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The Role of the Urine Dipstick Test in the Detection of Abnormal Proteinuria Using Different Cut-off Levels in Hypertensive Pregnancies

Hipertansif Gebeliklerde Farklı Kesim Değerleri Kullanılarak Anormal Proteinüri Saptanmasında Spot İdrar Protein Ölçümünün Rolü

Taha TAKMAZ[1]
0000-0003-0793-2348
Irana GORCHIYEVA[1]
0000-0001-8653-1301
Belfin Nur ARICI HALICI[1]
0000-0002-8822-4740
Ali TOPRAK[2]
0000-0003-4471-2790
Çağlar ÇETİN[1]
0000-0001-6733-592X
Mehmet Serdar KÜTÜK[1]
0000-0001-7895-9180

[1]Department of Obstetrics and Gynecology, Bezmialem University Faculty of Medicine, İstanbul, Turkey

[2]Department of Biostatistics and Medical Informatics, Bezmialem University Faculty of Medicine, Istanbul, Turkey

Corresponding Author
Sorumlu Yazar
Taha TAKMAZ
thtkmz@hotmail.com

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ABSTRACT

Aim: The aim of this study was to determine the diagnostic accuracy of different urine dipstick protein threshold levels in predicting the presence of abnormal proteinuria in pregnant women with hypertension.
Material and Methods: A total of 326 singleton pregnant women who underwent 501 urine protein tests and who had suspected preeclampsia were included in this retrospective study. Patient data was taken including medical and obstetric history. The results of dipstick urinalysis and concurrent 24-hour urine protein excretion measurements were compared to determine the accuracy of urinalysis.
Results: A dipstick result of 1+ was found to be the best cut-off to predict 500 mg of protein excretion per day, with sensitivity and specificity of 62.09% and 88.97%, respectively. A 2+ proteinuria dipstick cut-off had high specificity and positive predictive value (PPV) (99.05% and 98.84%, respectively) for the prediction of 300 mg of protein excretion per day; this cut-off had low sensitivity (21.46%). A cut-off of 1+ also provided satisfactory specificity and PPV (91.43% and 94.48%, respectively) for the detection of 300 mg of protein excretion per day, but sensitivity was compromised (38.89%). Among 301 patients with negative dipstick results, 212 had a 24-hour urine protein extraction greater than 300 mg, with a false negative rate of 70.43%.
Conclusion: The results suggest that the urine protein dipstick measurement has limited quantitative ability for the prediction of abnormal proteinuria. Additionally, the use of 500 mg 24-hours protein excretion as a cut-off value for abnormal proteinuria may provide useful data.
Keywords: 24-hour urine protein; dipstick urinalysis; preeclampsia; pregnancy; proteinuria.

ÖZ

Amaç: Bu çalışmanın amacı, hipertansif gebelerde anormal proteinüri varlığını öngörmede farklı idrar ölçüm çubuğu protein eşik seviyelerinin tanısal doğruluğunu belirlemektir.
Gereç ve Yöntemler: Bu geriye dönük çalışmaya, preeklampsiden şüphelenilen toplam 326 tekiz gebe kadından elde edilen 501 idrar protein testi sonucu dahil edilmiştir. Hastaların tıbbi ve obstetrik geçmiş verileri kaydedildi. İdrar tahlilinin doğruluğunu belirlemek için idrar ölçüm çubuğu protein tahlili ve eşzamanlı 24 saatlik idrar protein atılım ölçümlerinin sonuçları karşılaştırıldı.
Bulgular: 1+ spot idrar protein ölçüm sonucu, 500 mg günlük protein atılımını sırasıyla %62,09 duyarlılık ve %88,97 özgüllük ile öngörmede en iyi kesim değeri olarak bulundu. Spot idrarda 2+ proteinüri değeri; 300 mg günlük protein atılımını öngörmede yüksek özgüllük ve pozitif tahmin değerine (PTD) (sırasıyla %99,05 ve %98,84) sahipken, bu kesim değerinin duyarlılığı düşüktür (%21,46). 1+ kesim değeri; 300 mg günlük protein atılımının saptanması için tatmin edici özgüllük ve pozitif tahmin değerine sahipti (sırasıyla %91,43 ve%94,48), ancak duyarlılığı düşüktü (%38,89). Spot idrar protein ölçümü negatif olan 301 hastadan 212'sinde günlük 300 mg üzeri 24 saatlik idrar protein atılımı tespit edildi (%70,43 yanlış negatiflik).
Sonuç: Sonuçlar, spot idrar protein ölçümünün anormal proteinüriyi tahmin etmek için sınırlı niceliksel kabiliyete sahip olduğunu göstermektedir. Ek olarak, anormal proteinüri için kesme değeri olarak 500 mg 24 saatlik protein atılımının kullanılması yararlı veriler sağlayabilir.
Anahtar kelimeler: 24 saatlik idrar proteini; daldırma çubuğu idrar tahlili; preeklampsi; gebelik; proteinüri.

