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Significance of urine albumin / creatinine ratio (UACR) and uric acid in women with preeclampsia and its comparison with healthy normotensive pregnant women in their third trimester

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Objective. To determine the significance of urine albumin / creatinine ratio (UACR) as to predict proteinuria in new-onset hypertension and uric acid in women with preeclampsia and its comparison with healthy normotensive pregnant women.

Methods. Healthy normotensive pregnant women (n = 45), women with preeclampsia (n = 36) were included in the study. The preeclamptic group was further divided into two subgroups: mild (n = 25) and severe preeclampsia (n = 11).

Results. Higher mean values of urine albumin / creatinine ratio (UACR) and uric acid were found in preeclamptic pregnant women (319.05 ± 247.56 mg/g, 5.98 ± 2.1 mg/dl) as compared to healthy normotensive pregnant women (22.15 ± 8.1 mg/g, 4.07 ± 0.91 mg/dl) in the third trimester with highly significant difference ($p < 0.001$) statistically. When comparison of the mean values of urine albumin / creatinine ratio and uric acid was done between mild (199.9 ± 46.78 mg/g, 5.24 ± 1.89 mg/dl) and severe preeclamptic pregnant women (589.67 ± 305.38 mg/g, 7.64 ± 1.4 mg/dl), the values were found to be elevated in the latter group with highly significant difference ($p < 0.001$) statistically. The positive and highly significant correlation was found in UACR / blood pressure, uric acid / blood pressure and UACR / uric acid.

Conclusion. It was concluded that UACR and serum uric acid levels increased as disease progressed from mild to severe conditions.

Key words: preeclampsia, urine albumin / creatinine ratio (UACR), uric acid, proteinuria

INTRODUCTION

Preeclampsia is a pregnancy specific syndrome and a leading cause of maternal and fetal morbidity and mortality (1). It is a complex multisystem syndrome affecting about 5–8% of all pregnancies (2). The pathophysiological mechanism is characterized by a failure of the trophoblastic invasion of spiral arteries, leading to maladaptation of maternal spiral arterioles, which may be associated with an increased vascular resistance of the uterine artery

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and a decreased perfusion of the placenta (3). Proteinuria is a major indicator of preeclampsia and also one of the diagnostic criteria of its severity. Proteinuria develops late in the course of the hypertensive disease and its presence is a sign of worsening hypertensive disease, especially preeclampsia. As the proteinuria increases, the likelihood of complications also increases, and hence a rapid and accurate detection and quantization of proteinuria are essential for the management of hypertension pregnant women. However, 24-hour urine collection in patients with hypertensive disorders of pregnancy is a gold standard for diagnosis of significant proteinuria, it is time consuming, subject to collection error, and requires good patient compliance. In recent years, the urine albumin : creatinine ratio has been suggested as a rapid test for prediction of 24-hour protein excretion (4). Also visual dip stick urinalysis has also been used but the results are inaccurate giving high numbers of false positive and false negative results. The National Kidney Foundation guidelines have suggested that the urine albumin : creatinine ratio should be used to detect and monitor proteinuria (5). Also the Australasian Society for the Study of Hypertension in Pregnancy and the International Society for the Study of Hypertension in Pregnancy have proposed use of the urine albumin : creatinine ratio as an alternative to 24-hour urine collection (6). Proteinuria in preeclampsia is a nonselective type of proteinuria. When it is overt and persistent, maternal and fetal risks are increased. But the degree of proteinuria does not always indicate the severity of the disease (7).

Hyperuricemia in preeclampsia induces endothelial dysfunction and may induce hypertension and vascular disease. Its production increases probably secondary due to tissue ischemia and oxidative stress and impairs the generation of nitric oxide in endothelial cells. Therefore the modification of uric acid metabolism during pregnancy could be one of the potential causes of preeclampsia (7).

MATERIALS AND METHODS

This study was conducted in the Department of Biochemistry, M. G. M. Medical College and associated M. Y. Hospital, Indore. The subjects were pregnant women clinically diagnosed as preeclampsia patients during the third trimester (28–40 weeks) with the age 18–35 years (Group B) visiting the Obstetrics OPD and wards of the MY Hospital, The study group was further divided into two subgroups. It comprised 25 mild preeclamptic pregnant women (Subgroup B1) and 11 severe preeclamptic pregnant women (Subgroup B2) on the basis of blood pressure (both systolic and diastolic), proteinuria and pathological edema, which are the diagnostic criteria of preeclampsia. As a control group, 45 healthy normotensive pregnant women (Group A) were taken. The healthy normotensive pregnant women were also in the third trimester (28–40 weeks) of their pregnancy with the age 18–35 years. Inclusion criteria for women included in the study were the following: should not be using any kind of oral contraceptives, anticoagulant drugs, should be non-smokers and non-alcoholics. Exclusion criteria were as follows: past history of diabetes, systemic or endocrine disorder, chronic infection, chronic renal disease and hypertension (in Group A only), women in the labor pains were excluded from the study. For collection of urine, women with a concurrent diagnosis of upper tract infection, chronic hypertension, chronic renal disease, pathological vaginal discharge, diabetes mellitus / gestational diabetes mellitus, etc. were excluded from the study.

