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ORIGINAL ARTICLE

Urine albumin/creatinine ratio for the assessment of albuminuria in pregnancy hypertension

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Abstract

Background. An accurate method to assess albuminuria in pregnancy is mandatory to diagnose pre-eclampsia. Twenty-four-hour urine collection is still the only universally accepted method. This is, however, a cumbersome and inconvenient method. Therefore, the present study aimed at assessing the accuracy of a spot urine albumin/creatinine ratio in pregnant women with hypertension. *Material and methods.* In 54 pregnant women with blood pressure $\geq$140/90 mmHg, 24-h albumin excretion and subsequent albumin/creatinine ratio on morning spot urine were analyzed in the individual patients. Altogether 75 paired samples were included. Receiver operating characteristic curves, relating different albumin/creatinine ratio cut-off values to 24-h albumin excretion $>$300 mg were constructed. Correlations were assessed by Spearman rank correlation tests. *Results.* The area under the receiver operating characteristic curve was 0.985. At the optimal cut-off albumin/creatinine ratio value of 27 mg/mmol the sensitivity, specificity, positive and negative predictive value for detecting albuminuria $>$300 mg/24 h were: 95, 100, 100 and 86% respectively. There was a close correlation between albumin/creatinine ratio and 24-h albumin excretion values ($r=0.95$; $p<0.001$). *Conclusions.* It is suggested that in most cases the more cumbersome 24-h urine collection can be replaced by the more convenient albumin/creatinine ratio on spot urine.

Key words: *Albuminuria, albumin/creatinine ratio, hypertension, pregnancy, pre-eclampsia*

Pre-eclampsia is still an important contributor to perinatal and maternal morbidity/mortality. Therefore, a rapid and reliable diagnosis is mandatory. In addition to hypertension, proteinuria of at least 0.3 g/24 h is required for a diagnosis of pre-eclampsia (1). Twenty-four-hour collection of urine is, however, cumbersome, results in at least a 24-h delay in diagnosis, and is prone to errors due to incomplete urine collection. Thus, a more rapid and less cumbersome test would be desirable.

Detecting proteinuria with dipsticks has been shown to be inaccurate with both high false positive (2) and false negative (3) rates. Moreover, urinary protein concentration in spot samples varies throughout the day. This source of error can, however, be eliminated by measuring the urine protein/creatinine ratio instead of the protein concentration itself (4).

Results from several studies (4–6) but not all (7) have shown excellent correlations between 24-h protein excretion and the protein/creatinine ratio, with correlation coefficients in most studies above 0.9. In many Scandinavian centers (8–10) albumin excretion is measured instead of total protein excretion as the former is considered to give a more accurate reflection of glomerular damage than the latter (11,12). To our knowledge the relationship between 24-h renal albumin excretion and the urine albumin/creatinine ratio (ACR) in women with significant albuminuria has not been evaluated. The aim of the present study was thus to evaluate the usefulness of this ratio to detect significant albuminuria in patients with a suspicion of pre-eclampsia.

Material and methods

This study was undertaken between April 2004 and August 2005 on pregnant patients with hypertension ($\geq$140/90 mmHg), who were assessed for the

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presence of pre-eclampsia or underlying renal disease. Patients with a urinary tract infection were not included. All had at least 1+ for proteinuria on Dipstick (Uristix®, Bayer Diagnostics, Bridgend, UK) corresponding to a urinary albumin concentration of 0.3 g/l. After consent to participate was obtained, urine was collected for 24 h from 8 a.m. to 8 a.m. the next morning. Immediately prior to the collection period patients also provided a spot urine sample from which the ACR, given in milligrams per millimoles, was calculated.

Measurements of albumin and creatinine in urine were performed on Modular Roche equipment with a Tinaquant Albumin turbidimetric method and a modified Jaffe creatinine method (Roche). Analytic imprecision (coefficient of variation) for albumin was 15% at 13 mg/l and 7% at 142 mg/l, while imprecision for creatinine was 4% at 7.6 mmol/l.

Altogether 75 paired samples (24-h collections plus spot samples) were obtained from 54 patients. Sixty-eight percent were previously healthy and had *de novo* hypertension after 20 weeks pregnancy, 15% had chronic hypertension, and 17% had a diagnosis of underlying renal disorder, the most common being lupus nephritis (10%). Forty-nine percent of the patients were nulliparous. Urine samples were obtained between 12 and 38 weeks gestation (median 35 weeks).

