Urine protein-to-creatinine ratio in an untimed urine collection is a reliable measure of proteinuria in lupus nephritis

Y. Y. Leung, C. C. Szeto¹, L. S. Tam¹, C. W. K. Lam², E. K. Li¹, K. C. Wong¹, S. W. Yu¹ and E. W. Kun

Objective. To evaluate the accuracy of urine protein-to-creatinine (P/C) ratio in an untimed urine specimen as compared with 24 h total protein excretion for measurement of proteinuria in patients with lupus nephritis.

Methods. Proteinuria in patients with lupus nephritis was assessed by 24 h total protein excretion and spot urine P/C ratio. Correlation and limits of agreement between the two methods were evaluated. The discriminant cutoff values for spot urine P/C ratio in predicting 24 h protein ‘threshold’ excretion of ≥0.3, ≥0.5, ≥1.0 and ≥3.5 g/day were determined using receiver operating characteristic curves.

Results. A total of 165 samples were available for assessment with 21.8% excluded due to inadequate collection. A strong correlation (r = 0.91, P < 0.0001) was found between spot urine P/C ratio and 24 h urine protein excretion. Bland–Altman plot showed the two tests had acceptable limits of agreement in low level of protein excretion (−0.86 to +0.92 g/day when protein excretion was <2.0 g/day). The limits became wider as the protein excretion increased. The spot urine P/C ratios of 0.45 (sensitivity 0.92; specificity 0.88), 0.7 (0.92; 0.89) and 1.84 (1.0; 0.86) mg/mg reliably predicted 24 h urine total protein equivalent ‘thresholds’ at ≥0.5, 1.0 and 3.5 g/day.

Conclusion. This study supports the recommendation of using spot urine P/C ratio in screening and monitoring proteinuria in patients with lupus nephritis. However, in assessing the exact amount of proteinuria, the urine P/C ratio may have unacceptably wide limits of agreement in high protein excretion range.

KEY WORDS: Proteinuria, Urine protein-to-creatinine ratio, Lupus nephritis.

Introduction

Quantifying proteinuria accurately and precisely is vital in the monitoring disease activity in patients with lupus nephritis. The measurement by 24 h urine collection has been regarded as the ‘gold standard’ [1]. However, such collection is cumbersome to use and frequently inaccurate due to collection errors [2, 3]. The urine protein-to-creatinine (P/C) ratio corrects for variations in urinary protein concentration due to hydration and is not affected by a decrease in urine output in patients with renal insufficiency. It is far more convenient than timed urine collections. The numerical outcome of the urine P/C ratio in mg/mg is roughly equal to the 24 h protein excretion in g/day/1.73 m² body surface area. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines of the US National Kidney Foundation, the urine albumin-to-creatinine ratio in an untimed urine specimen should replace protein excretion in a 24 h collection as the preferred method for measuring proteinuria. If the albumin-to-creatinine ratio is high (>500–1000 mg/mg), urine P/C ratio could be used [4].

The Renal Disease Subcommittee of the American College of Rheumatology (ACR) has recently adopted the utilization of spot urine P/C ratio of <0.2 mg/mg and 0.2–2.0 mg/mg as complete and partial remission criteria, respectively in proliferative and membranous lupus nephritis [5]. These recommendations were based on correlation studies. The ratio of protein or albumin-to-creatinine in an untimed urine sample has high correlation with 24 h total protein [2, 6]. This method has been validated in diabetic [7] and non-diabetic [8] nephropathy.

However, correlation and agreement between two measuring methods are different matters. The agreement between two methods should be assessed before replacing one with the other. There is also paucity of data regarding the utility of urine P/C ratio in monitoring proteinuria in patients with lupus nephritis [9, 10]. The aim of this study is to evaluate the agreement of urine P/C ratio in untimed specimens with proteinuria measured by 24 h urinary collection in patients with lupus nephritis.

Methods

Proteinuria in patients with biopsy proven lupus nephritis attending a specialist clinic of a regional hospital in Hong Kong Special Administrative Region was assessed. This study was conducted from 20 January to 30 June 2006. Demographic data including age, sex, body weight and height were collected during clinic visits. Body weight was measured to the nearest 0.1 kg by a standard beam balance. Body height was measured to the nearest 0.5 cm without shoes. The total body surface area (TBSA) was calculated by the DuBois and DuBois formula [11]. Disease activity and damage were calculated by Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) [12] and Systemic Lupus International Collaborating Clinics

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Quantification of proteinuria is vital for monitoring disease activity and the response to therapies in patients with lupus.
proteinuria with spot urine P/C ratio. The Renal Subcommittee of the ACR has also adopted spot urine P/C ratio of < 0.5 g/day as one of the remission criteria for lupus nephritis in 2006. These recommendations are based on correlation studies. The correlation coefficient measures the strength of a relation between the two variables, but not the agreement between them. A new method should be tested with sufficient agreement before an old method could be replaced. Few studies have investigated the agreement between 24 h urine total protein and spot urine P/C ratio while none evaluated the use of spot urine P/C ratio in patients with lupus nephritis. Our study simulated the use of spot urine P/C ratio in a real clinic setting among patients with lupus nephritis, and aimed to evaluate the limits of agreement between this alternative parameter and the 24 h urine total protein.

We found a strong correlation between spot urine P/C ratio and 24 h urine total protein. The two tests have acceptable limits of agreement in patients with proteinuria around 0.5–2 g/day. The limits of agreement become wider as the proteinuria increased. On the Bland–Altman plot, the limits of agreement became similar over a wide range of urinary protein excretion values when the data were log-transformed. This implies reasonable agreement in the “usual” range of proteinuria (~0.5–2 g/day), but a larger absolute difference between the two methods occurred as proteinuria excretion increased. This result was not explained by inadequate 24 h urine collection, age, sex and whether or not the spot urine was collected on the same day. Studies of other patient groups that examined the agreement between urine albumin or P/C ratio and 24 h urine total protein also reported wide limits of agreement especially at high levels of protein excretion despite very good correlation [18–20].

