

## SHORT REPORT

## Accuracy of the urinary albumin to creatinine ratio as a predictor of albuminuria in adults with sickle cell disease

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**Aim:** To test the usefulness of a random urine specimen albumin to creatinine ratio (A/C) in predicting 12 hour urinary albumin excretion (12UA) in patients with sickle cell disease.

**Methods:** 12UA and A/C were measured in nocturnal urine collections and random morning urine samples, respectively, of 72 patients with sickle cell disease.

**Results:** The correlation of A/C values with 12UA values did not provide support for the use of random urine specimens for predicting urinary albumin excretion (UAE) in these patients. However, values of A/C  $\geq 0.45$  and  $< 0.45$  were indicative of raised and normal UAE, respectively. The sensitivity, specificity, and accuracy of the test were 100.0%, 87.2%, and 91.7%, respectively.

**Conclusions:** This method cannot be recommended for predicting 12UA in patients with sickle cell disease, but it is useful for selecting patients who should collect 12 hour urine for the estimation of UAE.

nine ratio (P/C) in single random urine specimens can be used as an alternative to 24 hour urine collection to predict urinary protein excretion in various diseases.<sup>5-8</sup>

"Overnight or 24 hour urine collections are inconvenient and frequently unreliable because of errors in collection, raising questions of accuracy"

In our study, we aimed to assess the usefulness of the albumin to creatinine ratio (A/C) in predicting 12 hour urinary albumin excretion (12UA) in patients with sickle cell disease because this has not been investigated to date.

**METHODS****Subjects**

Our study comprised 72 adult patients with sickle cell disease and 50 controls, who all gave informed consent (table 1).

**Methods**

UAE was measured by a nephelometric method in nocturnal 12UA collections and random samples taken between 8:00 and 10:00 am on the morning after the nocturnal urine collections. 12UA values were considered as the gold standard for the estimation of UAE. Urinary creatinine excretion (UC) in random samples and serum creatinine were assessed by the Jaffé rate method. The glomerular filtration rate was measured according to a previously described method.<sup>10</sup>

Renal involvement similar to that seen in diabetic nephropathy is common in sickle cell disease,<sup>1</sup> and at older ages is a major cause of illness and death.<sup>2</sup> Because microalbuminuria has been described as a preclinical indicator of glomerular damage,<sup>3</sup> and a reduction in albuminuria has been seen during angiotensin converting enzyme (ACE) inhibitor treatment,<sup>4</sup> the measurement of urinary albumin excretion (UAE) has become a routine procedure in these patients.

Proteinuria has been determined by overnight or 24 hour urine collections. However, this procedure is inconvenient and frequently unreliable because of errors in collection, raising questions of accuracy.<sup>3</sup> Over the past decade, several reports have suggested that the measurement of the protein to creati-

**Abbreviations:** A/C, albumin to creatinine ratio; ACE, angiotensin converting enzyme; CI, confidence interval; P/C, protein to creatinine ratio; 12UA, 12 hour urinary albumin excretion; UAE, urinary albumin excretion; UC, urinary creatinine excretion

**Table 1** Baseline clinical and laboratory data in 72 outpatients with sickle cell disease and 50 controls enrolled in the study

Variable	Patients		Controls
	Normal UAE	Raised UAE	
Number	47	25	50
Male/female	21/26	12/13	25/25
Haemoglobinopathy	34 SS, 4 S $\beta$ , 9 SC	20 SS, 3 S $\beta$ , 2 SC	
Age (years)	29.19 (11.12)	31.60 (9.98)	34.0 (9.0)
Serum creatinine (mg/dl)	0.50 (0.14)	0.55 (0.17)	-
GFR (ml/min/1.73 m <sup>2</sup> )	135.94 (42.28)	120.59 (26.84)	-
12UA (mcg/min)	6.55 (5.35)	258.00 (411.71)	-
Urinary creatinine (mg/dl)	68.66 (35.21)	63.01 (21.66)	124.7 (73.8)
A/C (mg/l/mg/dl)	0.25 (0.27)	4.80 (7.50)	0.05 (0.03)

Data are number or mean (SD).

