Urinary Protein/Creatinine Ratio Weighted by Estimated Urinary Creatinine Improves the Accuracy of Predicting Daily Proteinuria

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Abstract: *Background:* The spot urine protein/creatinine ratio (UPCR) is proposed to be a substitute for 24-hour urinary protein (24h-UP). This study is aimed to determine whether the predictive accuracy of 24h-UP using UPCR can be improved by simply multiplying estimated daily urine creatinine excretion (eUCr) and UPCR together. *Methods:* This study enrolled 120 participants to investigate the correlation between spot UPCR and 24h-UP. Three sets of spot urine samples were randomly collected throughout the day and night, along with the first morning void. UPCR was weighted by eUCr to investigate the improvement of accuracy in using spot urine samples to predict 24h-UP. *Results:* There were strong correlation and concordance between UPCR and 24h-UP irrespective of the time of spot urine sampling, and the correlation, concordance and agreement were improved after multiplying the UPCR value by the eUCr. Greater improvement was found in the subgroups with measured daily urine creatinine excretion $\leq$0.8 g/d and $\geq$1.2 g/d. *Conclusions:* This investigation demonstrated that multiplying UPCR by eUCr can improve the accuracy of only using UPCR to predict 24h-UP.

Key Indexing Terms: Spot urine protein-to-creatinine ratio; Urine PCR; UPCR; Daily urine protein; 24-hour urine protein. **[Am J Med Sci 2015;349(6):477–487.]**

Urine biochemistry is one of the most important tests in the field of nephrology, and urine biochemical assessments can facilitate accurate diagnosis of kidney diseases. Urine protein, a major characteristic of most kidney diseases, is highly associated with the rate of kidney function decline.[1] Accurate quantification of urine protein can help doctors to diagnose kidney disease, make therapeutic decision and monitor therapeutic effects. Traditionally, doctors have used 24-hour timed urine collection to determine the amount of urine protein excretion, thus avoiding the potential fluctuations caused by daily activity. However, this procedure, especially in outpatients, is time-consuming, cumbersome and frequently unreliable because of missed collection of urine samples. The spot urine protein-to-creatinine ratio (UPCR) has been used as a substitute for timed urine protein collection on the basis of the assumption that the urine protein excretion rate, which is proportional to the urine creatinine excretion, is relatively constant throughout the day.[2] Several studies have confirmed the high correlation between the UPCR and 24-hour urine protein (24h-UP) with different regression coefficients (r = 0.92–0.97).[2–5] The National Kidney Foundation has also recommended that untimed (spot) urine samples should be used to detect and monitor proteinuria in adults or children and that it is not necessary to perform timed urine collection (overnight or 24-hour).[6] However, the amount of urine creatinine excretion per day has been found to be highly variable between individuals, depending on age, gender and body weight,[7] and the differences may influence the accuracy of the UPCR in predicting 24h-UP. In patients with extremely high or low daily urine creatinine excretion, the UPCR may be even double or half of the 24h-UP. As a result, the UPCR should not be used for initial risk stratification in glomerular diseases such as membranous nephropathy. In addition, the time of spot urine sampling and the use of medications may potentially contribute to differences in the values for UPCR and 24h-UP.

This study aims primarily to determine whether there is a high correlation, concordance and agreement between UPCR and 24h-UP values and to examine the circadian fluctuations of the UPCR in patients with chronic kidney disease. A second aim is to investigate whether the accuracy of using UPCR in predicting 24h-UP would be improved after multiplying the UPCR value by the estimated daily urine creatinine excretion (eUCr) based on the Cockcroft-Gault equation,[7] especially in patients with extremely high or low daily urine creatinine excretion. Finally, the authors investigate whether the differences in the amount of 24h-UP, renal function and use of renin-angiotensin-aldosterone system (RAAS) blockers affect the correlation between the UPCR and 24h-UP.

MATERIALS AND METHODS

Patient Selection

The study group consisted of 120 participants who met the following inclusion criteria: (1) chronic kidney disease with stable renal function for 3 months before the commencement of the study and (2) daily urine protein level higher than 100 mg or

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UPCR higher than 0.1 (g/g). These participants were regularly monitored by nephrology outpatient services in Taipei Veterans General Hospital. All enrolled participants were asked to maintain their regular dietary intake and medications for underlying diseases. Participants who were unsure of accurate compliance in collecting urine samples or who had collected 24h-UP with less than 100 mg per day were excluded from the analysis. Furthermore, participants with the ratio of measured daily urine creatinine excretion (mUCr) and eUCr more than 1.5 or less than 0.5 were also excluded. After obtaining informed consent from every participant in this study, urine samples were collected according to the following protocol.

