Albumin/creatinine ratio for prediction of 24-hour albumin excretion of ≥ 2 g in manifest preeclampsia

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Summary

Purpose of investigation: To compare whether albumin/creatinine ratios obtained from random or 8-hour urine collected in different periods of day differ in prediction of albumin excretion ≥ 2 g in 24-hour urine collection in preeclampsia. *Methods:* From a total of 70 women, 24-hour urine collected by three consecutive periods of eight hours and three random urine samples were taken before each period. The variation of albumin-creatinine ratios in samples across the day was analyzed by the Friedman and inter-assay coefficient variation. For each sample, receiver operator characteristic (ROC) curves were constructed to determine an optimal albumin/creatinine ratio value in the prediction of albuminuria ≥ 2 g. *Results:* The albumin/creatinine ratio did not vary significantly over time when all samples pooled. However, there was considerable intra-individual variation in both random and timed urine samples. On ROC analysis, the albumin/creatinine ratio in both random and timed urine samples predicted the 24-hour urine results and there was no difference between samples in prediction of albuminuria ≥ 2 g. A single optimal cut-off point was not available between samples. The positive and negative predictive values for optimal cut-offs ranged from 48%-88% and 94%-100%, respectively. *Conclusions:* The random urine albumin/creatinine ratio was a poor predictor for proteinuria ≥ 2 g in patients with preeclampsia.

Key words: Albumin-to-creatinine ratio; Albuminuria; Preeclampsia; Urine creatinine; ROC curve.

Introduction

Sampling random urine for the protein/creatinine ratio or albumin/creatinine ratio has been investigated as an alternative to 24-hour urine collection. There is sufficient data in the literature to support a strong correlation between the protein/creatinine ratio in a random urine sample and 24-hour protein excretion [1, 2]. However, there is no consensus regarding accuracy of the protein/creatinine ratio in prediction of significant proteinuria during pregnancy, possibly due to a high degree of variation in urinary protein concentrations during the course of the day [3, 4]. As a diagnostic test, it has a high number of false-positive and false-negative test results. Currently, the random protein/creatinine ratio has been advocated for ruling out significant proteinuria during pregnancy [1, 5].

Urinary albumin is considered to give a more accurate reflection of glomerular damage than total protein. Some investigators advocate the use of albumin as an alternative to total protein measurement [6-8]. Similar but few data exist for use of an albumin/creatinine ratio in pregnancy as a protein/creatinine ratio. In recent reports, however, it has been reported that both protein/creatinine ratio and albumin/creatinine ratio did not vary significantly over time in hospitalized patients. Data is limited as to whether it is a reliable method in detecting severe albuminuria or proteinuria (> 2 g/day or > 5 g). It is suggested that the protein/creatinine ratio underestimates the true level of proteinuria at higher levels of protein excretion [9, 10].

The objective of this study was to compare whether albumin/creatinine ratios calculated from random or 8-hour urine collected in different periods of the day differ in prediction of albumin excretion ≥ 2 g in 24-hour urine collection in preeclampsia. We also investigated whether these ratios vary across the day.

Material and Methods

The study was conducted prospectively between December 2006 and November 2007 at Aziziye Hospital. It was approved by the Ataturk University Intuitional Review Board.

All pregnant women at > 20 weeks of gestation who had new-onset elevations of systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm measured twice at least six hours apart and who had a repeated positive spot urine test for proteinuria of ≥ 0.3 g/dl were eligible for the study. Only women with significant proteinuria (≥ 300 mg) in the 24-hour urine sample were included in the final analysis. Patients were excluded if they had coexisting urinary tract infections based on culture, pre-existing intrinsic renal disease or diabetes. All eligible women were enrolled the study after giving informed consent.

