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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

PREEKLAMPSİ TANISINDA SPOT İDRAR PROTEİN / KREATİNİN ORANININ SENSİTİVİTESİNİN İDRAR VERME ZAMANI VE BEKLEME SÜRESİ GİBİ DEĞİŞKENLER İLE BİRLİKTE BELİRLENMESİ

DETERMINING SPOT URINE PROTEIN / CREATININE RATIO SENSITIVITY IN THE DIAGNOSIS OF PREECLAMPSIA WITH VARIABLES SUCH AS URINE SAMPLING TIME AND WAITING TIME

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ÖZET

AMAÇ: Bu çalışmada 24 saatlik idrar proteinürisini öngörmede spot idrar protein / kreatinin oranının başarısını, idrarın verilme zamanı ve idrarın bekleme süresi gibi farklı değişkenler ile karşılaştırmayı amaçladık.

GEREÇ VE YÖNTEM: Çalışmaya Mart 2014 - Aralık 2017 tarihleri arasında tansiyon yüksekliği nedeniyle kliniğimize başvuran, 24 saatlik idrarda protein çalışılan ve eş zamanlı spot idrarda protein/kreatinin oranı bakılan 100 gebe dahil edilmiştir. Çalışmaya katılan gebeler 24 saatlik idrar proteinürisi normal sınırlarda olanlar ve olmayanlar olarak ikiyi ayrılmıştır. Spot idrarın veriliş zamanı, bekleme süresi ve hastaların demografik verileriyle; spot idrar kreatinin oranın 24 saatlik idrar proteinürisini öngörmedeki başarısı karşılaştırılmıştır.

BULGULAR: Spot idrar protein / kreatinin oranının 24 saatlik idrarda proteinürisi olan ve olmayan gruplara ait en iyi kestirim noktası 0.315 olarak belirlenmiştir. İdrar verilme zamanı ve idrar bekleme süreleri karşılaştırılmış ancak istatistiksel olarak anlamlı bir fark olmadığı görülmüştür.

SONUÇ: Preeklampsi şüphesi olan gebelerde spot idrar protein/kreatinin oranı bakılması, 24 saatlik idrarda proteinüri bakılmasının yerini alabilir ancak çalışmamıza göre idrar verilme zamanı ve analiz öncesi idrar bekleme süresi testin duyarlılığını etkilememiştir.

ANAHTAR KELİMELER: Pre-eklampsi, Gebelik toksemileri, Proteinüri

ABSTRACT

OBJECTIVE: The present study aims to compare the success of spot urine protein/creatinine ratio in predicting 24-h proteinuria with different variables such as urine sampling time and urine wait time before analysis.

MATERIAL AND METHODS: The study included 100 pregnant women who were tested for their 24-h urine protein levels and simultaneously checked for spot urine protein/creatinine ratio upon admission to our clinic with a complaint of high blood pressure between March 2014 and December 2017. The pregnant women included in the study were divided into two groups: those with a normal range for the level of 24-h proteinuria and those with an abnormal range for 24-h proteinuria. The success of spot urine protein/creatinine level in predicting 24-h urine proteinuria was assessed in relation to spot urine sampling time, wait time, and patients' demographic data.

RESULTS: The optimal cut-off value of spot urine protein / creatinine ratio for groups with and without proteinuria in 24-h urine was determined to be 0.315 (cut-off). Urine sampling time and wait time before analysis were compared but no statistically significant difference was found.

CONCLUSIONS: The spot urine protein/creatinine ratio in pregnant women with suspected preeclampsia may replace testing patients for proteinuria in their 24-h urine. However, according to our study, urine sampling time and wait time before analysis did not affect the sensitivity of the test.

KEYWORDS: Preeclampsia, Pregnancy Toxemia, Proteinuria

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INTRODUCTION

Hypertensive diseases complicate almost 10 % of pregnancies around the world (1). They are among the most important causes of maternal and perinatal morbidity and mortality (2).