INTRODUCTION

Pregnancy-related hypertensive disorders are one of the leading causes of maternal and perinatal mortality globally. Preeclampsia is a pregnancy-specific hypertensive disease with multi-system involvement. It affects 3-8% of all pregnancies worldwide and is also a financial burden on healthcare systems and society (1,2). Formerly, preeclampsia was recognized as hypertension with proteinuria. Although an abnormal level of protein excretion was known to be a hallmark of preeclampsia, the Task Force on Hypertension eliminated the dependence of the diagnosis on proteinuria in 2013 (3). Recent guidelines noted that, in the absence of proteinuria, acute onset hypertension with evidence of end-organ dysfunction is adequate for the diagnosis of preeclampsia (4,5). Although proteinuria is no longer required for diagnosis, it still occurs in approximately 75% of cases (6) and is associated with more severe neonatal outcomes (7-9). The accurate detection of proteinuria in pregnant women with suspected preeclampsia is therefore still valuable in daily practice.

Three methods are available for the assessment of urinary protein excretion: 1) dipstick urinalysis, 2) urine protein-to-creatinine ratio (UPCR), and 3) 24-hour urine protein testing. During gestation, physiological limits of urinary protein excretion may increase up to 150-250 mg per day and the recommended threshold value to define clinically significant proteinuria is 300 mg per day (10). 24-hour urine collection is the gold standard method for evaluation of the level of proteinuria (11). However, this test has some limitations: firstly, the technique is time-consuming, which hampers rapid diagnosis, and secondly, it can be cumbersome for ambulatory patients and it presents practical difficulties associated with urine collection. In current practice, many clinicians opt for dipstick urinalysis for the evaluation of abnormal proteinuria. This method is fast, easy, and cheap, but provides limited quantitative information. Urinary protein excretion is variable throughout the day and hydration or diuresis may influence the accuracy of the test. The American College of Obstetricians and Gynecologists (ACOG) recommends urine dipstick testing using ≥2+ (100 mg/dL) as the discriminant value only if other quantitative methods are not available (4). On the other hand, the International Society for the Study of Hypertension in Pregnancy (ISSHP) suggests initial assessment using dipstick urinalysis. If the protein level is found to be ≥1+ (30 mg/dL), then other quantitative methods are applied (5).

The current study was undertaken to determine the diagnostic accuracy of different urine dipstick protein threshold levels in predicting the presence of abnormal proteinuria in pregnant women with hypertension.

MATERIAL AND METHODS

This single-center, retrospective cohort study was conducted in a tertiary referral university hospital between January 2010 and January 2018 to assess the validity of dipstick urinalysis. The study protocol was approved by the local institutional ethics committee (Bezmialem Vakıf University Faculty of Medicine, 22.12.2020, 21/400) and was carried out in accordance with the principles set out in the Helsinki Declaration 2008.

A total of 326 singleton pregnant women who underwent 501 urine protein tests and had suspected preeclampsia were recruited. All patients had new-onset hypertension with greater than 140/90 mmHg blood pressure after 20 weeks of gestation. Patients younger than 18 years old, patients with bacteriuria, and patients with both a urine volume under 400 mL/day and a duration of over four days between dipstick urinalysis and 24-hour urine collection were excluded from the study. A detailed medical and obstetric history was taken, including age, gravida, parity, previous history of preeclampsia, associated pathologies, the results of dipstick urinalysis and 24-hour urine protein test, gestational age at the time of dipstick screening, and the time interval between dipstick urinalysis and 24-hour urine protein test.

Dipstick urinalysis was performed by an H-800 automatic urine analyzer (Dirui Industrial, Co. Ltd. China) on freshly evacuated midstream urine samples at any time during the day except the first voided morning specimen or before bedtime. The grades of proteinuria as provided by the manufacturers were presented as 0 (negative), trace (0-30 mg/dL), 1+ (30-100 mg/dL), 2+ (100-300 mg/dL), 3+ (>300 mg/dL). 24-hour urine samples were collected from outpatients or inpatients, in accordance with written instructions which were given to patients for proper collection. Urine collection started at 8.00 am in the morning after discarding the first urine sample of the day. 24-hour quantitative proteinuria was carried out according to the colorimetric method using an Architect C16000 clinical chemistry analyzer (Abbott Laboratories, Abbott Park, IL, USA).