All 24-hour urine collections were started between 07-08 hours in the morning immediately after the first voided morning urine and included final voiding at the completion of the 24-hour period. The patients were on modified bed rest in the hospital. The urine was collected in three separate drainage bags. The first drainage bag held the first eight hours of urine, the second container held the next eight hours of urine, and third one held the last eight-hour sample. When each time period ended, the urine volume in the drainage bag was measured and a 6-ml aliquot of urine sample was taken after the urine was stirred to ensure homogeneity. The first two 8-hour urine collections were store at 4°C and all 8-hour samples were pooled at the completion of the 24-hour period. A 6-ml aliquot of urine sample was taken from the total urine specimen. Three random

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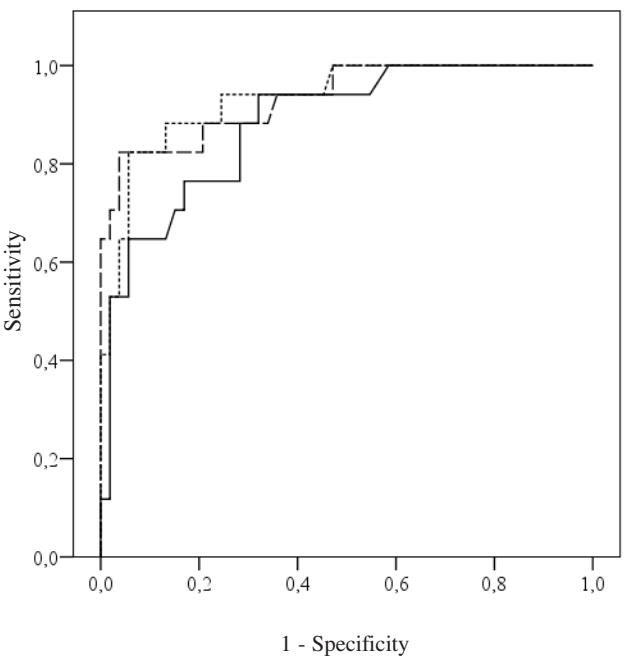

Figure 1. — Receiver operating characteristic curves for the random urinary albumin/creatinine ratio at different periods of the day as a predictor of albuminuria > 2 g (straight line represents 8 am, dotted line 4 pm, dashed line 0 pm).

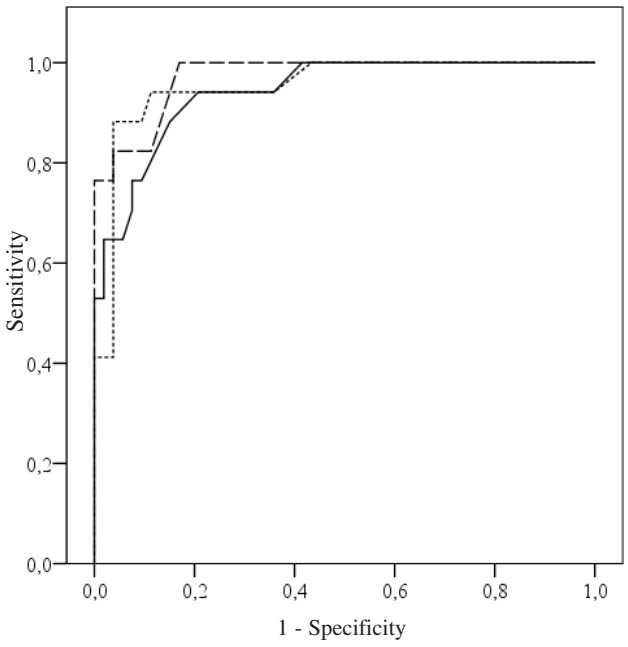

Figure 2. — Receiver operating characteristic curves for the timed urinary albumin/creatinine ratio at different periods of the day as a predictor of albuminuria > 2 g (straight line represents 08-16 period, dotted line 16-24 period, 00-08 period).

urine samples were collected before each time period. The first random urine sample was collected in the early morning (approx. 8 a.m.), the second random sample was collected in late afternoon (approx. 4 p.m.) and the third random urine sample was collected at midnight. An indwelling Foley catheter was used for collection of urine in all samples. Samples of creatinine were drawn from all of the patients at the initiation of the 24-hour urine collection.

