IJKD KIDNEY DISEASES

Study of The Relationship Between 24-hour Urine Protein Excretion Rate and Protein/Creatinine Ratio in Random Urine Specimen of Women with Preeclampsia

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Keywords. proteinuria, creatinine, preeclampsia

Introduction. Early diagnosis and management of preeclampsia are very important to reduce fetal and maternal complications. In this study, we examined the ratio of protein to creatinine in a random urine sample and its relationship to the rate of 24-hour urine protein excretion for quick detection and prompt management of this condition in women with preeclampsia.

Methods. In this descriptive-analytical cross-sectional study, 60 pregnant women with preeclampsia referred to the maternity ward of Ali Ebn -e Abitaleb hospital of Zahedan in 2019 were recruited. The 24-hour urine protein excretion and the ratio of protein to creatinine in a random urine sample were compared in these patients.

Results. The results showed that there was a positive correlation between the 24-hour urinary protein excretion and the protein to creatinine ratio of the random urine sample in preeclampsia ($P < .001$, $r = 0.515$). Women with a higher 24-hour protein excretion also had a higher urinary protein to creatinine ratio.

Conclusion. In general, based on the results of this study, it can be concluded that the ratio of protein to creatinine in the random urine sample has a good diagnostic efficiency in suspected preeclampsia. It is a quick alternative method for detecting suspicious proteinuria and could be used as a screening test in emergency situations.

IJKD 2023;17:184-90
www.ijkd.org
DOI: 10.52547/ijkd.7457

Original Paper

INTRODUCTION

Pre-eclampsia is a multisystem disorder typically manifesting during the 20th week of pregnancy, affecting 2 to 8% of all pregnancies worldwide, and 10% of pregnancies in underdeveloped countries, and accompanied with a common complication of kidney failure.[1-6] These conditions are known to cause miscarriage, preterm labor, low birth weight, fetal growth restriction (FGR), and an increased risk of postpartum respiratory distress syndrome. They are also a significant cause of maternal and fetal mortality during the prenatal period (RDS).[7] Pre-eclampsia causes an estimated 76,000 deaths worldwide; more than 90% of which occurs in underdeveloped countries. In 2013, the American College of Obstetricians and Gynecologists classified the disease as non-severe, and severe. [3-8]

Non–severe preeclampsia is defined as hypertension (systolic and diastolic blood pressure greater than 140 and 90 mmHg, respectively) and proteinuria (24-hour urinary protein excretion greater than or equal to 300 mg/d) or the

protein-to-creatinine ratio in a random urine sample (equivalent to 0.3 mg/dL) after 20 weeks of gestation.[9] Severe pre-eclampsia is defined as systolic pressure greater than 160 mmHg or diastolic pressure greater than 110 mmHg accompanied with proteinuria of more than 300 mg/d.[10,11] Routine measurement of blood pressure and urine protein readings are the fundamentals of antenatal screening protocols of preeclampsia. The gold standard 24-hour urine collection test is always conducted after this initial screening because of the high rate of false positives and false negative results of urinalysis. This test is flawed, and it is not always possible to obtain a 24-hour urine sample.[12] The ratio of urine protein to creatinine in a ratio of albumin to creatinine in a random urine sample.[3] According to Jan *et al.*, there is a significant association between 24-hour urinary protein excretion and the protein to creatinine ratio of a random urine.[12] When the protein / creatinine ratio is below 150 mg/g, a review by Papanna *et al.* revealed that the protein-to-creatinine ratio in random urine is helpful and protein-to-creatinine ratio o f300 mg/g has poor sensitivity and specificity, but reliable findings require 24-hour urine protein measurement.[14] Non-severe preeclampsia is defined as the presence of new onset proteinuria (more than or equal to 300 mg/d) or protein-to-creatinine ratio (0.3 mg/dL) equivalent after 20 weeks in more than one random urine sample, as well as the development of hypertension (systolic and diastolic over 140 and 90 mmHg, respectively.[15] Preeclampsia that is considered to be severe has a systolic pressure larger than or equal to 160 mmHg or a diastolic pressure greater than or equal to 110 mmHg, together with proteinuria that may are accompanied by end-organ symptoms.[16] In gestational hypertension, the diagnostic criteria is BP ≥ 140/90 and proteinuria less than 300 mg. Preeclampsia screening was performed with routine measurement of blood pressure and random urine protein and also 24-hour urine collection test should always be done after this screening because of the high rate of false positives and false negatives. It is not always possible to obtain 24-hour urine in all patients.[17] The preferred technique for determining proteinuria has recently been shown to be the ratio of urine protein-to-creatinine in a random urine specimen.[16]

In this study, we examined the ratio of protein to creatinine in a random urine sample and its relationship with the amount of 24-hour urinary protein excretion in women with preeclampsia in the maternity ward of Ali Ebn-e-Abitaleb Hospital of Zahedan from 2018 to 2019 for rapid diagnosis of this disease.

