Original Article

The Relationship between Random Urinary Protein-to-Creatinine Ratio and 24-hours Urine Protein in Diagnosis of Proteinuria in Mild Preeclampsia

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ABSTRACT

Background: The purpose of this study was to evaluate whether a random urinary protein / creatinine ratio is a clinically useful predictor of significant proteinuria ($\geq$300 mg/24 hr) instead of 24- hours urine protein, among women with suspected preeclampsia.

Methods: Women with suspected preeclampsia and gestational age of $\geq$20 weeks were included in a prospective study. Patients with chronic hypertension, diabetes mellitus, or preexisting renal disease were excluded. Protein/creatinine ratio was obtained before 24-hours urine collection. Positive and negative predictive values and sensitivity and specificity of the protein/creatinine ratio for significant proteinuria ($\geq$ 300 mg) were calculated, based on 24-hours urine total protein.

Results: 100 women were evaluated totally. Mean maternal and gestational ages were 27.3 years and 33.26 weeks, respectively.73% of cases had significant proteinuria based on 24-hours urine collection. Good correlations were found between the protein/creatinine ratio in random urine samples and both the 24-hours urine protein excretion and the 24-hours urine protein/creatinine ratio in patients with mild preeclampsia ($r=0.484$, $P<0.0001$, and $r=0.345$, $P<0.0001$, respectively) .Receiver operator characteristic (ROC) analysis revealed an area under the curve of 0.944. The best cutoff value was of >0.18 which yields a sensitivity of 86.3%, a specificity of 100%, with a positive predictive value of 100%, and a negative predictive value of 73%.

Conclusion: The random urinary protein –to- creatinine (P: C) ratio is strongly associated with the 24-hours total protein excretion. A cutoff value of > 0.18 is a good predictor of significant proteinuria .P: C ratio could replace the 24-hours urine collection as a simpler, faster, and more accurate method for the diagnosis of significant proteinuria.

Key words: Preeclampsia, significant proteinuria, protein / creatinine (P: C) ratio, 24- hours urine total protein level

Hypertensive disease complicates 5-7% of Pregnancies and is classified according to preexisting chronic hypertension or pregnancy- induced hypertension with or without proteinuria. Assessment of proteinuria is important in establishing a diagnosis of preeclampsia and its ongoing management.1 In pregnancy, proteinuria is defined as a 24- hours protein excretion rate of greater than 300 mg and is considered to be severe when the excretion is greater than 5 g.1 The gold standard test for the diagnosis of significant proteinuria remains the 24-hours urine collection 2.

These criteria are based on measurement of proteinuria in a timed, 24-hours urine collection 1. Twenty- four-hours urine collections have been criticized as being cumbersome and inaccurate, especially in ambulatory patients.3 This procedure also delays diagnosis by at least 24 hours. Shortening the time of the diagnosis of preeclampsia would be valuable for

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management purposes, as well as for decreasing hospital cost and inconvenience. Studies have shown the urinary dipstick is a poor predictor of 24-hours urine total protein level [4]. In the nonpregnant state, random protein /creatinine ratios have shown an excellent correlation with the 24-hours protein excretion [3, 5]. Recent studies have suggested an excellent correlation between the random urinary protein / creatinine ratio and 24-hours urine total protein level in pregnant women with a confirmed diagnosis of preeclampsia [6, 9]. Few studies have evaluated the usefulness of the protein/ creatinine ratio as a screening tool for the evaluation of proteinuria in women with suspected preeclampsia [2, 7, 10].

Despite several studies that have showed a strong linear association between the random urinary protein-to-creatinine ratio and the 24-hours total protein excretion in pregnant women [1, 6, 7, 12] three studies have suggested that no single cutoff could adequately distinguish the presence of significant proteinuria [2, 4, 11]. Although these studies have shown a strong correlation, there are some aspects of difference with our study. In one study, the results were limited by minimizing the collection size 11. In another one, study was done in pregnant, not preeclamptic women [2]. In the third study with enough sample size, both mild and severe proteinuria were evaluated (besides, this study was simultaneous to our study) [5]. To date, three studies have evaluated the ROC curve for the random urinary protein-to-creatinine ratio as a predictor of proteinuria during pregnancy [2, 11, 12] and only one was performed in women suspected of preeclampsia [5].

Because of these differences, we undertook this study to determine the usefulness of the protein /creatinine ratio in the prediction of proteinuria by 24-hours urine collection among women who undergo evaluation for suspected preeclampsia (mild).

Subjects and methods

The study was carried out in Alzahra and Zaynabiyeh hospitals, referal centers, of Isfahan and Shiraz universities of medical sciences, between January 2001 and Desember 2003.