In most clinical settings, physicians look at the ‘threshold’ of 24 h protein excretion rather than absolute values. For example, 24 h urine total protein < 0.5 g/day has been used as one of the remission criteria and scores were given in the SLEDAI-2K if persistent proteinuria was higher than this level. Proteinuria of > 1 g/day is considered as clinically significant or a threshold to recommend renal biopsy, while proteinuria > 3.5 g/day is severe in the nephrotic range. The discriminant values for spot urine P/C ratio to predict 24 h urine total protein at these ‘threshold’ levels were calculated with good sensitivity, specificity and area under ROC curve. A proportion of patients would not have complete collection and the spot urine P/C ratio becomes the only ‘reliable’ test. The sensitivity and specificity described here would, therefore, be an underestimate. In general, a spot urine P/C ratio > 0.45 mg/mg and > 0.7 mg/mg should predict reliably proteinuria of > 0.5 and > 1.0 g/day, respectively; while a spot urine P/C ratio > 1.85 mg/mg predicts nephrotic range of proteinuria. These discriminant spot urine P/C ratios serve well in clinical decision-making and research methodology as the remission criteria. However, when the exact amount of proteinuria is to be assessed, the spot urine P/C ratio will only be within the acceptable limits of agreement if protein excretion is reasonably low.

In the present study, we have recruited patients with various degrees of renal impairment and proteinuria. It is unlikely that a higher number of patients would substantially alter the study result. In fact, previous studies showed that the effect size of different renal function on the precision of urine P/C ratio is minimal [3, 6, 21]. It should be noted that we have excluded patients who are treated with cimetidine or cotrimoxazole, which would affect renal excretion of creatinine. A small proportion of patients are taking ciclosporin A or cyclophosphamide, which may affect renal function. However, neither ciclosporin nor cyclophosphamide selectively affects renal tubular creatinine handling. Analysis of our data after excluding patients taking ciclosporin A or cyclophosphamide yields similar results (details not shown). Previous study on renal transplant recipients, most of whom were treated with ciclosporin A, showed that

![Fig. 2. (A) Limits of agreement of spot urine protein-to-creatine (P/C) ratio and 24 h urinary total protein. (B) limits of agreement of log transformed spot urine P/C ratio and 24 h urinary total protein. P/C ratio, protein-to-creatine ratio.](Image)

TABLE 2. Discriminant spot urine P/C ratio that predict ‘threshold’ proteinuria at ≥ 0.3, 0.5, 1.0 and 3.5 g/day

<table>
<thead>
<tr>
<th>24 h urine total protein threshold (g/day)</th>
<th>Discriminant values of spot urine P/C ratio (mg/mg)</th>
<th>Sensitivity% (95% CI)</th>
<th>Specificity% (95% CI)</th>
<th>Area under ROC curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.3</td>
<td>0.37 (0.3, 0.5)</td>
<td>88.9 (86.1–91.6)</td>
<td>97.1 (95.4–98.8)</td>
<td>0.964</td>
</tr>
<tr>
<td>≥ 0.5</td>
<td>0.45 (0.4, 0.5)</td>
<td>93.2 (91.4–95.0)</td>
<td>88.2 (86.4–90.0)</td>
<td>0.961</td>
</tr>
<tr>
<td>≥ 1.0</td>
<td>0.70 (0.6, 0.8)</td>
<td>92.3 (90.5–94.1)</td>
<td>89 (87.2–91.8)</td>
<td>0.909 (0.890–0.928)</td>
</tr>
<tr>
<td>≥ 3.5</td>
<td>1.84 (1.7, 2.0)</td>
<td>100 (98.2–100)</td>
<td>86.4 (84.6–88.2)</td>
<td>0.957</td>
</tr>
</tbody>
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95% CI, 95% confident intervals; ROC curve, receiver operating characteristic curve.

Since 2002, the US National Kidney Foundation has recommended replacement of 24 h urine collection for quantifying

nephritis [1, 17]. Until recently, utilizing 24 h urine total protein has been the standard of practice. As 24 h urinary collections are cumbersome and frequently unreliable due to inadequate collection, a reliable and easy measure like the spot urine P/C ratio would be ideal in clinical practice. Patients in this study were young and represented a highly trained group in 24 h urinary collection. However, more than 20% of 24 h urinary collections were inadequately collected as defined by measured creatinine production < 20% of the predicted. This implies an intrinsic problem with timed urinary collection method and makes it highly unreliable.

Since 2002, the US National Kidney Foundation has recommended replacement of 24 h urine collection for quantifying

proteinuria with spot urine P/C ratio. The Renal Subcommittee of the ACR has also adopted spot urine P/C ratio of < 0.5 g/day as one of the remission criteria for lupus nephritis in 2006. These recommendations are based on correlation studies. The correlation coefficient measures the strength of a relation between the two variables, but not the agreement between them. A new method should be tested with sufficient agreement before an old method could be replaced. Few studies have investigated the agreement between 24 h urine total protein and spot urine P/C ratio while none evaluated the use of spot urine P/C ratio in patients with lupus nephritis. Our study simulated the use of spot urine P/C ratio in a real clinic setting among patients with lupus nephritis, and aimed to evaluate the limits of agreement between this alternative parameter and the 24 h urine total protein.

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