Sensitivity, specificity, positive and negative likelihood ratios were calculated for different cut-off ACR values against a 24-h albumin excretion >300 mg (i.e. our Gold standard). The positive (negative) likelihood ratios represent the ratio between the probability of a positive (or negative) ACR in women with albuminuria >300 mg and the probability of the same test result in those with albuminuria <300 mg. Thus, the greater the positive likelihood ratio, the more useful the test. A ratio >10 is considered valuable in clinical decision making. Receiver operating characteristic (ROC) curves (plots of sensitivity versus [1 −specificity]) were generated using MedCalc® (MedCalc Software, Belgium). The relationship between 24-h albumin excretion and ACR was also assessed by nonparametric correlation statistics (Spearman rank correlation test).

Results

In 35 of the 54 subjects with a positive dipstick, 24-h albumin excretion was >300 mg/24 h; i.e. a positive predictive value of 65% for the dipstick method.

ROC curve analysis with regard to the relationship between ACR and 24-h albumin excretion demonstrated an area under the curve of 0.985 (95% confidence interval 0.925–0.998; Figure 1). At a cut-off value of 27 mg albumin/mmol creatinine sensitivity was 95% (53/56) and specificity 100% (19/19). The positive predictive value (the proportion of samples with albuminuria >300 mg/24 h out of those with ACR >27 mg/mmol) was 100% (53/53) and the negative predictive value (the proportion of samples with non significant albuminuria; i.e. <300 mg/24 h out of those with ACR ≤27 mg/mmol) 86% (19/22). Two of the three false negative samples had albumin excretions of 302 and 385 mg, respectively; the third had a value of 755 mg. As a positive likelihood ratio cannot be calculated when specificity is 100%, we calculated positive and negative likelihood ratios for a cut-off value of 24 mg/mmol. These were found to be 18.0 and 0.06 respectively.

There was a close correlation between ACR and 24-h albumin excretion ($r=0.95$; $p<0.001$). The correlation coefficient was similar among those samples with albumin excretion <300 mg/24 h ($r=0.89$) and those with excretion >300 mg/24 h ($r=0.88$). After exclusion of repeated samples in the same individual, the correlation improved slightly ($n=54$; $r=0.97$; $p<0.001$), as did the negative predictive value – (19/21) 90%. Sensitivity fell marginally to 94% (33/35). Specificity, positive predictive value, positive and negative likelihood ratios as well as area under the ROC curve remained unchanged when only one sample from each patient was included.

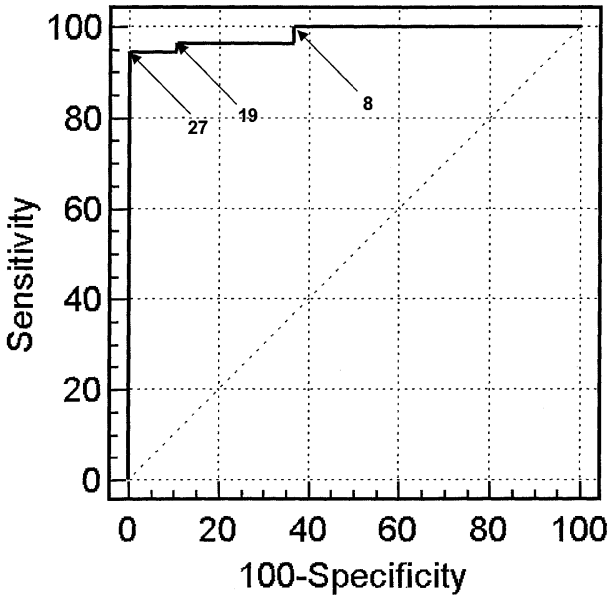

Figure 1. ROC curve demonstrating sensitivities and specificities for different albumin/creatinine cut-off values in predicting significant albuminuria (>300 mg/24 h). Three cut-off values given in mg/mmol are depicted with arrows.