MATERIALS AND METHODS

This study was a cross-sectional observational study approved by the ethics committee of Zahedan university of medical sciences (IR.ZAUMS.REC.1398.307). Considering the values of $\alpha = 0.01$, $\beta = 0.05$, and Pearson correlation coefficient according to Durnwald *et al.* study [18], the minimum sample required for this study was 60.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2}{\left(\frac{1}{2}\ln\left(\frac{1+r}{1-r}\right)\right)^2} + 3$$

Inclusion criteria were: age 18 to 45 years, Iranian, hypertension (systolic blood pressure of equal or greater than 140 mmHg and diastolic blood pressure of equal or greater than 90 mmHg or both), gestational age ≥ 20 weeks, proteinuria 1+ in random urine sample or above 300 mg/d in 24-hour , platelets below 100,000, creatinine above 1.2, doubling of liver enzymes, neurologic symptoms of headache and blurred vision, and eclamptic seizures. Exclusion criteria were: gestational hypertension, chronic hypertension, gestational age of less than 20 weeks, history of other underlying diseases such as collagen vascular diseases, history of renal impairment, diabetes mellitus, urinary tract infection, and molar pregnancy. All patients signed an informed consent and the data collected from patients' records included 24-hour urinary protein excretion, random urinary creatinine, random urinary protein-to-creatinine ratio, gestational age (mentioned as week), gravidity and parity, and maternal age. After collecting clinical and laboratory information, quantitative data were described by using statistical indicators such as mean, standard deviation, minimum and maximum values, etc. and qualitative data were summarized by using numbers and percentages. Pearson's correlation coefficient was used to check the correlation between urine protein and the ratio of protein to creatinine in random urine specimen. In the whole study, the level of significance was

considered .01. The highest must be one number/value; here we see two numbers.

RESULTS

Among 60 patients with preeclampsia, the highest age of women was 26 to 35 years (45%) and the lowest age was 36 to 45 years (13.3%), the mean of gestational age was 29.18 weeks, 15 (25%) had severe preeclampsia, and 45 (75%) had mild preeclampsia. The mean protein-to-creatinine ratio in a random urine specimen was 3.52 ± 5.29 mg/g, and the mean 24-hour urine protein excretion rate was 2306.60 ± 2098.57 mg/d. Out of 60 patients, 32 patients (53.3%) had a 24-hour urinary protein excretion above 300 mg/d, 24 (40%) had a 24-hour urinary protein excretion above 1000 mg/d, and 4 (6.7%) had a 24-hour urinary protein excretion above 3000 mg/d.

The highest 24-hour urine protein excretion and random protein to creatinine ratio in urine samples were seen in the age group of 16 to 25 with values of 2601 mg/day and 3.93 mg/g, respectively. With an increase in the age, the rate of 24-hour urinary protein excretion and the protein to creatinine ratio in random urine samples decreased (Figure 1). The highest 24-hour urine protein excretion and protein to creatinine ratio of random urine samples were seen in the fourth and fifth pregnancies, respectively. Moreover, with the increasing parity ≥ 5, the rate of 24-hour urinary protein excretion and the ratio of protein to creatinine in the random urine sample decreased (Figure 2).