Women with singletone pregnancies of ≥ 20 weeks of gestation who were undergoing evaluation for "suspected preeclampsia" were studied prospectively in a cross – sectional study.

We included women who were undergoing evaluation for the possibility of preeclampsia on the basis of clinical findings that included new- onset proteinuria of ≥1+ on urinary dipstick, mild hypertension (≥140/90,≤160/110), and/or edema.Women were excluded if they had a concurrent diagnosis of chronic hypertension, diabetes mellitus, or preexisting renal disease. No patients in the study group had a coexisting urinary tract infection, hematuria or preexisting proteinuria (<20 weeks). Patients with underlying renal disease were diagnosed with usual screening tests such as Bun (blood urea nitrogen), serum creatinine, urinanalysis, and kidney sonography (if indicated). For each patient, a random urine collection was collected for the calculation of the protein/ creatinine ratio. All random samples were collected before the 24-hours urine collections. None of the samples were first voided morning urine. Significant Proteinuria was defined as ≥ 300 mg protein in a 24-hours urine collection. Urinary protein quantitation was determined by trichloroacetic acid method, and urinary creatinine was determined by the modified Jaffe reaction [13, 14].

The medical records of 100 women who completed both a random urinary protein-to-creatinine ratio and a 24-hours urine collection for the evaluation of significant proteinuria were reviewed.

Statistical analyses were performed with the spss-11.5 statistical software (Research consultation center of Shiraz university of medical sciences), using simple linear regression with calculation of a Pearson correlation coefficient and chi-square. Mean values (±SD) were calculated. With the use of the 24-hours urine results as the gold standard, sensitivity, specificity, and positive and negative predictive values of random urinary protein-to-creatinine

ratio at several cutoff values were determined for the prediction of significant proteinuria. Receiver operator characteristic (ROC) curves were evaluated to determine an optimal protein/ creatinine ratio value that maximized increased the sensitivity and specificity in identification of significant proteinuria that was based on 24-hours urine collections .Area under the curve was calculated.

Results

During the study period, 100 women completed both a random urinary protein- to-creatinine ratio and a 24-hours urine collection. The mean maternal and gestational age at collection were 27.3($\pm$6.290) years and 33.26 ($\pm$4.029) weeks, respectively (range, 16-46 years, and 20-40 weeks, respectively). Ninthy – two percent of the patients were in the third trimester and eight percent were in second trimester. Thirthy - seven percent of the women who were studied were nulliparous.

Seventy – three percent of the study population (n=73) had significant proteinuria as determined by the 24-hours urine collection (All of them had mild proteinuria).The remaining 27% had insignificant proteinuria (<300mg) on the 24-hours urine collection. Mean 24- hour urine protein and random urinary protein – to-creatinine ratio were 836 mg and 1050 mg/gr,

respectively. On initial testing, 52% of women had a protein/ creatinine ratio of $\geq$ 300 mg / g (range 300-8180). The random urinary protein-to -creatinine ratio was highly correlated with the 24-hours total protein excretion (P<0.0001, r = 0.484; Figure 1).

The correlation between the random urinary protein/ creatinine ratio and the protein/ creatinine ratio of the 24-hours urine collection was calculated by chi-square (χ^2) and a significant relationship was identified between them (P< 0.0001, r = 0.345, Figure 2).

The ROC curve for the random urinary protein- to- creatinine ratio is shown in figure 3. The area under the ROC curve is 0.94 (95% confidence interval, 0.880 and 0.980; standard error, 0.022). The sensitivity, specificity, positive predictive value, and negative predictive value for various cutoffs are shown in the table 1.

The cutoff value of> 0.18 yields a sensitivity of 86.3% and a specificity of 100%. With the use of this cutoff, there was 27 false–negative and no false –positive test results. Of the false-negative results, 24-hours urine total protein levels ranged from 300 to 1100 mg and 70 % of cases had 300 to 500 mg of protein. Decreasing the cutoff value below that suggested by ROC analysis improved sensitivity, besides, it increases negative predictive value.

Table 1. Predictive values of the random urinary protein/creatinine ratio for the detection of significant proteinuria with the use of various cutoff values, including that identified by ROC analysis (cutoff value> 0.18).