A/C, albumin to creatinine ratio; GFR, glomerular filtration rate measured by <sup>51</sup>Cr-EDTA; S $\beta$ , haemoglobin S with  $\beta$  thalassaemia; SC, haemoglobin SC; SS, sickle cell anaemia; 12UA, 12 hour urinary albumin excretion; UAE, urinary albumin excretion.

**Table 2** Predicted 12 hour urinary albumin excretion values for selected random urine albumin to creatinine ratio values obtained from the regression equation:  $y = \exp(3.48 + 0.94 \log A/C)$

A/C (mg/l/mg/dl)	Predicted 12UA ( $\mu\text{g}/\text{min}$ )	Predicted 12UA (CI) ( $\mu\text{g}/\text{min}$ )
0.02	0.82	0.14 to 4.88
0.10	3.74	0.65 to 21.49
0.45	15.41	2.70 to 87.88
2.00	63.49	11.00 to 366.56
9.00	263.42	44.18 to 1570.79
34.7	913.92	146.70 to 5693.62

A/C, albumin to creatinine ratio; CI, confidence interval; 12UA, 12 hour urinary albumin excretion.

Patients who had raised UAE values were asked to undergo ACE treatment (5 mg enalapril daily). In 11 patients undergoing treatment, second and third 12 hour urine collections with concomitant random urine specimens were obtained after three and six month periods and provided the evaluation of the A/C as a longitudinal test.

### Statistics

The relation between the A/C and 12UA values was tested by Spearman's variance analysis and linear regression analysis. The decision level of the A/C was defined using the receiver operating characteristic curve technique. The significance of the differences between groups was determined by the Wilcoxon rank test.

### RESULTS

A/C values correlated with 12UA values ( $r = 0.87$ ;  $p < 0.001$ ) after log/log transformation of the data. From this relation, 12UA could be predicted by the equation: predicted 12UA =  $\exp(3.48 + 0.94 \log A/C)$ . Using this equation, values of 12UA for selected A/C values were calculated to test the reliability of the estimations (table 2). The confidence intervals were large for all A/C values and increased as the A/C increased.

Comparisons of the per cent change of 12UA and A/C values from the first collection to the repeat measurements were made in patients undergoing ACE inhibitor treatment to

evaluate whether the degree of change of A/C and 12UA occurred in the same direction. No correlation was found with either the second ( $r = -0.227$ ;  $p = 0.46$ ) or the third ( $r = 0.515$ ;  $p = 0.13$ ) measurements.

A good correlation was found between albumin and A/C values on random urine specimens in both patients ( $r = 0.97$ ;  $p < 0.001$ ) and controls ( $r = 0.44$ ;  $p < 0.001$ ). The mean value of UC in patients was lower than that seen in controls ( $p < 0.001$ ), but similar values were seen in patients with normal and raised UAE values ( $p = 0.86$ ).