In the present study, the Pearson correlation test showed a positive correlation between 24-hour urinary protein excretion and the random protein to creatinine ratio ($P < .001$, r = 0.52). The correlation intensity was moderate, and the variance described was 26.5%. The results showed that patients with higher 24-hour protein excretion also had higher protein-to-creatinine ratios in the

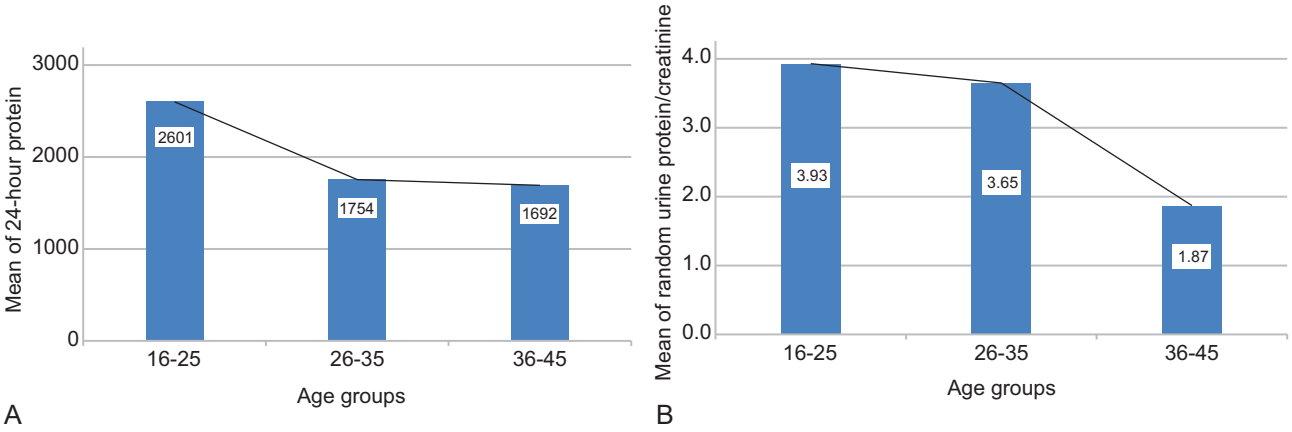

Figure 1. The mean 24-hour urinary protein excretion (A) and the protein to creatinine ratio of the random urine sample (B) by the age groups

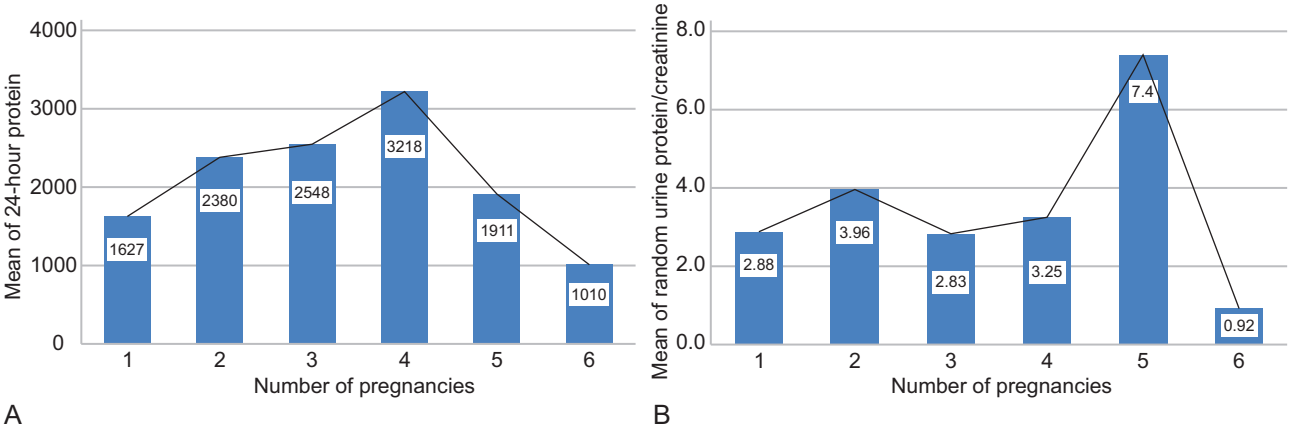

Figure 2. The mean 24-hour urine protein excretion (A), the protein to creatinine ratio of the random urine sample (B) by the number of pregnancies