Study Protocol for Urine Collection and Testing

A plastic bucket with cover was provided to each participant participating in this study. Participants had to void before the study began, and 24-hour urine collection began at 7:00 AM on the first morning of the study. Three sets of spot urine samples, each containing 10 mL of urine, were collected at random times throughout the day (7:00 AM to 3:00 PM; labeled as "Random daytime") and night (3:00 PM to 11:00 PM; labeled as "Random nighttime") and at 7:00 AM the next morning (labeled as "First morning"). These urine samples were then put in the plastic bucket and returned to the laboratory together with the 3 spot urine samples immediately after the urine collection is complete. In the meantime, confirmation of successful and complete collection of all urine samples was sought from the participants. The 24-hour urine samples and 3 sets of spot urine samples were analyzed for creatinine and total protein levels in the morning completing urine collection. Urine protein was measured by the pyrogallol red-molybdate method, and urine creatinine was measured by the autoanalyzer method with the Jaffe reaction.

The general data included age, gender, body weight (at the time of study), serum creatinine concentration (SCr), body mass index and the coincidence of diabetes mellitus and hypertension were recorded. Medical records were reviewed, and the use or nonuse of RAAS blockers was confirmed with the participants. The estimated glomerular filtration rate (eGFR) was calculated by simplified MDRD formula, and the staging of chronic kidney disease was determined according to the K/DOQI guideline.[6]

Statistical Analyses

Three statistical approaches were used to compare UPCR from different times of collection and 24h-UP. First, linear regression analysis was used to yield a regression equation: $y = \alpha + \beta x$, where UPCR served as "x" variable and 24h-UP served as "y" variable. Both the slope (β) and correlation coefficient (r^2) between individual UPCR and 24h-UP measurements were evaluated. The "β" value of the regression equation represents the accuracy of different methods used to predict 24h-UP. Any method with a "β" value close to 1 has a high accuracy to predict 24h-UP. Second, concordance correlation coefficient (CCC)[8] was used to evaluate the agreement between UPCR and 24h-UP. A CCC close to 1 shows strong concordance. Third, calibration plot[9] was used to verify the agreement between UPCR and 24h-UP. The *x* axis shows the value of 24h-UP, whereas the *y* axis represents the ratio of UPCR and 24h-UP (UPCR/24h-UP) in this plot. A mean value of ratio close to 1 represents high accuracy of using UPCR to predict 24h-UP, and smaller range between upper and lower limits of agreement ($\pm$1.96 SD) shows better agreement.

To eliminate the effect of variable urine creatinine excretion between individuals on the analysis, UPCR was multiplied by the eUCr value obtained by the Cockcroft-Gault equation[7]: 24-hour urine creatinine excretion (g) = {[140 − age (years)] × weight (kg)} / 5000 (×0.85 in females). The eUCr-weighted UPCR (eUPCR) was then used instead of UPCR in analyzing all participants and subgroups with mUCr ≤0.8 g/d, mUCr ≥1.2 g/d, mUCr >0.8 g/d and <1.2 g/d. Subgroup analysis according to the amount of urine protein (24h-UP >3g/d and ≤3g/d) and renal

TABLE 1. Baseline demographic and clinical characteristics of the study group

Variables	Values
Age (yrs; mean ± SD)	67 ± 14.83
Gender	
Male, *n* (%)	57 (63)
Female, *n* (%)	33 (37)
Body weight (kg; mean ± SD)	65.57 ± 12.91
SCr (mg/dL; mean ± SD)	2.84 ± 1.93
Body mass index (kg/m^2; mean ± SD)	24.94 ± 4.77
CKD, *n* (%)	
Stage 1 (eGFR ≥90)	7 (7.8)
Stage 2 (eGFR: 60–89)	7 (7.8)
Stage 3 (eGFR: 30–59)	29 (32.2)
Stage 4 (eGFR: 15–29)	29 (32.2)
Stage 5 (eGFR ≤15)	18 (20.0)
Diabetes mellitus, *n* (%)	38 (42.2)
Hypertension, *n* (%)	75 (83.3)
RAAS blockers use, *n* (%)	56 (62.2)

Staging of CKD is based on eGFR by MDRD formula: GFR (mL·min^{-1}·1.73 m^{-2}) = 175 × (SCr)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742, if female) × (1.212, if African American).

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; RAAS, renin-angiotensin-aldosterone axis; SCr, serum creatinine.

TABLE 2. Regression parameters and CCC of the study group

	UPCR vs. 24h-UP			eUPCR vs. 24h-UP		
	β	r^2	CCC	β	r^2	CCC
All patients (n = 90)						
Random daytime	0.848	0.857	0.918	0.942	0.944	0.971
Random nighttime	0.866	0.882	0.933	0.957	0.966	0.982
First morning	0.869	0.846	0.916	0.970	0.935	0.967

Regression equation: *24h-UP* = α + (β × *UPCR* [or eUPCR]).

For the regression coefficient, all $P < 0.001$.

CCCs, concordance correlation coefficients; 24h-UP, timed 24-hour urine protein; UPCR, urine protein-to-creatinine ratio; eUPCR, estimated daily urine creatinine excretion–weighted UPCR; random daytime, spot urine between 7:00 AM and 3:00 PM; random nighttime, spot urine between 3:00 AM and 11:00 PM; first morning, first voided at 7:00 AM the next morning.