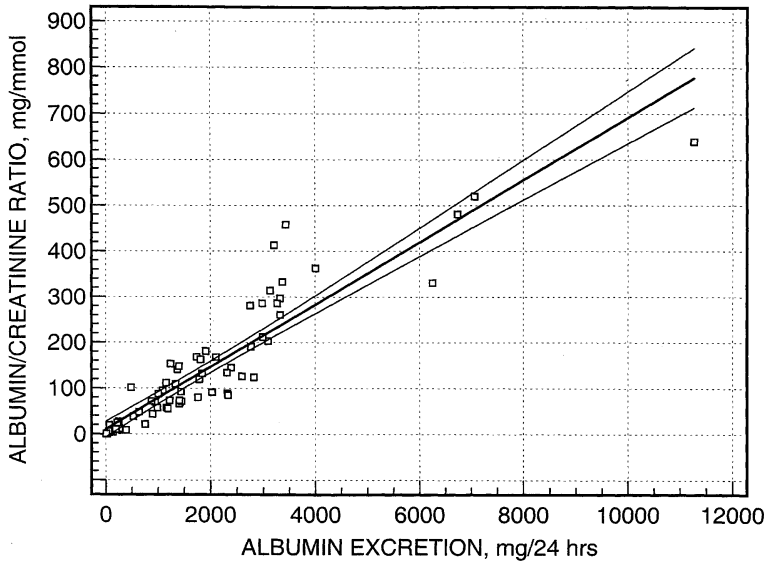

Figure 2. Relationship between albumin excretion in mg/24 h and albumin/creatinine ratio in mg/mmol. Correlation coefficient = 0.95. The regression line and its 95% confidence interval are presented.

Discussion

The amount of albumin excreted in the urine over a 24-h period is considered the gold standard for assessing albuminuria level. However, 24-h collections are cumbersome both for the patients and the staff handling the urine collections, and subject to error due to inaccurate timing and/or incompleteness. Thus, previous studies have demonstrated inadequate urine volumes in up to 37% of samples (13).

The albumin concentration in urine in itself is not a good measure of albumin leakage as its concentration is directly affected by the degree to which the urine is concentrated by the kidneys. The ratio between the urine concentration of albumin and creatinine will be independent of renal fluid handling.

From our ROC curve analyses and excellent correlation between 24-h albumin excretion and ACR, we believe that the latter test can safely replace 24-h urine collection. At the optimal discriminatory value of 27 mg/mmol, we had a false negative rate of 6% (2/35). None of these two patients, however, had severe albuminuria (385 and 755 mg excretion/24 h, respectively). It is of interest that the clinical relevance for the minimum amount of protein excretion for the diagnosis of pre-eclampsia has been questioned. For instance, it has recently been shown that 500 mg rather than 300 mg excretion will most likely predict adverse pregnancy outcome (14). By lowering the cut-off value to 19 mg albumin/mmol creatinine, the false negative rate would be halved, however at the expense of a false positive rate of 10%. By further reducing the ACR cut-off level to 8 mg/mmol, significant albuminuria can be excluded, however at the expense of a false positive rate of 37% (Figure 1). Our results are in principal in agreement with those of Risberg and coworkers (10). They found excellent agreements between ACR and 24-h albumin excretion throughout pregnancy (correlation coefficients between 0.8 and 1.0) in 19 women with hypertension. Only four of these, however, had significant albuminuria (>300 mg/24 h).

We measured albumin excretion rather than total protein excretion as it should reflect endothelial dysfunction and glomerular damage better than total protein excretion. The latter contains e.g. the Tamm-Horsfall glucoprotein, which is produced in the renal tubulus and thus in no way reflects glomerular damage. This glucoprotein may be found in the urine of healthy subjects at a concentration up to 200 mg/l (15). A growing number of prospective epidemiologic studies have reported that the degree of albuminuria and in fact also the ACR correlates with the risk for cardiovascular events (e.g. 16). As albuminuria reveals increased glomerular endothelial permeability, it may be an easily measured marker of endothelial dysfunction. From the results of a very recent study, the authors suggested that significant proteinuria in the absence of significant albuminuria might have a better prognosis and be less severe in cases of pre-eclampsia (17). Thus, urinary excretion of some proteins such as beta 2 microglobulin increases more than sixfold during normal pregnancy with no further increase in pre-eclampsia (12). A further support for extended use of the

ACR is a recent observation of a relationship between this ratio and fetal outcome (18).

In the present study ACR was measured in the early morning, precluding long physical activity, in the upright position before the urine sample was obtained. The question then arises if our results can be generalized to also be valid at other times of the day. The protein–creatinine ratio has been questioned as an alternative to measuring 24-h protein excretion, as the ratio may vary throughout the day. Recently, however, it was clearly shown that in pregnant subjects with hypertension the protein–creatinine ratio from a single voided urine sample does not vary significantly throughout the day and may be determined at any time (19).

Previous studies have demonstrated that maternal age, body size, renal function, gestational age, and parity are not confounding factors with regard to the protein/creatinine ratio (6,20). With this in mind, we believe that our results justify the introduction of the ACR into clinical practice. In cases with a great suspicion of pre-eclampsia based on the symptoms and an ACR below 27 mg/mmol, 24-h collection of the urine should be considered.

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