All urine samples were analyzed for albumin and creatinine immediately after taken. Urine albumin concentration was measured using an OLYMPUS AU2700 Analyzer (Tokyo, Japan) by the pyrogallol red spectrophotometric method (CV of 1.82%). The creatinine test was analyzed using the Jaffe rate method with the same analyzer. The albumin/creatinine ratio was calculated by dividing protein (mg/dl) by creatinine (mg/dl).

Statistical analyses were performed with the SPSS 15.0 (SPSS Inc., Chicago, IL) and MedCalc 7.2.0.0 (Frank Shoonjans, Mariakerke, Belgium) statistical packages. Since normality tests failed, associations between maternal age, gestational age, albumin/creatinine ratios and 24-hour urine total albumin were assessed with Spearman's rho correlation coefficient. The results of the 24-hour urine collection were used as the gold standard, and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the random urine albumin/creatinine ratios at various cut-offs for prediction of > 2 g albuminuria were estimated. Receiver operator characteristic (ROC) curves were constructed to determine an optimal albumin/creatinine ratio value that maximized sensitivity and specificity in the prediction of significant albuminuria. Urine albumin/creatinine values across the day were analyzed by the Friedman test after pooling all samples. The amount of individual variation in the albumin/creatinine ratio over time was analyzed separately for random and 8-hour urine samples evaluating the inter-assay coefficient variation. The coefficient variation (σ/μ, where σ is the standard deviation, μ is the mean) for each patient was calculated and then the mean coefficient variation with standard deviation was calculated.

Results

A total of 77 consecutive patients with preeclampsia were identified during the study period. A complete 24-hour urine collection was not available for seven patients. Thus 70 consecutive patients constituted the study group. The mean maternal age was 29.5 ± 7.9 years, and mean gestational age was 36.7 ± 4.6 weeks. Ten patients (14.3%) were in the second trimester and 60 (85.7%) in the third trimester. Twenty-seven women (38.6%) were nulliparous. Median blood creatinine level was 0.8 mg/dl (0.4-2.0). Ten patients (14.3%) had a blood creatinine level of ≥ 1 mg/dl.

The median albumin level was 0.6 g (0.1-8) in 24-hour urine of the patients. Twenty-six patients (37.1%) had albuminuria below 0.3 g in 24-hour urine collection. Seventeen patients (24.3%) had a 24-hour albumin excretion of ≥ 2 g and four (5.7%) had ≥ 5 g.

Spearman's rho correlation coefficient between the 24-hour albumin excretion with spot and 8-hour urine albumin/creatinine ratios are given in Table 1. When patients with a creatinine level of ≥ 1 mg/dl were excluded, correlation coefficients were similar (data not shown). The associations of maternal age and gestational age at collection with 24-hour urine total albumin and albumin/creatinine ratios (data not shown) were not significant.

Table 1. — *Test performance of albumin-creatinine ratios for optimal cut offvalues and correlation with 24 hour albumin.*

Sample	C.C.[1]	AUC (95% CI)[2]	Cut-off	Sensitivity (95% CI)[2]	Specifity (95% CI)[2]	+PV	–PV
Random (hour)							
8 am	.79	.88 (.79-.97)	0.6	94 (71- 99)	68(54- 80)	48	97
4 pm	.85	.93 (.87-1.0)	1.4	82(57- 96)	94(84- 99)	82	94
0 pm	.86	.93 (.86-1.0)	1.6	82(57- 96)	96(87- 99)	87	94
8-hour (time period)							
08-16	.91	.94 (.88-1.0)	0.9	94(71- 99)	79(66- 89)	59	98
16-24	.90	.95 (.90-1.0)	1.3	88(63- 98)	96(87- 99)	88	96
00-08	.91	.97 (.94-1.0)	0.7	100(80-100)	83(70- 92)	65	100

[1, 2] $p < 0.001$ for all samples; C.C, correlation coefficient; AUC, area under curve, CI, confidence interval, PV, predictive value.