Statistical Analysis

The descriptive statistics are given as mean±standard deviation or median (min-max) for numerical variables and frequency, percentage were given for categorical variables. The chi-squared test was used to compare distribution of categories to give sensitivity, specificity and predictive values (PPV, NPV, +LR, -LR) of the dipstick urinalysis. The statistical analysis were performed using SPSS, version 22 (IBM SPSS Statistics for Windows, Armonk, NY; IBM Corp., Released 2013) and Medcalc (MedCalc Software, Ostend, Belgium).

RESULTS

In this study, 501 urine samples were collected from 326 pregnant women who had suspected preeclampsia. The characteristics of the population are presented in Table 1. The mean age of the study group was 33.3±5.8 years. The median gravida was 2 (range, 1-9) and the median parity was 1 (range, 0-6). Almost half of the cases were nulliparous (149 out of 326, 45.7%) and 3.6% (n=12) of patients had previous history of preeclampsia. Furthermore, type 1 diabetes (1.8%, 6 cases); type 2 diabetes (6.4%, 21 cases) and gestational diabetes (14.7%, 48 cases) were observed as associated pathologies in the study group. The mean gestational age at the time of dipstick screening was 224.9±32.1 days. The median time interval between dipstick urinalysis and 24-hour urine protein testing was 2 (range, 0-4) days.

Table 2 indicates the diagnostic accuracy of dipstick urine analysis in predicting the presence of significant proteinuria levels in 24-hour urine collection. 1+ was found to be the best cut-off to predict 500 mg of protein excretion per day, with sensitivity and specificity of 62.09%

Table 1. The baseline demographic and clinical parameters

Characteristics	**(n=326)**
Maternal age (years)	33.3±5.8
Gravida	2 (1-9)
Parity	1 (0-6)
Nulliparous	149 (45.7%)
Previous history of preeclampsia	12 (3.6%)
Gestational age at the time of dipstick screening (days)[a]	224.9±32.1
Time interval between dipstick urinalysis and 24-h urine protein test (days)[a]	2 (0-4)
Associated pathologies	
Type 1 diabetes	6 (1.8%)
Type 2 diabetes	21 (6.4%)
Gestational diabetes	48 (14.7%)
24-h protein excretion range[a]	
Less than 300 mg/day	105 (20.9%)
300-500 mg/day	185 (36.9%)
500-5000 mg/day	197 (39.3%)
More than 5000 mg/day	14 (2.7%)
Dipstick proteinuria[a]	
Negative	301 (60%)
Trace	37 (7.3%)
1+	77 (15.3%)
2+	58 (11.5%)
3+	28 (5.5%)

[a]: n=501, values are expressed as n (%), mean±standard deviation or median (min-max)

Table 2. Diagnostic ability of dipstick urine analysis in predicting the presence of significant proteinuria levels in 24-hour urine collection

	24-h urine protein (mg/day)			
	≥300 (n=396)	**<300 (n=105)**	**≥500 (n=211)**	**<500 (n=290)**
Dipstick Proteinuria				
≥1+	154	9	131	32
<1+	242	96	80	258
		95% CI		**95% CI**
Sensitivity	38.89	34.06-43.89	62.09	55.17-68.66
Specificity	91.43	84.35-96.01	88.97	84.78-92.33
PPV	94.48	89.78-97.44	80.37	73.43-86.17
NPV	28.40	23.65-33.53	76.33	71.43-80.76
LR (+)	4.54	2.40-8.58	5.63	3.99-7.93
LR (-)	0.67	0.61-0.74	0.43	0.36-0.51

	24-h urine protein (mg/day)			
	≥300 (n=396)	**<300 (n=105)**	**≥500 (n=211)**	**<500 (n=290)**
Dipstick Proteinuria				
≥2+	85	1	76	10
<2+	311	104	135	280
		95% CI		**95% CI**
Sensitivity	21.46	17.52-25.84	36.02	29.54-42.89
Specificity	99.05	94.81-99.98	96.55	93.75-98.33
PPV	98.84	93.69-99.97	88.37	79.65-94.28
NPV	25.06	20.96-29.52	67.47	62.73-71.96
LR (+)	22.54	3.18-159.96	10.45	5.54-19.71
LR (-)	0.79	0.75-0.84	0.66	0.60-0.73

CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, LR(+): positive likelihood ratio, LR(-): negative likelihood ratio

and 88.97%, respectively. A 2+ proteinuria dipstick cut-off had high specificity and positive predictive value (PPV, 99.05% and 98.84%, respectively) for the prediction of 300 mg of protein excretion per day; this cut-off had low sensitivity (21.46%). A 1+ cut-off also provided satisfactory specificity and PPV (91.43% and 94.48%, respectively) for the detection of 300 mg of protein excretion per day, but sensitivity was compromised (38.89%). Among patients with negative dipstick results (n=301), 212 had a 24-hour urine protein extraction greater than 300 mg, with a false negative rate of 70.43%.