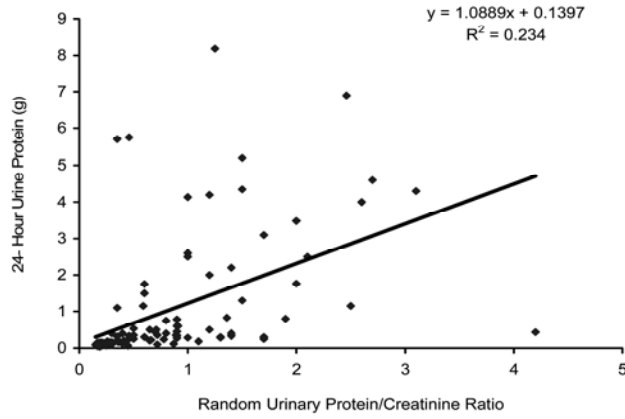| Cutoff	Sensitivity	Specificity	Positive predictive value	Negative predictive value
0.14	91.8	74.1	90.5	76.9
0.15	91.8	88.9	95.7	80
0.16	89	96.3	98.5	76.5
0.17	87.7	96.3	98.5	74.3
*0.18	86.3	100	100	73
0.20	80.8	100	100	65.6

$y = 1.0889x + 0.1397$
$R^2 = 0.234$

Fig. 1: Relationship between random urinary protein/creatinine ratio on admission and subsequent 24-hour total protein level for women with suspected preeclampsia
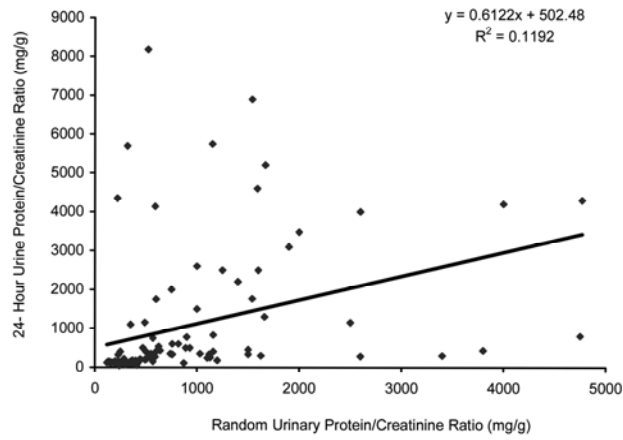
$y = 0.6122x + 502.48$
$R^2 = 0.1192$

Fig. 2: Correlation between the random urinary protein/creatinine ratio on admission and 24-hour total protein/creatinine ratio in women with suspected preeclampsia
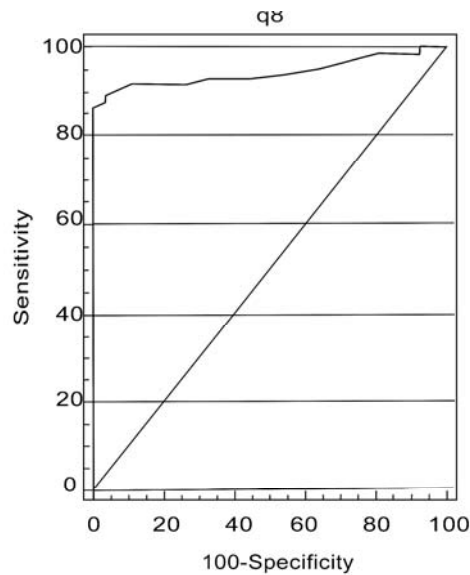
Fig.3: Roc curve for various cutoffs for the random urinary protein- to - creatinine ratio as predictor of significant proteinuria.

Discussion

One of the important signs of preeclampsia is excessive protein excretion, and its combination with hypertension markedly increases the risk to the fetus [15]. Preeclamptic women frequently need follow-up until fetal maturity and delivery. During this time, it is necessary to perform repeated laboratory examinations for quantitative determination of proteinuria [7].

The need for a simple reliable screening test to quantitate proteinuria is readily apparent [3]. Simpler methods (such as the urinary dipstick) have been criticized because they measure the urinary protein concentration only at 1 point in time [12]. Many studies have shown a high correlation between random urinary protein -to-creatinine ratio in both normotensive and hypertensive pregnant women [6, 7, 9, 11] and pregnant and nonpregnant patients with diabetes mellitus and underlying renal disease [3, 5, 11, 16]. This correlation is also showed in the present study. Correlation coefficients reported range from 0.80 to 0.995, and the degree of correlation did not vary by trimesters of pregnancy during which the sampling occurred [11, 17]. The correlation coefficient of 0.484 was yielded in our study that was lower in comparison to similar studies.

Despite the high degree of linear correlation, the best cutoff has not been described for pregnancy, and the test is not widely used during pregnancy [2, 10].

