82.8	0.154
Decreased	23	32.8	12	17.2	

Table 4: Distribution of urinary calcium creatinine ratio between both groups.

Variables	Pre-eclampsia (n=70)		Normal Pregnancy (n=70)		P Value
	n	%	n	%	
Normal	13	18.6	60	85.7	<0.001
Decreased	57	81.4	10	14.3	

Table 5: Association of clinical and biochemical variables with pre-eclampsia.

Variables	Category	OR*	95% CI**
Urinary Calcium	Decreased Normal	23.5	9.74-56.7
Urinary Ca/Cr	Decreased Normal	26.3	10.6-64.7
Oedema	Present Absent	0.02	0.01-0.05

Table 6: Binary logistic regression of risk factors associated with occurrence of pre-eclampsia.

Variables	Category	OR*	95% CI**	P value***
Urinary Calcium	Decreased Normal	22.37	3.96-24.7	0.001
Urinary Ca/Cr	Decreased Normal	25.13	4.58-27.9	0.001

Discussion

This case-control con-positive study was done in the Obstetrics & Gynecology department of Mymensingh Medical College Hospital. A total of 140 patients, all pregnant women (70 normal pregnant and 70 with pre-eclampsia), were taken by purposive non-random sampling; patients attending the OPD in the third trimester of gestation and admitted into the indoor of Mymensingh Medical College Hospital were the study population. The cases were selected according to inclusion and exclusion criteria. Different aspects of the study population were assessed. Regarding demographic variables, the maximum number of participants from both groups belonged to the age group of ≤ 30 years, 81.4% from the pre-eclampsia group and 72.8% from the normal pregnancy group, respectively. There was no statistically significant difference (p=0.05). The result was similar to Leppälahti et al.'s (2013) [33]. It has been found that the maximum number of pre-eclampsia women were ≤ 30 years. However, Lamminpää et al. (2012) had a different opinion [34]. They found that women of advanced maternal age (AMA) exhibited more pre-eclampsia (9.4%) than younger women (6.4%). In this study, women of the two groups did not show any significant difference regarding demographic variables like residence, educational status, occupation, or income. These results were similar to the study by Ramesh et al. (2014) [35]. However, according to demographic variables, Tereza et al. (2020) found a significant difference (p=0.002) between pre-eclampsia and the normal pregnant group [36]. Silva et al. (2008) reveal that women with low educational levels were more likely to develop pre-eclampsia (odds ratio 5.12; 95% confidence interval: 2.20, 11.93) than women with high educational levels [37]. Gravity and parity were also found statistically insignificant between pre-eclampsia and the normal pregnant group. Primigravida was noted in 80% of cases of pre-eclampsia and 68.7% of cases of normal pregnant patients. These results correlate well with the study outcome by Marvielet et al. (2008) and Hernandez et al. (2009) [38,39]. These results also correlate well with Qublan et al. (2008) and Duley L et al. (2009), where primigravida was noted in 30 (40%) cases of pre-eclampsia and 25 (33.33%) cases of normal pregnant patients [40,41]. Regarding parity, 58.6% of patients with pre-eclampsia and 64.3% of normal pregnant were multiparas. These results were similar to Kumar et al. (2010) [42]. Significant risk factors were identified in univariate analysis, where multipara women (OR=573) are the significant risk factor of pre-eclampsia. However, Manoj et al. (2017) did not agree with the result [43]. This study found primi parity to be an independent risk factor for the development of pre- (OR 4.51:2.76-736). Regarding clinical variables, no significant difference was observed concerning blood pressure (p>0.05). These results correlate well with the study outcome by Laura et al. (2012) [44]. The distribution of cinema revealed significant differences between the two groups. Oedema was the highest 58 (82.85%) in pre-eclampsia patients than in normal pregnancy. The result was similar to Emily et al. (2020) [45]. Regarding proteinuria, no significant difference was observed between pre-eclampsia and normal pregnancy (p>0.05). The result agreed with Pierre et al. (2019) [46]; regarding the study, proteinuria was more observed in a pre-eclamptic group than in a normal pregnancy. Analysis of urinary biochemical reveals that women with pre-eclampsia did not differ significantly from normal pregnant women regarding urinary creatinine concentration (p> 0.05). The study was comparable to Ingec et al. (2006) [17], which revealed that urinary creatinine concentration did not differ significantly between the two groups. Satya et al. (2009) did not agree with the result [47]. In this study, the mean creatinine clearance in the normal non-pregnant and pre-eclamptic groups was 102.63 ml/min and 71.98 ml/min, respectively, and the difference is significant (p<0.005). In the case of urinary calcium concentra, women showed reduced calcium excretion compared to normal pregnant women (p <0.001), and the results were significant. These results correlate well with the study outcome by Kristen et al. (2017) [38], indicating urinary calcium excretion was lower among women with pre-eclampsia than those with normotensive pregnancies (WMD -158.43, 95% CI -187.95 to 128.92). Another study by Valerie et al. (2005) revealed that Women with pre-eclampsia had significantly lower calciuria than normotensive patients (1.5 mmol/24h+/-1.0 versus 6.0 mmol/24h+/-4.2. p=0.0001) [49]. Vural et al. (2000) conducted a case-control study with 59 patients, concluding that hypocalciuria might be an important feature of pre-eclampsia [50]. Malas et al. (2001) and Bilgin et al. (2000) concluded from their studies that hypocalciuria is an important feature of pre-eclampsia [51-52]. Szmidt et al. (2006) conducted a case-control study that included 47 pre-eclamptic women [18]. A logistic regression analysis investigated the relationship between hypocalciuria and pre-eclampsia. Women with pre-eclampsia had significantly lower akiliria than normotensive patients (15 mmol/24h+/-10 versus 6.0 mmol/24h+/-42, -0.0001), and hypocalciuria was significantly associated with pre-eclampsia (82417442-00001)60.71 in this study calcium-creatinine ratio in a urine sample is evaluated as a predictor of pre-eclampsia. Here, the urinary calcium-creatinine ratio in women with pre-eclampsia is compared with normal pregnant women, and the result is highly significant (p<0.001). The ratio comes in pre-eclampsia