DISCUSSION

The results of the present study verify the limited quantitative ability of dipstick urine analysis for the prediction of proteinuria in pregnant women with hypertension. For all comparisons, the specificities were high (>85%), but sensitivities differed. The best correlation was observed between the 1+ dipstick threshold and 500 mg of protein excretion per day, with an overall accuracy of 77.6%. In addition, both 1+ and 2+ dipstick thresholds showed a better correlation with proteinuria of 500 mg/day compared with proteinuria of 300 mg/day.

The classical threshold established for the diagnosis of significant urine protein excretion in pregnancy is 300 mg per day. Although this dividing line is commonly accepted, this is solely based on expert opinion and the findings of previous studies with small sample sizes (10,12). Current studies indicate proteinuria of 500 mg/day as an appropriate cut-off for abnormal proteinuria, especially in healthy primiparous women during late pregnancy when carrying twins (13,14). Also, with a diagnostic cut-off value of 300 mg/day, the incidence of isolated proteinuria may reach 8% during pregnancy, whereas preeclampsia affects 3-8% of pregnancies (15). Given this uncertainty surrounding the cut-off value for the 24-hour urine protein test, in the present study, we investigated the association between dipstick proteinuria results and daily proteinuria levels at various grades. According to our results, both 1+ and 2+ proteinuria measured using the dipstick test are more highly correlated with proteinuria of 500 mg/day than with proteinuria of 300 mg/day. The overall accuracy of 1+ proteinuria measured using the dipstick test increased from 49.9% to 77.6% and that of 2+ proteinuria increased from 37.7% to 70.8%. At this threshold, the urine dipstick test provides better overall accuracy and may replace UPCR analysis. Given the wide availability, ease of use, and low cost, the urine dipstick test may still play an important role in clinical practice.

A brief review by ISSHP advised initial use of dipstick urine protein analysis in cases of suspected preeclampsia, and they recommend no further evaluation if the dipstick test is negative (5). However, our results do not entirely support that a negative dipstick reading can rule out abnormal proteinuria. In 212 out of 301 patients with negative dipstick urine protein analysis, the 24-hour urine protein test results were found to be positive, with a false negative rate of 70%. Previous studies have also shown widely varying sensitivity and specificity with this cut-off level for predicting abnormal proteinuria (16-22). In parallel with our results, Meyer et al. (16) also reported a false negative rate of 66% in 123 patients. A review from

Waugh et al. (23) showed sensitivity and specificity for this test range of 59% and 28%, respectively. They also indicated the usefulness of this threshold in informing clinical decision-making. In only one study, the dipstick test provided both sensitivity and specificity above 80% for reference standard testing (19).

Based on guidelines from the ACOG, the reference standards for screening urinary protein excretion are the 24-hour urine protein test and UPCR. They also recommend, in the absence of these, that a dipstick reading of 2+ alone is sufficient for diagnosis (4). Previous studies have displayed suitable sensitivity, but some lack specificity for defining abnormal protein excretion, or vice versa (16-18,20). In the present study, a dipstick reading of 2+ accurately predicted 85 of the 86 cases, with a PPV of 98.84%, with only one false positive case detected. Therefore, the threshold of 2+ for the dipstick test could be beneficial and practical for women requiring a rapid diagnosis, especially in patients with high-risk pregnancies.

The most important limitation of this study is its retrospective design and the disadvantages inherent to it. In addition, our study does not provide insight into the relationship between dipstick test results and perinatal outcomes, which would be the ideal outcome measure. However, the study also has important strengths. First, it includes one of the largest cohorts on this subject in the literature, with the trial conducted in a single center. Second, the short time interval between dipstick urinalysis and 24-hour urine protein test provided a reliable analysis and enabled us to assess the correlation between these two tests.

CONCLUSION

Our findings indicate that urine protein dipstick measurement has limited quantitative ability for the prediction of abnormal proteinuria. Given the growing body of evidence against the use of 300 mg 24-hours protein excretion as a cut-off value for abnormal proteinuria, our results may provide useful data for those selecting 500 mg 24-hours as the cut-off, as we do in our clinical practice. Additionally, given the uncertainty of the laboratory criteria for establishing proteinuria during pregnancy, it is important to encourage the accumulation and presentation of local data.

Ethics Committee Approval: The study was approved by the Clinical Researches Ethics Committee of Bezmialem Vakıf University (22.12.2020, 21/400).

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