Young et al[10] found no single Value to distinguish ideally significant proteinuria after ROC analysis but found that a value of<0.15(15omg/g) efficiently ruled out significant pregnancy- induced hypertension. Rodriguez- Thompson and Lieberman[2] performed ROC analysis and found a high area under the curve (0.91) but were unable to identify a clear cutoff point for delineating significant proteinuria. They elected to use a cutoff point of 190 mg/g. Durnwald et al [4] found 390 mg/g as "optimal" cutoff value for the protein/ creatinine ratio in the detection of significant proteinuria by ROC analysis. They concluded that this test was not useful for the exclusion of significant proteinuria in women with suspected pree-

clampsia. Although these studies showed a strong linear association, the ROC curves did not reveal a reliable cutoff. In one of these studies, sample size was limited and a number of their samples were collected after the 24-hour urine collection, which could alter the results if the patients remain at bed rest during the collection period.[18] In only one study (simultaneous to present study) which was done in preeclamptic patients, they found that the correlation between random urinary protein/creatinine ratio and 24-hours urine total protein was poor [4]. We chose to evaluate the usefulness of the random urinary protein-to-creatinine ratio that was collected before the 24-hours urine because it most closely resembles how the test would be used in practice. Our study revealed that the random urinary protein-to-creatinine ratio is an outstanding test for discriminating between significant and insignificant proteinuria as demonstrated by an area under the ROC curve of 0.94.

By increasing sensitivity, obtaining the best cutoff point, rules out the potential consequences of missing the diagnosis of preeclampsia. If falsely reassured, clinicians may not intervene for women who actually have preeclampsia.

Alternatively, a false positive protein /creatinine ratio would not lead necessarily to intervention in the absence of other findings.

A cutoff below 0.05 ruled out significant proteinuria, however the specificity was only 7.4%. As shown in table 1, to maximize the specificity while maintaining a sensitivity of ≥90%, we set our criterion of positivity as>0.15. This yielded a sensitivity of 91.8% and a specificity of 88.9 % .The negative predictive value was 80% in our population (the prevalence of significant proteinuria was 73%). According to the table 1, we yielded a range of cutoffs of 0.14 to 0.18 with relatively high specificities and sensitivities.

Unfortunatelly, present study could not determine a definite cutoff point for detection of significant proteinuria. The best cutoff value of >0.18 that yielded by ROC analysis had a high

specificity (100%), but its sensitivity was < 90% (86.3%).

With the cutoff point of >0.18 that was suggested by the optimization of sensitivity and specificity through ROC analysis, false negative results would increase to 27% (with no false positive results), while with the cutoff point of > 0.15, it would decrease to 20% (with 4.3% false positive results).

In Rodriguez et al study, most of the false negative and false – positive test results were within 50 mg of the cutoff point of 300 mg for a 24-hours urine, while in our study , false negative results ranged from 300 to 1100 mg (mean value of 518 mg)[2].

The main concern with the discordant values is the false – negative test results, because real cases may be missed; these are not likely to be due to collection errors with the 24-hours urine sample. However, most of the false – negative test results had proteinuria of 300-450 mg based on 24-hours urine collection and only 3 cases had proteinunia more than 450mg.

Of the false - positive results, it is unclear how many of these may actually represent true- positive results. We were unable to assess the usefulness of the random urine protein-to-creatinine ratio for the diagnosis of severe proteinuria in our data set, because there was no patient with proteinuria above 5 g on the 24-hours urine collection.

Our study population was nonambulatory and hospitalized, but obtaining random samples before the 24-hours urine collection reduces the potential for a falsely elevated protein / creatinine ratio after the completion of the 24-hours urine collection because of progression of the disease, but there is a question whether this sample can be extrapolated to an ambulatory setting. Also it avoided the potential impact of prolonged bed rest before sampling on the protein/ creatinine ratio. Our study population was clinically appropriate.

For patients with a high pretest probability of disease and a negative random urinary protein- to- creatinine ratio , repeating the test or proceeding with collection of a 24-hours urine is a reasonable option.Repeating a random sample is much easier and quicker to accomplish it[2].

In present study, the random urinary protein-to- creatinine ratios relationship (as an easier method for evaluation of proteinuria in women with suspected preeclampsia) with the 24-hours protein excretions have been evaluated and show an excellent correlation, independent of gestational age, parity, height, weight and the degree of proteinuria .

Besides, it decreases hospital cost and patient inconvenience, especially when frequent or even daily determinations are necessary. Reliance on a voided urine P: C ratio decreases the need for patient compliance and, minimizes collection and laboratory errors (so increases its accuracy), and saves almost a day in ascertaining results. In addition, the P:C ratio appears to follow trends in protein excretion over time. Use of a random urinaty protein – to – creatinine ratio seems to be an excellent alternative to the 24-hours urine protein excretion for determination of significant proteinuria. We recommend this test as an screening test in women with suspected preeclampsia. Further studies are necessary and patients should be followed up till termination. So the usefulness of this test for prediction of the disease progression can be evaluated.

Acknowledgments

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