Hypertensive diseases occur in four different forms during pregnancy. These include preeclampsia–eclampsia, chronic hypertension, preeclampsia superimposed on chronic hypertension, and gestational hypertension. Preeclampsia is not only a hypertensive condition but also a disease with a course progressing with multisystemic involvement. According to the American College of Obstetricans Obstetricians and Gynecologists' latest report, approximately 50.000 to 60.000 maternal death/year are associated with preeclampsia. The maternal risks in the acute period of the disease include eclampsia, stroke, placental abruption, disseminated intravascular coagulation, HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome, liver rupture, pulmonary edema, acute respiratory distress syndrome, and acute renal insufficiency, whereas the risks in the chronic period of the disease include hypertension, diabetes mellitus, coronary artery disease, and neurological deficits. Preeclampsia is also one of the most important causes of perinatal morbidity; therefore, early recognition is important. One of the diagnostic criteria is the detection of protein in urine with concomitant hypertension. Proteinuria is diagnosed with protein excretion exceeding 300 mg in 24-hours urine, a protein/creatinine ratio of 0.3 and higher in spot urine, or detection of a persistent protein level of 30 mg/dL (1+ in dipstick testing) (3). In the evaluation of proteinuria, the level of protein in 24-hour (24-h) urine is considered the gold standard (4). However, 24 h of testing can lead to a delay in the diagnosis of preeclampsia as it is also both troublesome and a method with incorrect results when stored and not analyzed under appropriate conditions. Collecting urine samples in an amount less than necessary can also ultimately lead to errors. Recently, spot urine protein/creatinine ratio has also been used in diagnosis (5). Recent studies have reported that there is a strong linear relationship between the 24-h urine protein and the spot urine protein/creatinine ratio in pregnant women with hypertension and without hypertension (6, 7).

However, studies on the detection of proteinuria in pregnant women and its diagnostic reliability are not yet sufficient (8). In some studies, the correlation between 24-h protein levels and spot urine protein/creatinine ratio has not been confirmed (9 -11). Based on all these results, the test needs certain standards regarding its use in pregnant patients.

Our hypothesis in this study is that the urine sampling time and the wait time before analysis in the lab can affect the sensitivity of the test.

MATERIALS AND METHODS

The present study included pregnant women admitted to Gazi University Faculty of Medicine Gynecology and Obstetrics Department for high blood pressure and those pregnant women who were detected to have high blood pressure during clinical follow-ups and therefore tested for 24-h urine protein and simultaneously checked for spot urine protein/creatinine ratio between March 2014 and December 2017.

The study was conducted in accordance with the principles of the Helsinki Declaration. The data on 24-h urine proteinuria and spot urine protein/creatinine ratios were retrospectively obtained from the database. In our hospital to speed up the diagnosis and treatment of pregnant women presenting with high blood pressure, first of all, spot urine protein/creatinine ratio and then 24-hour urine proteinuria test are performed. The study included 100 pregnant women aged between 19 and 43 years who were in gestational week 20 and further and who did not have additional renal diseases. Patients with suspected urinary tract infections and the interval between 24-hour urine results and spot urine protein/creatinine results longer than 24 hours were excluded. Results of the pregnant women included in the study were evaluated and the patients were grouped as those with abnormal 24-h urine proteinuria of 300 mg/day and higher (50 patients) and those with normal 24-h urine proteinuria under 300

mg/day (50 patients). When assessing spot urine protein/creatinine ratios, the urine samples given between 06:00 and 12:00 were considered morning urine, and those given outside these hours were considered afternoon urine.

The spot urine protein/creatinine ratios in the first-morning urine samples were statistically compared with those of the afternoon urine samples. Spot urine protein/creatinine ratios were studied in four groups, which were the first-hour results group, second-hour results group, third-hour results group, and the group of the results obtained after 3 h according to the durations calculated between the laboratory admission time and result time. Whether the urine wait time had a significant effect on sensitivity and specificity for spot urine protein/creatinine ratios was analyzed. Patients were divided into three groups of nulliparous, primiparous, and multiparous patients based on their demographic data. The sensitivity and specificity of the ratios of spot urine protein/creatinine of the three groups were compared statistically.

Ethical Committee

The study was approved by Gazi University Faculty of Medicine Clinical Researches Ethics Committee with the ethical committee decision dated December 25, 2017, and numbered 24074710-01.