Preeclampsia was diagnosed according to the American College of Obstetrics and Gynecology (ACOG) criteria: blood pressure higher than 140/90 mm Hg and proteinuria more than 300 mg/24 h were observed on at least two occasions more than 6 h apart after the 20th week of pregnancy. Preeclampsia was classified as severe if blood pressure was higher than 160/110 mmHg, proteinuria more than 5 000 mg/24 h, and in the presence of headache, visual disturbances, epigastric pain, oliguria, elevated LFT, elevated RFT, thrombocytopenia.

Urine collection for the urine albumin : creatinine ratio was done. Microalbuminuria was measured by the latex turbidimetric method and urine creatinine was measured by the alkaline picrate method. The test was performed on a fully automated analyzer. Blood samples were collected in the morning in a plain bulb with aseptic conditions. In the preeclampsia group, blood samples were collected when the patients

presented for evaluation and before initiation of medical therapy. Serum uric acid was measured by kits using the Uricase / Peroxidase method. The results were expressed as mean ± SD and the groups were compared using ANOVA.

Statistical analysis was carried out by using SPSS software, version 20. The level of significance was set at <0.05.

RESULTS

The anthropometric factors of the study groups are summarized in Table 1.

Maternal age and body mass index (BMI) showed no significant difference between the groups ($p > 0.05$, Table 1). Gestational age, systolic and diastolic blood pressures were highly significant in preeclamptic pregnant women as compared to healthy normotensive pregnant women ($p < 0.001$, Table 1). The same when compared between mild and severe preeclamptic pregnant women, the difference was highly significant in the latter group ($p < 0.001$, Table 1).

Urine albumin / creatinine ratio and uric acid were found to be higher in preeclamptic pregnant women (319.05 ± 247.56 mg/g, 5.98 ± 2.1 mg/dl) as compared to healthy normotensive pregnant women (22.15 ± 8.1 mg/g, 4.07 ± 0.91 mg/dl) with highly significant difference ($p < 0.0001$, Table 2) statistically. When the urine albumin / creatinine ratio and uric acid in mild preeclamptic women (199.9 ± 46.78 mg/g, 5.24 ± 1.89 mg/dl) were compared with severe preeclamptic women (589.67 ± 305.38 mg/g, 7.64 ± 1.4 mg/dl), higher values in the latter group were observed with the highly significant difference ($p < 0.001$, Table 2) statistically.

In the present study, UACR and uric acid levels increased with the severity of the disease. Therefore, we correlated these two parameters with blood pressure within preeclampsia groups. Blood pressure is an indicator for the severity of

Table 1. Comparison of the mean and standard deviation of anthropometric factors of Control and Preeclamptic groups

Anthropometric factors	Group A Healthy normotensive pregnant women (n = 45)	Group B Preeclamptic pregnant women (n = 36)	Subgroup B1 Mild preeclamptic pregnant women (n = 25)	Subgroup B2 Severe preeclamptic pregnant women (n = 11)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age, yrs	23.02 ± 2.97	23.13 ± 3.28	23.2 ± 3.57	23 ± 2.68
BMI, kg/m^2	24.01 ± 1.64	24.37 ± 1.67	24.50 ± 1.43	24.06 ± 2.06
Gestational age, wks	38.91 ± 2.69	36.75 ± 1.94	37.2 ± 1.73	35.72 ± 2.1
Systolic blood pressure, mm of Hg	113.33 ± 6.74	147.5 ± 17.46	139.2 ± 7.02	166.36 ± 19.63
Diastolic blood pressure, mm of Hg	75.33 ± 5.47	96.77 ± 14.5	89.76 ± 6.17	112.72 ± 15.55

Table 2. Comparison of the mean and standard deviation of clinical parameters of Control and Preeclamptic groups

