24-Hour Proteinuria Versus Spot Protein-Creatinine Ratio for Kidney Transplant Management in Clinical Practice

C. Rodelo-Haad[a,b,*], E. Esquivias-Motta[a,b], M.L. Agüera[a,b], P. Aljama[a,b], and A. Rodríguez-Benot[a,b]

[a]Instituto Maimonides de Investigacion Biomedica de Cordoba, Córdoba, Spain; and [b]Nephrology Department, Reina Sofia University Hospital, Córdoba, Spain

ABSTRACT

Background. 24-hour proteinuria (24h-P) has been the most widespread test for clinical follow-up of proteinuria after kidney transplantation (KT), but urine collection is often not properly collected. Spot protein-creatinine ratio (P/Cr) has become the alternative to 24h-P for proteinuria evaluation in many KT units. However, its reliability, equivalence to 24h-P, and prognostic value regarding allograft outcome remain unknown. Therefore, the aim of this study was to evaluate the correlation and agreement between both methods for assessing proteinuria and to analyze which of them is a better predictor of graft survival.

Methods. We collected proteinuria measurements from KT patients in our center. 24h-P was adjusted for body surface area. Pearson correlation test and the Bland-Altman method were used to analyze correlation and agreement. Survival analysis was performed with the use of the Kaplan-Meier method and multivariate Cox proportional hazard model.

Results. A total of 8,549 urine samples were analyzed from 472 patients in whom 24h-P and P/Cr were simultaneously measured. A significant correlation was observed between 24h-P and P/Cr ($r = .76$; $P < .001$); however, the agreement between methods showed that P/Cr overestimated proteinuria compared with 24h-P, particularly when the latter was >1 g/24 h. The Cox regression multivariate model showed an increased risk of graft loss associated with proteinuria when assessed by either 24h-P (hazard ratio [HR] 6.53, 95% confidence interval [CI] 2.49–17.1) or P/Cr (HR 3.34, 95% CI 1.04–10.7).

Conclusions. P/Cr is an method interchangeable with 24h-P for detecting proteinuria after KT. When proteinuria increases, the P/Cr overestimates 24h-P, even though it also has a significant and similar prognostic value for predicting graft survival.

PROTEINURIA is a strong risk factor for chronic kidney disease (CKD) [1]. Indeed, it has been established as the single most important marker for CKD progression [1–3]. Therefore, a simple and reliable method to detect proteinuria is required for diagnosis, treatment, and prognosis of CKD [1]. After kidney transplantation (KT), proteinuria is also tightly associated with both worse allograft outcome and cardiovascular and noncardiovascular mortality [4–7]. 24-hour proteinuria collection (24h-P) has been classically considered to be the criterion standard for proteinuria measurement because of the variability of protein excretion throughout the day [1,2,8]. However, urinary protein excretion is highly influenced by urine output, fluid intake, and collecting errors; thus, sensitivity and specificity for 24h-P decreases. Recently, body surface area–adjusted 24-hour proteinuria (BSA-adjusted 24h-P) and protein-creatinine ratio (P/Cr) have been proposed to partially or fully correct the variability induced by this physiologic mechanism [9,10]. In nontransplanted CKD patients with proteinuria, good correlation between 24h-P and P/Cr for nonnephrotic degrees of proteinuria has been noted [11]. This correlation decreases as proteinuria

The first two authors contributed equally to this work.

*Address correspondence to Cristian Rodelo-Haad, Nephrology Department, Hospital Universitario Reina Sofía, 14004 Córdoba, Spain. E-mail: crisroha@yahoo.com

0041-1345/18
https://doi.org/10.1016/j.transproceed.2017.09.071

Table 1. Demographic Characteristics of the Entire Included Population

Sex male	339 (78.1%)
Donor age, y	46.7 ± 17
Recipient age, y	48 ± 14
Waiting list time, d	466 (1–3,082)
Primary renal diagnosis	
Primary glomerulopathy	93 (20)
Glomeruloesclerosis	30 (7)
Unknown	112 (24)
Pyelonephritis	138 (29)
Others	71 (15)
Time since Tx, d	1,531 (1–3,664)
Cold ischemia time, h	11 ± 4
24h-P, g/24 h	0.59 ± 0.77
P/Cr, mg/mg	0.48 ± 0.68
eGFR, mL/min/1.73 m^2	53.7 ± 19.9
HLA mismatches	3.7 ± 1.5

Values are presented as *n* (%), mean ± SD, or median (range).
Abbreviations: Tx, transplantation; 24h-P, 24-h proteinuria; P/Cr, spot protein-creatinine ratio; eGFR, estimated glomerular filtration rate.

increases, such that both methods might not be interchangeable [11–13]. To our knowledge, few studies have assessed the correlation and agreement between these 2 methods for evaluating proteinuria after KT. In fact, in a recent published systematic review, the authors conclude that there is no evidence enough to recommend P/Cr as the only method in the decision making for KT recipients [14]. Therefore, the aim of the present study was to evaluate whether P/Cr could replace 24h-P for detection, evaluation, and follow-up of proteinuria in daily clinical practice after KT.