ROC curves for spot urine albumin-creatinine ratio values and 8-hour urine albumin-creatinine ratio values are shown in Figures 1 and 2, respectively. The area under the ROC curve was significant for each urine sample (Table 1). The areas under the ROC curves were not different in pairwise comparisons after pooling all samples (data not shown). The optimal albumin/creatinine ratio cut-off point that maximizes sensitivity and specificity are shown in the Table 1. The highest cut-off points that yielded 100% sensitivity for spot and 8-hour albumin/creatinine tests with PPV, false-positive rates (1-specifity), and percentage of screen positive patients are shown in Table 2.

Table 2. — *Test performance of albumin-creatinine ratio as a screening test to rule out albumin excretion ≥ 2 g.*

Sample	Cuf-off	False-positive rate (95% CI)	+PV (%)	Secreen positive (%)
Random (hour)				
08	0.37	58 (44-72)	35	67
16	0.39	47(33-61)	42	60
24	0.36	47(61-33)	41	59
8-hour (time period)				
08-16	0.46	41(28-54)	44	56
16-24	0.36	43(30-38)	43	57
00-08	0.75	27(8-28)	65	37

CI, confidence interval; PV, predictive value.

The albumin/creatinine ratio were not different between samples over time when both spot urine and 8-hour collection were analyzed as a whole. Inter-assay coefficient variation was 35.1% (± 26.2) in spot urine samples and 35.4% (± 33.8) in 8-hour urine samples.

Discussion

We found a strong correlation between the albumin/creatinine ratio and 24-hour albumin in women with preeclampsia. The albumin/creatinine ratio did not vary significantly across time when all samples were pooled. However, there was considerable intra-individual variation in both random and timed urine samples. On ROC analysis, the areas under the ROC curves showed that the albumin/creatinine ratio for both random samples and 8-hour urine collections were accurate in predicting the 24-hour urine results and there was no difference between samples. However, a single optimal albumin/creatinine ratio cut-off point for identifying albumin excretion ≥ 2 g was not available.

Interpretation of a test varies by prior probability of the disease. In the present study, we found the ratio of severe albuminuria to be 24.3% in a group of consecutive patients who had preeclampsia. The PPVs of the tests for optimal cut-offs were low and the test results above these cut-offs were not diagnostic for significant proteinuria. However, the NPVs of albumin/creatinine ratios were too high to be substituted for 24-hour collection. It seems, except for the 0-08 time period, that an albumin/creatinine cut-off point ranging from 0.36-0.46 can accurately exclude severe albuminuria with 100% sensitivity. The protein/creatinine ratio can be used as a screening test in preeclampsia for albuminuria to rule out 24-hour albumin excretion of ≥ 2 g.

Sampling random urine for a protein/creatinine ratio is based on the assumption that urinary protein and creatinine excretion in the presence of a stable glomerular filtration rate during the day remains constant [11]. Protein excretion rates, however, can vary hour to hour in preeclampsia due to renal vasoconstriction [3, 12]. Chesley reported up to a 5-fold variation of protein excretion in four hourly collections [3]. In most previous studies, a significant correlation between the protein/creatinine ratio or albumin/creatinine ratio with 24-hour urine were reported in women with hypertensive disease of pregnancy [1, 2, 13-15]. However, a high correlation does not necessarily support the fact that the ratio varies within a narrow range across the day. The albumin/creatinine ratio might be a better estimate of renal function at that moment than 24-hour collection. However, if it is necessary to know the total amount of the albumin excreted, a 24-hour urine sample must be collected.

Conclusions

The albumin/creatinine ratio is a poor predictor of albuminuria ≥ 2 g in patients with preeclampsia and should not replace the 24-hour urine collection as a diagnostic test. It has high intra-individual variation across the day. The ratio can be used to rule out albuminuria proteinuria ≥ 2 g due to high NPV. However, a single albumin-protein cut-off point is not available.

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