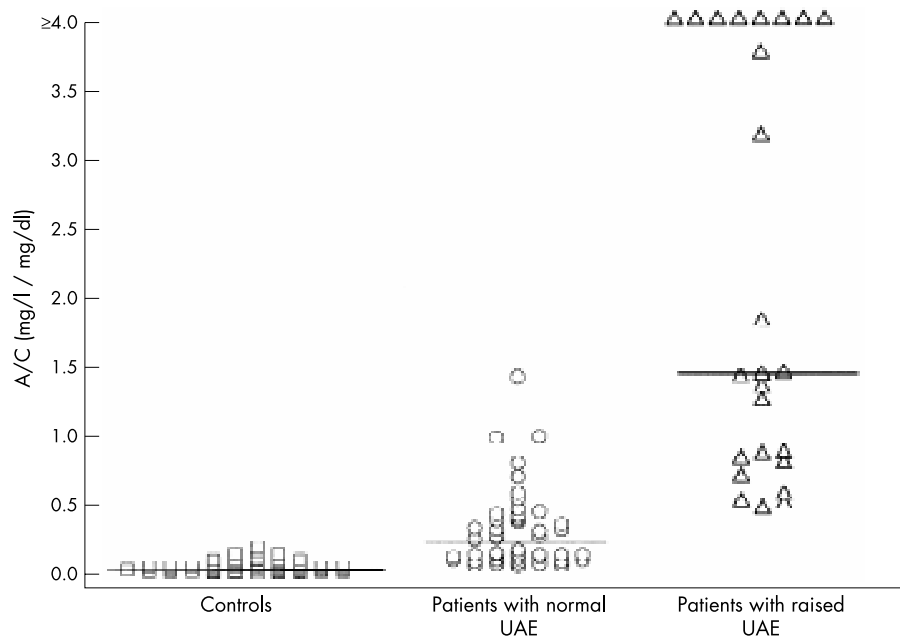
The mean value of A/C was higher in patients with raised UAE values than in those with normal UAE values ( $p < 0.001$ ). In addition, the mean A/C values in patients with normal UAE values were higher than in controls ( $p < 0.001$ ; fig 1). Values of A/C  $\geq 0.45$  and  $< 0.45$  were indicative of raised and normal UAE values, respectively. The sensitivity and specificity of the test were 100.0% (95% confidence interval (CI), 100% to 100%) and 87.2% (95% CI, 74.2% to 95.1%), respectively. The positive and negative predictive values were 80.6% and 100.0%, respectively and the accuracy was 91.7%.

### DISCUSSION

In our study, we evaluated the random urine A/C for predicting 12UA in patients with sickle cell disease. Because the confidence intervals were large for all A/C values considered, and increased when A/C increased, we concluded that this method cannot be recommended for this purpose in patients with sickle cell disease. No correlation was found in comparisons of the per cent change of A/C and 12UA values from the first and repeat measurements in patients undergoing enalapril treatment, suggesting that the method cannot be used for longitudinal patient analysis.

In addition, Rodby and colleagues<sup>7</sup> found similar results using the P/C method for predicting 24 hour urinary protein excretion in patients with diabetic nephropathy, who presented renal involvement similar to that seen in patients with sickle cell disease.

"Because the confidence intervals were large for all albumin to creatinine ratios (A/C) considered, and increased when A/C increased, we concluded that this method cannot be recommended for this purpose in patients with sickle cell disease"



**Figure 1** Distribution of urinary albumin to creatinine ratio (A/C) values in random samples in 50 controls, 47 patients with sickle cell disease and normal urinary albumin excretion (normal UAE), and 25 patients with sickle cell disease with raised urinary albumin excretion (raised UAE). The horizontal lines represent the median values of each distribution.

### Take home messages

- Albumin to creatinine ratio (A/C) values cannot be recommended for predicting 12 hour urinary albumin excretion (12UA) values in patients with sickle cell disease or longitudinal patient analysis in those undergoing enalapril treatment
- However, values of A/C  $\geq 0.45$  and  $< 0.45$  were indicative of raised and normal urinary albumin excretion (UAE), respectively, with a sensitivity, specificity, and accuracy of 100.0%, 87.2%, and 91.7%, respectively
- The measurement of A/C values is useful for selecting patients who should collect 12 hour urine for the estimation of UAE

In our study, we also evaluated the usefulness of A/C as a method for selecting patients with normal and raised UAE values. We initially found lower UC values in patients than in controls, according to a previous report,<sup>8</sup> despite the well known increased secretion of creatinine in renal proximal tubules.<sup>19</sup> We postulated that the urinary creatinine could have been diluted by the high urinary volume that results from the impaired urinary concentrating ability seen in patients with sickle cell disease.<sup>19</sup> As expected, the mean value of A/C in patients with raised UAE was higher than that found in patients with normal UAE.

Based on the decision level of A/C used in our study, we identified all patients with raised UAE values and most of the patients with normal UAE values.

We conclude from the high sensitivity, specificity, positive and negative predictive values, and the accuracy of the A/C in detecting patients with normal and raised UAE values in our study, that the measurement of A/C is a good method for selecting patients who should collect 12 hour urine samples for albumin estimation.

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