Clinical parameters	Group A Healthy normotensive pregnant women (n = 45)	Group B Preeclamptic pregnant women (n = 36)	Subgroup B1 Mild preeclamptic pregnant women (n = 25)	Subgroup B2 Severe preeclamptic pregnant women (n = 11)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
UACR, mg/g	22.15 ± 8.1	319.05 ± 247.56*	199.9 ± 46.78#	589.67 ± 305.38**
Serum uric acid, mg/dl	4.07 ± 0.91	5.98 ± 2.1*	5.24 ± 1.89#	7.64 ± 1.4**

* $p < 0.001$ compared with healthy normotensive pregnant women;
# $p < 0.001$ compared with healthy normotensive pregnant women;
** $p < 0.001$ compared with healthy normotensive pregnant women and mild preeclamptic pregnant women

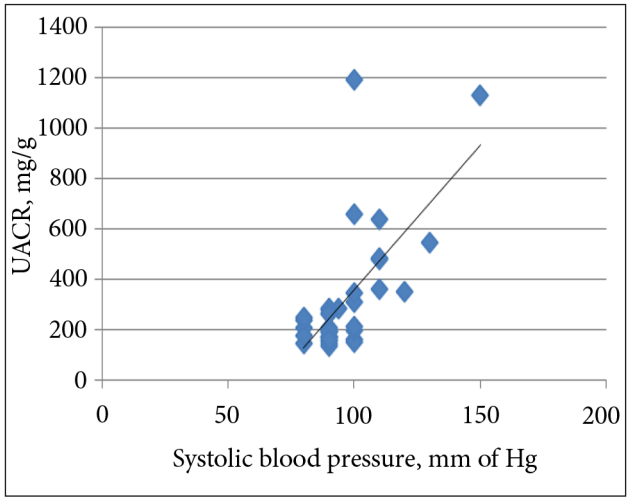

Fig. 1. Correlation of systolic (X axis) with UACR (Y axis) in the study group

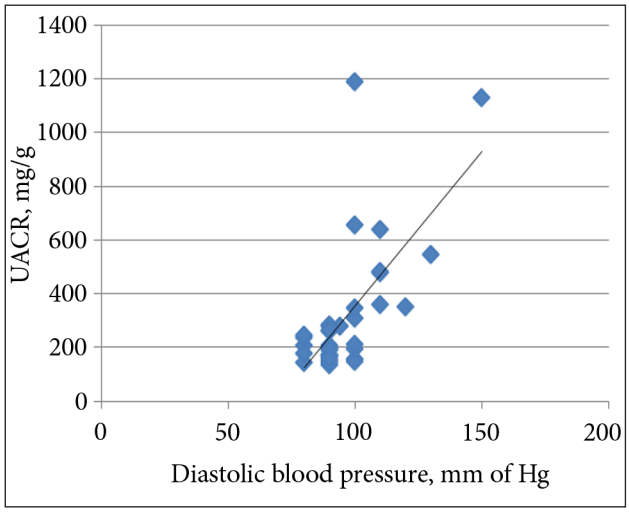

Fig. 2. Correlation of diastolic blood pressure (X axis) with UACR (Y axis) in the study group

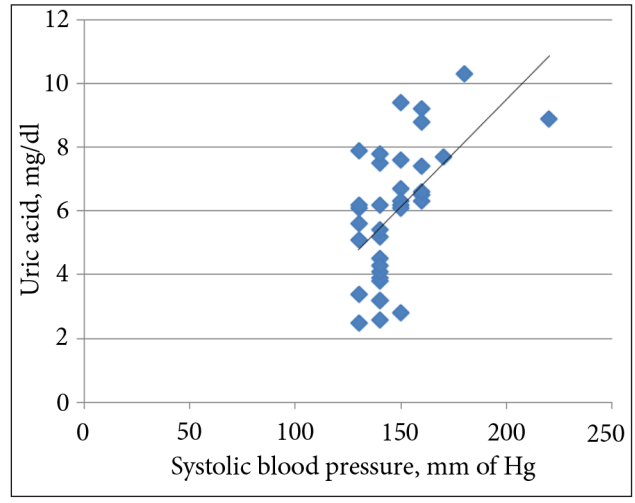

Fig. 3. Correlation of systolic blood pressure (X axis) with uric acid (Y axis) in the study group