METHODS

Patients

We designed an observational and longitudinal study to compare values of BSA-adjusted 24h-P and P/Cr that were measured simultaneously from the same urine sample ≥3 months after transplantation to ensure that the measured proteinuria was from the graft and not from the native kidneys. We studied a cohort of 472 adult recipients, who underwent renal transplantation at our center from January 2004 to December 2013; 95.3% received transplants from deceased donors. Because of multiple urine measurements, we calculated the mean value for 24h-P or P/Cr from each patient during the study period. The study was approved by the hospital Ethics Committee.

Proteinuria

24h-P and the P/Cr were performed on the same analyzer with the use of a spectrophotometric assay (Abbott Architect c16000). Proteinuria was considered to be positive when its value was >0.10 mg/mg or >100 mg/24 h. 24h-P was stratified into 4 groups according to different thresholds: 1: <300 mg/24 h; 2: 300–500 mg/24 h; 3: 500–1000 mg/24 h; and 4: >1,000 mg/24 h. P/Cr also was stratified into 4 groups, assuming a conversion value of 100 over 1 for statistical comparative analysis: 1: <0.3 mg/mg; 2: 0.3–0.5 mg/mg; 3: 0.5–1 mg/mg; and 4: >1 mg/mg. We further adjusted 24h-P for body surface area (BSA-adjusted 24h-P).

Statistical Analysis

Demographics were expressed as mean ± SD or median (interquartile range [IQR]) as appropriate. Linear regression and correlation between BSA-adjusted 24h-P and P/Cr were calculated by means of Pearson correlation coefficient. The agreement between both measurements was analyzed by means of the Bland-Altman method representing in a graphic the mean difference of each pair of values [15]. The Kaplan-Meier method was used to assess kidney graft survival, and the Cox regression hazard model was used to establish the risk of graft loss according to proteinuria thresholds. For each model, the dependent variable was time to transplant failure. Variables included in the multivariate analysis were donor and recipient age at the time of transplantation, recipient sex, cold ischemia time, waiting list time, glomerular filtration rate estimated by means of the Modification of Diet in Renal Disease 4 formula (eGFR), HLA mismatches, and type of donor (either living or deceased). For all tests, statistical significance was assumed at $P < .05$. Data were analyzed with the use of SPSS statistics software version 15.0 (SPSS, Chicago, Illinois).

RESULTS

Population and Correlation Analysis

Overall, 8,549 urine samples from 472 recipients with simultaneous proteinuria measurement by means of both methods were included for analysis. The mean number urine samples for each patient was 16 ± 9 samples. Baseline characteristics of the entire population are summarized in Table 1. The mean values were 0.48 ± 0.68 mg/mg for P/Cr and 0.59 ± 0.77 g/24 h for BSA-adjusted 24h-P.

Patients with higher 24h-P and P/Cr were older ($P = .002$ and $P < .001$, respectively) and received grafts from older donors (Table 2). Cold ischemia time and HLA mismatches were similar within groups (Table 2).

BSA-adjusted 24h-P and P/Cr correlation was good and significant ($r = .760$; $P < .001$).

Agreement Analysis

According to the Bland-Altman method, the agreement between 24h-P and P/Cr was not regular, and the proportional bias increased as proteinuria increased (mean difference −0.150, 95% confidence interval [CI] −1.51 to 0.68; $P < .001$; Fig 1). However, the agreement decreased for proteinuria values >1 g/24 h (mean difference −0.597 mg, 95% CI −3.97 to 5.86; $P < .001$).

Kidney Graft Survival

The median follow-up time after transplantation was 4.49 years (IQR 2.0–7.0). Death-censored graft survival analysis according to BSA-adjusted 24h-P showed worse graft survival for patients with proteinuria >0.5 g/24 h and >1 g/24 h (Fig 2A). Regarding graft survival according to P/Cr, again worse graft survival was observed in those patients with P/Cr >0.5 and >1 mg/mg (Fig 2B).

Cox proportional hazard models showed that BSA-adjusted 24h-P and P/Cr were both identified as independent risk factors for graft loss in patients with proteinuria >0.5 g/24 h or 0.5 mg/mg, respectively (Table 3).