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA) package program. The Kolmogorov–Smirnov test was used to investigate whether the distribution of continuous numerical variables was close to normal. Descriptive statistics were expressed in the form of mean ± standard deviation or median with a minimum-maximum range for continuous numeric variables, whereas categorical variables were expressed in case numbers and (%). The significance of the difference between the groups in terms of continuous numerical variables was assessed using the Mann–Whitney U test in cases of two independent groups, whereas the significance of the difference among more than two independent groups was assessed using Kruskal–Wallis test. Categorical variables were assessed using Pearson's Chi-squared, Yates' Continuity Correction Chi-squared, or Fisher's exact test. The area under the receiver operating characteristic (ROC) curve and a confidence interval of 95% was used to investigate whether the spot urine proteinuria ratio is a statistically significant marker in differentiating groups with normal and abnormal levels of 24-h urine proteinuria. The value at which the sum of sensitivity and specificity levels reached the maximum based on the ROC analysis results was considered the optimal cut-off value. Subsequently, the sensitivity and specificity rates, positive and negative estimated values, and diagnostic accuracy rates related to the spot urine protein/creatinine ratio at the optimal cut-off value were calculated. Results for $p < 0.05$ were considered statistically significant unless otherwise stated. However, Bonferroni Correction was made to check Type I errors in all possible multiple comparisons.

RESULTS

The mean age of the pregnant women participating in the study was 32.0 ± 5.7 (min–max: 19–43). The mean gestational week of the patients was 31.9 ± 4.5. Of the 100 pregnant women, 58 were nulliparous, 21 were primiparous, and 21 were multiparous **(Table I)**.

Table1: Demographic and clinical variables of the patients

Number of Patients	**n=100**
Age (years)	32,0±5,7
Age range (years)	19-44
Gravida	2 (1-10)
Parity	0 (0-4)
Primiparous	21 (%21,0)
Nulliparous	58 (%58,0)
Multiparous	21 (%21,0)
Pregnancy Week	31,9±4,5

Eighty-seven pregnant women did not have a chronic or gestational disease. Four of the participating pregnant women had diabetes mellitus (without a known renal involvement), three had gestational diabetes mellitus, two had pregnancy cholestasis, one had idiopathic thrombocytopenic purpura, one had chronic hypertension, one other patient had hypothyroidism, and another patient had aplastic anemia.

Of the 100 pregnant women, 37 were observed to give urine samples in the morning and 73 in the afternoon for spot urine protein/creatinine ratio testing. The average time until laboratory

study after urine delivery to the laboratory was 2 h (min–max: 1–12). Spot urine proteinuria rates were compared between normal (<300 mg/day) and abnormal (≥300 mg/day) groups of 24-h urine proteinuria. The spot urine protein/creatinine ratios were 0.15 (0.06–0.60) and 0.56 (0.10–6.80) in the groups with normal 24-h urine proteinuria and abnormal 24-h urine proteinuria, respectively. The spot urine protein/creatinine ratio of the group with normal 24-h urine proteinuria was statistically lower than that of the abnormal group ($p < 0.001$).

The area under the ROC curve (AURC) of spot urine protein/creatinine ratio was found to be statistically important to distinguish between normal and abnormal groups of 24-h urine proteinuria (AURC = 0.837; 95% confidence interval range: 0.756–0.918 and $p < 0.001$) **(Figure 1) (Table II)**.

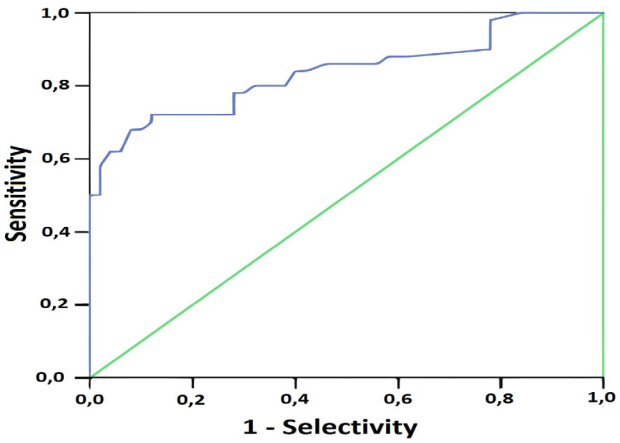

Figure 1: ROC curve of spot urine protein/creatinine ratio to distinguish between normal and abnormal groups of 24-h urine proteinuria