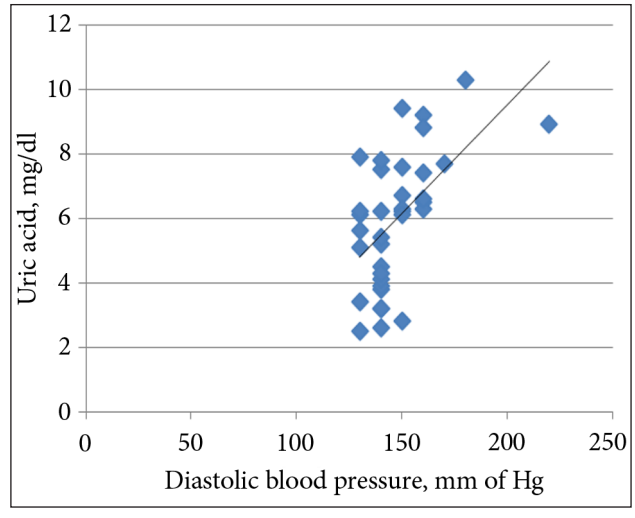

Fig. 4. Correlation of diastolic blood pressure (X axis) with uric acid (Y axis) in the study group

the preeclampsia. We found UACR and uric acid levels were highly significantly ($p < 0.001$) and positively correlated with blood pressure (UACR/SBP $R^2 = 0.607$, UACR/DBP $R^2 = 0.452$, Table 3 and Figs. 1, 2, and uric acid/SBP $R^2 = 0.321$, uric acid/DBP R2 = 0.113, Table 3 and Figs. 3, 4). In addition, we found a highly significant and positive correlation between UACR and uric acid concentrations in pregnancies complicated with preeclampsia ($R^2 = 0.111$, Table 3, Fig. 5).

DISCUSSION

The clinical syndrome of preeclampsia is thought to be due to maternal endothelial dysfunction. This is thought to result from the interaction between

Table 3. Pearson's correlation between systolic blood pressure and parameters

	R^2 value for SBP	R^2 value for DBP
UACR, mg/g	0.607**	0.452**
Uric acid, mg/dl	0.321**	0.113**

** R^2 value between UACR and uric acid is 0.111.
** Highly significant and positive correlation ($p < 0.001$).

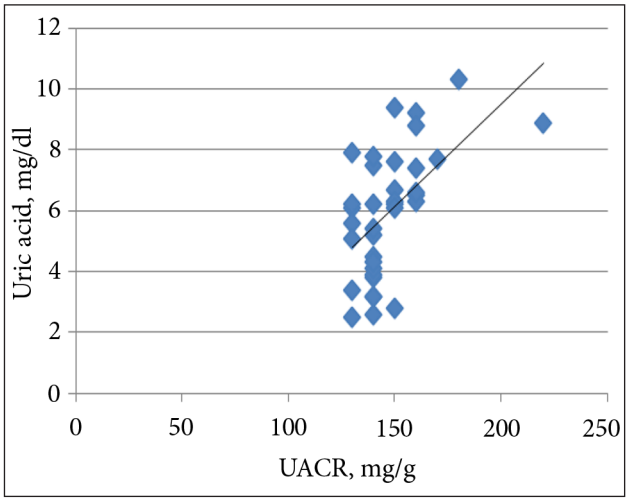

Fig. 5. Correlation of UACR (X axis) with uric acid (Y axis) in the study group

a normal placenta and conditions that make the mother susceptible to micro vascular disease (9). The net result of this endothelial dysfunction is an increase in vascular permeability systematically and at glomerular level. Proteinuria occurs due to renal glomerular endotheliosis, a manifestation of widespread endothelial damage in preeclampsia (10). Microalbuminuria occurs as a result of this endothelial dysfunction (11). Furthermore, urinary albumin has been shown to be a sensitive marker for early changes in glomerular permeability and thus the UACR may detect structural renal changes associated with preeclampsia at an earlier stage (12).

Studies have shown that UACR were significantly higher in preeclamptic women as compared to healthy pregnant women. The levels of UACR in the severe preeclamptic group as compared with that of the mild preeclamptic group were significantly higher with similar chronological age, gestational age and body mass index (Table 2) (13, 14). The present results support the hypothesis that detection of proteinuria by UACR is one of the useful predictor of preeclampsia. In accordance with the previous reports our study concludes that preeclampsia is associated with increased UACR as compared with healthy pregnant women.

Uric acid is the end product of purines metabolism and is synthesized by enzymes xanthine oxidase. It is a marker of oxidative stress, tissue injury and renal dysfunction and is an independent risk factor for cardiovascular disease (15). During uncomplicated pregnancies serum uric acid concentration decreases by 25% to 35% in early pregnancy but then increases throughout pregnancy until towards the end of pregnancy when they approach non pregnant levels (16). It is proposed that these pregnancy mediated changes in serum uric acid are primarily the result of altered renal handling. Increased serum uric acid in preeclampsia is secondary to reduced renal urate clearance because of renal dysfunction (17) and also due to increased xanthine oxidase activity (18). Thus hyperuricemia may induce endothelial dysfunction (19). The mean serum uric acid in severe preeclamptic women was more than in healthy pregnant women and mild preeclamptic women and the difference was highly significant among all the groups ($p < 0.001$, Table 2). The present findings are similar to the findings of previous studies (20, 21).