patients in comparison to normal pregnant. These results correlate very well with several previous studies. Anjali et al. (2016) revealed that urinary CCR had a sensitivity of 63.63% and a specificity of 94.87%, and urinary CCR will be an effective screening method for pre-eclampsia [53]. Anita et al. (2017) showed that a study was conducted over seven months, and a total of 100 patients were included in the study, out of which 50 were pre-eclamptic patients and (group 1) another 50 belonged to the normotensive group (group 2) [54]. The urinary calcium to creatinine ratio was significantly reduced (t-value=3.57, p=0.0005) in pre-eclampsia patients compared to the normotensive group. Another study by Sinha et al. (2016) found that CCR had a sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of 81.2%, 96.4%, 86.6%, and 94.7%, respectively, with a statistical accuracy of 93.1% and p-value of <0.001 (strongly significant) [55]. It was found to be a good test for the prediction of pre-eclampsia. Similarly, Nagalakshmi et al. (2016) revealed that among the cases, 84% of the patients had CCR ≤0.04, in contrast to 6% of controls with CCR ≤0.04 [56]. The Chi-square (x) value was 58.34, showing that the ratio is highly significant (p<0.0001). Kazerooni et al. (2003) conducted a similar with 102 patients, and the result favoured a significantly lowered calcium-creatinine ratio in pre-eclampsia [9]. Likewise, the outcome of research worked by Szmidt et al. (2006) has also revealed the same results in favour of the present proposition in a case-control study of 47 pre-eclampsia women and 50 controls [18]. Similar findings by Rizk et al. (2007) demonstrated a predictive nature of spot urine calcium/ creatinine ratio in pre-eclampsia [57]. However, Lindita et al. (2021) had the opposite opinion [58]. The study found that the sensitivity of proteinuria as a predictor of pre-eclampsia was 96.6% (P=0.000) and specificity was 21.3%, whereas, for the urine calcium/creatinine ratio, the sensitivity was 87.9% (P=0.000) and the specificity 40.7%, which corresponds to a value of 0.105 (cutoff). So, the role of the calcium/creatinine ratio in urine is inferior to proteinuria in predicting pre-eclampsia Another study outcome by David et al. (2016) reported that on statistical analysis, it was found that when CCR alone is taken as high-risk factor for prediction of pre-eclampsia, p < 0.001 was statistically significant, sensitivity was 80 %, specificity 98.04 % PPV 80 %, NPV 98.04 %, and diagnostic accuracy So this test was satisfactory as an early predictor for development pre-eclampsia.

Limitations of the study: This study is a single-centre, hospital-based investigation primarily focusing on individuals from a particular region. Consequently, the findings presented here may differ significantly from those of broader studies conducted over more extended periods. The sample size was restricted, and the study duration was brief. The research does not compare the urinary calcium-creatinine ratio with other pre-eclampsia screening tools. Furthermore, budgetary constraints may have impacted the scope of the study.

Conclusion and Recommendations

This study showed a close relationship between urinary calcium creatinine ratios in e-eclampsia patients. The level of urinary calcium creatinine was significantly decreased in pre-tempting patients compared to normotensive women. This test can be used as a screening tool to predict the development of pre-eclampsia in symptom-free patients. So, measurement of urinary calcium creatinine ratio is a non-invasive, inexpensive and easy-to-carry method for predicting pre-eclampsia and thereby helps initiate prompt education of the patients and timely prophylactic interventions, thus minimizing the severity of pre-eclampsia.

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Conflict of Interest

None declared

Ethical Approval:

The study was approved by the Institutional Ethics Committee

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