Table 2: The area under the receiver operating characteristic (ROC) curve of the spot urine protein/creatinine ratio to distinguish between normal and abnormal groups with 24-h urine proteinuria, 95% confidence interval, the optimal cut-off value, and diagnostic performance indicators in this respect

	Identification	All cases	Morning	Afternoon
AURC		0.837	0.809	0.842
95% confidence interval		0.756-0.918	0.651-0.968	0.744-0.939
p-value		**<0.001**	**0.002**	**<0.001**
Optimal cut-off value		>0.315	>0.275	>0.315
Sensitivity	TP / (TP + FN)	34/50 (68.0%)	11/15 (73.3%)	25/35 (71.4%)
Specificity	TN / (TN + FP)	46/50 (92.0%)	19/22 (86.4%)	27/28 (96.4%)
PPV	TP / (TP + FP)	34/38 (89.5%)	11/14 (78.6%)	25/26 (96.2%)
NPV	TN / (FN + TN)	46/62 (74.2%)	19/23 (82.6%)	27/37 (73.0%)
Accuracy	(TP + TN)/(N)	80/100 (80.0%)	30/37 (81.1%)	52/63 (82.6%)
p-value		**<0.001**	**<0.001**	**<0.001**

TP: True Positivitye, FN: False Negative, TN: True Negative, FP: False Positive, N: Number of cases.

In distinguishing groups with normal and abnormal values, the optimal cut-off value for spot urine protein/creatinine ratio was 0.315, the sensitivity of spot urine protein/creatinine ratio was 68%, specificity 92%, positive and negative estimated values were 89.5% and 74.2%, respectively, whereas diagnostic accuracy was 80%. The area under the ROC curve of spot urine protein/creatinine ratio in distinguishing between normal and abnormal groups of 24-h urine proteinuria among the cases of morning spot urination and afternoon spot urination was found statistically significant ($p < 0.001$; $p < 0.001$). Diagnostic indicators of the spot urine protein/creatinine ratio in this respect are shown in Table II. In addition, there was no statistically significant difference between the area under the ROC curve of the morning urinating group and that of the afternoon urinating group ($p = 0.718$).

When evaluated with the optimal cut-off value of 0.315 as calculated in the ROC analysis made on all of the cases and among only the cases with normal 24-h urine proteinuria, it was observed that the specificity in the morning urinating group [19/22 (86.4%)] did not differ from that of the afternoon urinating group [27/28 (96.4%)] at a statistically significant level ($p = 0.308$) (Table II).

If we keep the cutting point at 0.315 for the spot protein/creatinine ratio, the sensitivity, specificity, positive and negative predictive value (PPV, NPV), and accuracy rates of the test in distinguishing the groups are given in **Table III**.

Groups were divided by gravida, urine sampling time, and urine wait time. The cutting point of 0.315 was found to have a statistically significant decisiveness in all of the patient groups in differentiating groups with normal and abnormal 24-h urine proteinuria.

Table 3: Diagnostic performance indicators related to spot urine protein/creatinine ratio to distinguish between normal and abnormal groups of 24-h urine proteinuria when a constant cut-off value of 0.315 is kept according to parity, urinary time, and urine wait time