In our study (Table 3 and Figs. 1, 2) a highly significant and positive correlation between UACR and blood pressure was found. Similarly a highly significant and positive correlation between uric acid and blood pressure was found (Table 3 and Figs. 3, 4). In preeclampsia, the epithelial lining of glomerulus may be damaged due to high blood pressure (22). This endothelial damage leads to decrease in the renal tubular excretion thus causing renal dysfunction. This may be the probable cause of increase in proteinuria. Further decreased tubular excretion or placental tissue breakdown due to high blood pressure may be the responsible cause for increase in uric acid levels in preeclamptic patients (23). Also a highly significant and positive correlation between UACR and uric acid was found in the study group (Table 3, Fig. 5).

CONCLUSIONS

It is concluded from the study that high levels of the urine albumin / creatinine ratio and uric acid were found in the preeclamptic group as compared to the healthy pregnant group. As compared with the mild preeclamptic group, the level of the urine albumin / creatinine ratio and uric acid was significantly higher in the severe preeclamptic group giving the evidences that elevated levels of the urine albumin / creatinine ratio and uric acid are the valuable markers of preeclampsia as opposed to have a role in the pathogenesis and also indicates that the severity of disease increases as the disease

progresses from a mild type to a severe type. Also for detecting significant proteinuria in pregnant women with suspected preeclampsia, the UACR alternative to the 24-hour urine collection is one of the important screening tests with high accuracy. We also found a highly significant and positive correlation between UACR, uric acid and blood pressure and also between UACR and uric acid.

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ŠLAPIMO ALBUMINO IR KREATININO SANTYKIS BEI ŠLAPIMO RŪGŠTIES KONCENTRACIJA TREČIĄ NĖŠTUMO TRIMESTRĄ PREEKLAMPSIJA SERGANČIŲ MOTERŲ IR SVEIKŲ NĖŠČIŲJŲ

Santrauka

Tikslas. Prognozuojant proteinurijos atsiradimą preeklampsija sergančioms moterims, nustatyti šlapimo albumino ir kreatinino santykį (ŠAKS) bei šlapimo rūgšties koncentraciją ir palyginti su normalų kraujospūdį turinčių sveikų nėščių moterų rodikliais.

Metodai. Į tyrimą įtrauktos sveikos, normalų kraujospūdį turinčios nėščios moterys (n = 45) ir moterys, sergančios preeklampsija (n = 36). Preeklampsija sergančių moterų grupė suskirstyta į du pogrupius: lengva (n = 25) ir sunkia preeklampsijos (n = 11) forma sergančiąsias.

Rezultatai. Preeklampsija sergančioms nėščioms moterims trečią nėštumo trimestrą buvo nustatyti statistiškai reikšmingi (p < 0,001) aukštesni vidutiniai šlapimo albumino ir kreatinino santykio (ŠAKS) bei šlapimo rūgšties dydžiai (319,05 ± 247,56 mg/g, 5,98 ± 2,1 mg/dl), palyginti su sveikomis nėščiosiomis (22,15 ± 8,1 mg/g, 4,07 ± 0,91 mg/dl). Palyginus vidutinius šlapimo albumino ir kreatinino santykio bei šlapimo rūgšties koncentracijos dydžius lengva (199,9 ± 46,78 mg/g, 5,24 ± 1,89 mg/dl) ir sunkia preeklampsijos forma sergančių nėščiųjų (589,67 ± 305,38 mg/g, 7,64 ± 1,4 mg/dl), pastarojoje grupėje buvo nustatytas statistiškai reikšmingas padidėjimas (p < 0,001). Teigiama ir labai reikšminga koreliacija buvo nustatyta tarp ŠAKS ir kraujospūdžio, šlapimo rūgšties ir kraujospūdžio, taip pat tarp ŠAKS ir šlapimo rūgšties.

Išvada. Nustatyta, kad ŠAKS ir šlapimo rūgšties kiekis serume padidėjo ligai progresuojant nuo lengvos iki sunkios formos.

Raktažodžiai: preeklampsija, šlapimo albumino ir kreatinino santykis (ŠAKS), šlapimo rūgštis, proteinurija