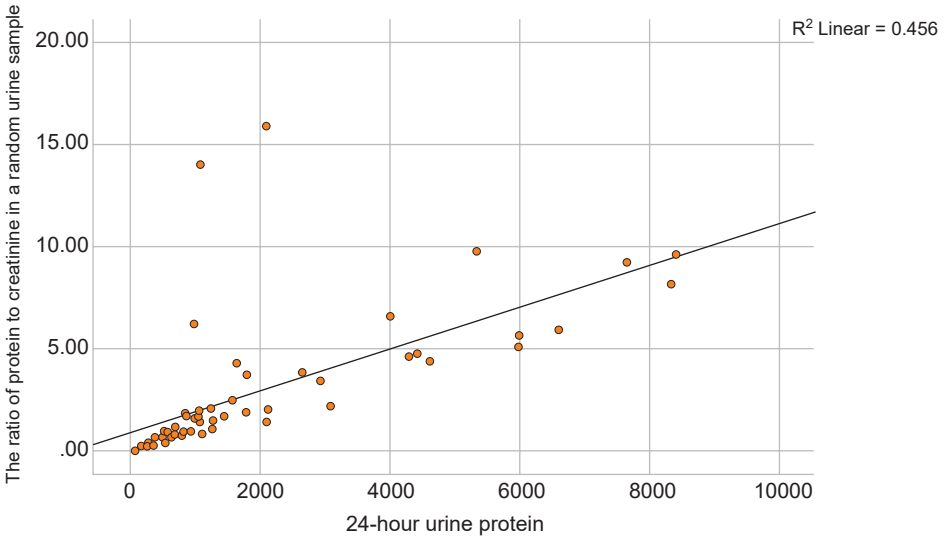

Figure 3. Distribution of the protein to creatinine ratio in the random urine sample and the 24-hour urine protein in the studied preeclampsia patients (n = 60)

random urine sample.

As can be seen in the distribution diagram, by removing the far point and calculating the correlation between the ratio of protein to creatinine in the random urine sample and 24-hour urine protein in the remaining 60 samples, the correlation coefficient is 0.68 ($P < .001$). The variance described was 45.6%. The results show that patients with higher 24-hour protein excretion also had higher protein-to-creatinine ratios in the random urine sample (Figure 3).

DISCUSSION

Currently, 24-hour urine protein is the gold standard method for the assessment of proteinuria. Shortening the test duration, by using protein to creatinine ratio instead of 24-hour urine protein, and early detection of proteinuria will result in a lower rate of premature labor and early glucocorticoids administration. On the other hand, women who do not meet the criteria for preeclampsia will be discharged sooner, and hospital costs will be reduced. The results of previous studies have shown that rapid urinary dipstick tests are not as accurate as 24-hour urinary protein in diagnosis of severe preeclampsia.[10-15] This study aimed to evaluate the rapid and efficient diagnostic method in women with preeclampsia. In the present study, the mean age of patients was 28.37 years, gravid was 2.57, and gestational age was 29.18 weeks. Variables of age, gestational age, race, and education showed a normal distribution, and 45% of patients were in the age group of 26 to 35 years. However, most patients with preeclampsia were seen in early pregnancies, and the prevalence of preeclampsia decreased with increasing gravidity. Also, in the present study, 15 patients (25%) had severe preeclampsia, and 45 patients (75%) had mild preeclampsia.

In women with severe preeclampsia, the extracellular fluid volume increases, which manifests as edema and is usually much more severe than normal pregnant women. The endothelial injury appears to be the initial cause of pathological fluid retention. In addition to generalized edema and proteinuria, these women also experience a reduction in plasma oncotic pressure, which leads to imbalanced filtration and increases the displacement of intravascular fluids to the interstitial space around the arteries. Electrolyte imbalance is not significantly different in pregnant women with or without preeclampsia. However, with the use of diuretics, sodium restriction, and oxytocin-containing fluids administration, which have anti-diuretic effects, generalized edema disappears. After an eclamptic seizure, due to lactic acidosis and compensatory loss of carbon dioxide by respiration, serum pH and bicarbonate levels decrease. The severity of acidosis depends on the amount of lactic acid produced and the rate of carbon dioxide loss in the exhaled air.[19] During normal pregnancy, plasma renin-angiotensin, angiotensin,

aldosterone, and atrial natriuretic peptide (ANP) levels significantly increase. Deoxycorticosterone is a potent mineralocorticoid significantly increasing in a normal pregnancy mostly due to the conversion of plasma progesterone to deoxycorticosterone rather than increased maternal adrenal secretion. Therefore, deoxycorticosterone secretion is not reduced by sodium retention or hypertension, which explains why women with preeclampsia have sodium retention.[33,34] During pregnancy, the sensitivity of the mineralocorticoid receptor to aldosterone decreases. Vasopressin levels are similar in non-pregnant, normal pregnant, and pregnant women with preeclampsia.[20]