	Sensitivity TP/(TP+FN)	Specificity TN/(TN+FP)	PPV TP/(TP+FP)	NPV TN/(FN+TN)	Accuracy (TP+TN)/(N)
Parity					
Primiparous	6/11 (54,5%)	9/10 (90%)	6/7 (85,7%)	9/14 (64,3%)	15/21 (71,5%)
Nulliparous	22/31 (71,0%)	25/27 (92,6 %)	22/24 (91,7%)	25/34 (73,5%)	47/58 (81,0%)
Multiparous	6/8 (75,0 %)	12/13 (92,3%)	6/7 (85,7%)	12/14 (85,7%)	18/21 (85,7%)
Urination Time					
Morning	9/15 (60,0%)	19/22 (86,4%)	9/12 /75,0%)	19/25 (76,0%)	28/37 (75,7%)
Afternoon	25/35 (71,4%)	27/28 (96,4%)	25/26 (96,2%)	27/37 (73%)	52/63 (82,6%)
Urine Wait Time					
1 h	9/17(52,9%)	20/21 (95,2%)	9/10 (90,0%)	20/28 (71,4%)	29/38 (76,3%)
2 h	9/11(81,8%)	7/9 (77,8%)	9/11 (81,8%)	7/9 (77,8%)	16/20 (80,0%)
3 h	8/10 (80,0%)	10/11 (90,9%)	8/9 (88,9%)	10/12 (83,3%)	18/21 (85,7)
>3 h	8/12 (66,7%)	9/9 (100,0%)	8/8 (100,0%)	9/13 (69,2%)	17/21 (81,0%)

TP: True Positivite, FN: False Negative, TN: True Negative, FP: False Positive, N: Number of cases.

DISCUSSION

Proteinuria in preeclampsia is glomerular proteinuria, and the level of protein in 24-h urine is considered the gold standard to test for proteinuria (12). However, methods such as spot urine protein/creatinine ratio of >0.3 or persistent proteinuria level of 30 mg/dL (1+ in dipstick testing) are also used to evaluate proteinuria. In the present study, the optimal cut-off value of spot urine protein/creatinine ratio for groups with and without 24-h urine proteinuria was determined as 0.315. Parity, urine sampling times, and urine wait times were compared, but there was no statistically significant difference.

Spot urine protein/creatinine ratio is a method with higher applicability in terms of patient compliance. Recent studies reported that there was a strong linear relationship between 24-h urine proteinuria and spot urine protein/creatinine ratio in pregnant women with and without hypertension (13 - 15). However, studies on this test conducted to detect proteinuria in pregnant patients and its diagnostic reliability are not yet sufficient (8). Protein excretion in urine can vary because of many factors during the day. In particular, the spot urine content can vary depending on the time it is delivered during the day, the waiting time of urine, and the physical activity of the patient before. Among the reasons that affect the excretion of protein in urine during the day are daily fluid intake and excretion, urine flow rate, diet, and physical activity, which increase the amount of proteinuria (16, 17). Proteinuria increases throughout the day compared with the first urine in the morning. The protein/creatinine ratio is affected by the amount of urinary creatinine. The average daily creatinine excretion is 1000 mg. In people with excess muscle mass, this amount is higher. In cachectic patients, creatinine excretion will be less than normal because the muscle mass is low (18).

A meta-analysis conducted in 2021 a diagnostic test accuracy for both sensitivity and specificity was higher when the first morning void was excluded (excluded first void: sensitivity 93%, specificity 93%; did not specifically exclude first void: sensitivity 87%, specificity 84%) (19). The high specificity and sensitivity, excluding the patient's first voiding, can be explained by the fact that the patient is resting all night, and suggests that the protein/creatinine ratio may change during the day. In our study, random spot urine samples were used instead of first void morning urine because the features of preeclampsia can present at any time, and waiting for the morning urine collection may have delayed the diagnosis.

A prospective study conducted by Demirci et al. in 2015 to compare 24-h urine proteinuria (≥300 mg /day) and spot urine protein/creatinine ratio in a group of 264 pregnant women including 211 preeclamptic patients with an optimal cut-off value of 0.45, sensitivity was 74%, specificity 94%, PPV 98%, and NPV 47% (20). Although sensitivity, specificity, and PPV values are similar to those in the present study, the negative predictive value herein seems more significant. According to the study by Demirci et al., protein/creatinine ratio and 24-h urine proteinuria are correlated by 75%. However, the study only included inpatients and did not include outpatient clinic patients. Protein excretion can vary due to prolonged bed rest and be affected by whether a patient is mobile or exercising. Prolonged bed rest reduces protein excretion. We believe that carrying out the study only on inpatients will affect the results. In the present study, inpatients and outpatients were evaluated together.

In 2008, Cote et al. reviewed 13 studies including 1214 pregnant women with gestational hypertension (21). In nine of these studies, sensitivity and specificity were determined, and the predictive value was calculated in eight studies (0.226–0.339). The prediction value of the present study was within this range. Studies showed that there was no statistically significant difference between the predictive values in terms of proteinuria. The sensitivity and specificity of nine studies were assessed together, and sensitivity was 83.6% (77.5%–89.7%) and specificity 76.3% (72.6%–80.0%).

In many studies, there is a strong connection between 24-h urine proteinuria protein and spot urine protein/creatinine ratio by a correlation coefficient ranging from 0.80 to 0.97 (22 - 24). Similar to the studies conducted, the

correlation coefficient was found to be 83% in the present study. In a study protein/creatinine ratio is e poor predictor for 24-hour proteinuria with a cut-off value of 0.28, the sensitivity and specificity were 60.4% and 77.9%, respectively (25). However, they found protein/creatinine ratio at the cut-off value of 0.77 a good predictor of proteinuria more than 2 g/day. In a study conducted by Lindow and Davey in 1992, it is argued that the protein/creatinine ratio is not an accurate marker for predicting proteinuria (26). But they only focused on correlation in their study where they did not calculate any predictive value either. They noted that protein excretion varies substantially during the day. In the present study, we believe that protein excretion is variable during the day, although there is no statistically significant difference between the morning urinating group and the afternoon urinating group. However, in the present study, it was found that the wait time following urine delivery was significantly longer in the afternoon urine group. Wait time may change protein/creatinine ratios, but this change does not affect the correlation between protein/creatinine ratio and 24-h urine proteinuria to an extent where it renders it insignificant.

In the present study, there was no statistically significant difference between primiparous, nulliparous, and multiparous groups in terms of median 24-h urine proteinuria and spot protein/creatinine ratios. However many studies suggest that testing and using spot urine protein/creatinine ratio should not be associated with maternal age, gestational age, and parity (9, 15, 27).

Verdonk et al. conducted a prospective study with 112 patients in 2014 and compared 24-h urine proteinuria and spot urine protein/creatinine ratio (28). Unlike other studies, they tested patients for spot urine protein/creatinine ratio at three different times during the day (08:00, 12:00, and 17:00). They found the median protein/creatinine ratio of morning urine to be significantly lower than that for the urine given at 12:00, but the difference was not statistically significant compared with the median protein/creatinine ratio of the urine given at 17:00. In the present study, we saw no statistically significant difference in median 24-h urine proteinuria and spot urine protein/creatinine ratios based on different urine sampling times. With a protein/creatinine predictive value of 0.3, similar to the present study, there was no statistically significant difference between the urine sampling times in terms of sensitivity and specificity.

In the present study, in terms of the relation between urine wait times and frequency of normal/abnormal proteinuria levels, the median spot urine protein/creatinine ratio was statistically significantly higher in the group with abnormal 24-h urine proteinuria compared with the group with normal 24-h urine proteinuria according to the tests run on the urine samples within the first, second, third, and later hours following the urination time. Although the median spot urine protein/creatinine ratio was higher in the urine samples tested after the third hour, there was no statistically significant difference between the groups. We believe that the urine wait time has a negative effect on the spot urine protein/creatinine ratio and diminishes the prediction value of the test.

The present study has some limitations. A retrospective study and a limited number of patients are our significant drawbacks. The inclusion of urine analyses conducted at different times during the day and with different urine wait times and subgroup analyzes are among the important advantages of the present study. There is a requirement for further multi-centric and prospective studies where patient numbers are high and similar variables are evaluated.

In testing for proteinuria, the level of protein in 24-h urine is considered the golden standard. However, in recent times, spot urine protein/creatinine ratio has also been used for diagnostic purposes. The protein/creatinine ratio is a method with higher applicability in terms of patient compliance. To make an evaluation using the literature data, the spot urine protein/creatinine ratio was found to be highly sensitive. A proteinuria analysis in spot urine with a predictive value of 0.3 will be sufficient for preeclampsia management. Protein analysis in 24-h urine, which is a rather exhausting and laborious test for patients, should now be used less frequently.

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