Baca *et al.* reported a prevalence of severe preeclampsia in 35% of preeclamptic women.[21] Kaul *et al.* examined the diagnostic value of protein to creatinine ratio in a random urine sample, and stated that only 13% of the patients met criteria for severe preeclampsia.[3,34] In the present study, the mean protein to creatinine ratio of a random urine sample was 3.52 mg/g, with a standard deviation of 5.29, the mean of 24-hour urine protein excretion was of 2098.57 mg/d, and a standard deviation of 2306.60. The Pearson correlation test showed a positive correlation between 24-hour urine protein excretion and protein-to-creatinine ratio in a random urine sample ($P < .001$, r = 0.515); with moderate correlation intensity; the variance described was 26.5%. The results showed that patients with higher 24-hour protein excretion also had higher protein-to-creatinine ratios in the random urine sample. The findings of this study are in line with the findings of Mohseni *et al.*, which also showed that there is a positive correlation between the protein to creatinine ratio in random urine sample and 24-hour urinary protein (r = 0.502) and suggested that protein to creatinine ratio in a random urine sample could be an acceptable screening test in emergency conditions.[22] Demirci *et al.* also reported a strong positive correlation between protein to creatinine ratio in a random urine sample and 24-hour urine protein (r = 0.758) and reported that the random protein to creatinine ratio could be a rapid alternative test for the diagnosis of proteinuria in women with suspected preeclampsia.[23] In a study of 150 patients admitted to the gynecology ward of Ghaem Hospital, Rudsari *et al.* have reported that measuring the random protein-to-creatinine ratio is an appropriate alternative for measuring 24-hour urine protein which is rapid, reliable, and cost-effective.[24] Yamasmit *et al.*, reported a strong correlation between the two variables of the random protein to creatinine ratio and the measurements of 24-hour urine protein.[25] Nasiri *et al.* reported that the random protein to creatinine ratio could be used as a quick and easy screening test for the detection of proteinuria in women with preeclampsia.[26] The correlation coefficient reported in the study conducted by Rodriguez *et al.* [27] was high (r = 0.8, $P < .001$), and in the study conducted by Neithardt,[28] was excellent ($P < .001$, r = 0.93),while in the Donald's study, the correlation was weak (r = 0.41, $P < .001$). The study conducted by Ragip,[29] similar the present study, a moderate correlation was reported (r = 56, $P < .01$); however, the differences in the results of the above studies can be due to the differences in the study methods, sample collection methods, study population characteristics, sample size, the prevalence of overt proteinuria in patients, and inclusion and exclusion criteria. Therefore, review studies in this regard are recommended. In a cross-sectional study conducted in Brazil by Ramos *et al.* on 47 women with hypertension and 20 weeks of gestational age and older, the correlation coefficient between 24-hour proteinuria and the ratio of protein to creatinine in random urine was 94.0. The specificity, sensitivity, and positive predictive value for protein to creatinine ratio was greater than or equal to 0.8.[30] A study by Robert *et al.* on 71 participants, aimed to evaluate the protein-to-creatinine ratio in a random urine sample to quantitatively assess 24-hour urine protein in pregnant patients with hypertension. The results showed that the correlation coefficient between the random protein to creatinine ratio and the amount of protein in 24-hour urine was 0.94, indicating a strong correlation.[31] In another study examining the protein to creatinine ratio in a random urine sample and 24-hour proteinuria in 51 patients, Kristal *et al.* found a significant linear relationship between the two tests.[32] There are a number of factors that can be the cause of the disparities in the results of the studies. Firstly, the patients were different with different high risk which may be one of the reasons for the disparity in results. Secondly, some studies have only examined the diagnostic value of random protein to creatinine to predict proteinuria above 300 mg (as in the

present study), while others have examined the occurrence of preeclampsia. This will also make a difference in results of the studies.

CONCLUSION

Overall, based on the findings of this study, in women with suspected preeclampsia, the protein to creatinine ratio in a random urine sample shows a good diagnostic accuracy. Protein/creatinine ratio method is a rapid alternative for diagnosis of suspected proteinuria and serves an appropriate screening test in emergency situations.

Finally, a study with a larger sample size and a multicentric design in patients with suspected preeclampsia is recommended.

CONFLICT OF INTEREST

The authors declare no competing interest.

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Received April 2023
Revised May 2023
Accepted June 2023