

Research Article

Spot Urinary Protein to Creatinine Ratio as an Alternative Measurement for 24 Hour Urinary Proteins in Renal Transplant Recipients

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OPEN ACCESS**Keywords**

- Proteinuria
- 24 hr Urinary protein
- Spot protein to creatinine ratio
- Renal transplant

Abstract

Purpose: The cause of proteinuria after renal transplantation is complicated and needs continuous monitoring. Even though 24hr urine collection is cumbersome it is the best method available to estimate proteinuria and spot protein to creatinine ratio seems to be a simple, rapid alternative method to assess the protein excretion. The aim of the study is to determine the correlation between 24hr urinary protein (24UP) and spot protein to creatinine ratio (SPCR) in renal transplant recipients of Mahavir and KIMS Hospitals.

Method: The correlation and degree of bias between SPCR in random urine specimens and urinary protein excretion in 24-hr collections were analyzed in 183 renal transplant recipients.

Result: A very good correlation (Spearman correlation $r=0.986$, $P=0.0001$) was observed between 24hr urine protein and spot protein to creatinine ratio. Bland-Altman plot showed a good agreement at low levels and less agreement at higher level with a bias of 142.2mg and 95%CI limits of agreement from -442.8 to 727.3mg/day of protein. The measurement of agreement was strong between both the methods as shown by Kappa.

Conclusion: Spot Protein to creatinine ratio is a convenient, simple, accurate and rapid method that can be used as an alternative method for the estimation of proteinuria.

ABBREVIATIONS

UP: Urinary Protein; SPCR: Spot Protein to Creatinine Ratio; NKF: National Kidney Foundation; KIDOQI: Kidney Disease Outcomes Quality Initiative

INTRODUCTION

Proteinuria is very common after kidney transplantation. Glomerular disease causing proteinuria is associated with reduced kidney graft function [1]. The cause for post transplant

proteinuria is multifaceted, as it may originate from the allograft or from native kidneys, or may be due to various allograft pathologies, or may be a side effect of immunosuppressive medications. It is unclear whether proteinuria is due to focal glomerular disease or is indication of progressive proximal tubular dysfunction. Studies [2] show that 45% of renal transplant patients excrete protein even though it may not be in nephrotic range. Measurement of protein excretion is a useful predictive marker after renal transplantation adding information in addition offered by other biochemical, or histologic variables.

These possibilities deserve investigation, not only to better understand the prognostic implications of proteinuria, but also to investigate possible effective therapies. Thus, monitoring urine protein excretion after transplant [3] and investigating the cause of even low levels of proteinuria, would be helpful in early treatment.

Protein excretion varies in the course of the day, for this reason 24-hour urinary protein (24UP) has been considered as gold standard method for protein determination [4]. The collection of urine for 24 hours is cumbersome and error prone. An alternative method to quantify proteinuria is the measurement of protein to creatinine ratio (SPCR) in spot random urine specimen, a convenient method and is recommended by NKF, KIDQI guidelines [7-10]. Although the correlation between SPCR and 24UP has been established, previous studies suggested that this correlation varies in accordance with different levels of proteinuria [5,7,9,11]. The purpose of this study was to examine the correlation, degree of limits and the utility of the random urine protein to creatinine ratio with 24 hour proteinuria as the comparator in assessing proteinuria in renal transplant recipients with or without overt nephropathy and in the screening of the donors.

MATERIALS AND METHODS

Patients

A prospective observational study conducted between March 2010 and March 2013. Study was approved by the hospital ethical committee and obtained informed consent from all the patients. One hundred and eighty three (Male-118, Female- 65) renal transplant recipients with or without proteinuria aged above 18 years were included in the study. All patients were recruited at an outpatient clinic or during an in-patient stay in the Kidney Transplant units of Mahavir, and KIMS hospitals, Hyderabad, India.

Method for estimation of protein and creatinine in urine

Patients were instructed to collect the 24 hour urine accurately. Random urine sample was collected within two day period (either 5ml from the second sample of 24UP or random sample while depositing the 24hr sample) for measuring protein to creatinine ratio. The creatinine concentration in urine was determined by modified Jaffé's method and the concentration of protein in the urine was measured by turbidimetric method. Protein to creatinine ratio was calculated by dividing urinary protein (mg/dl) by urinary creatinine (g/dl).

Statistical analysis

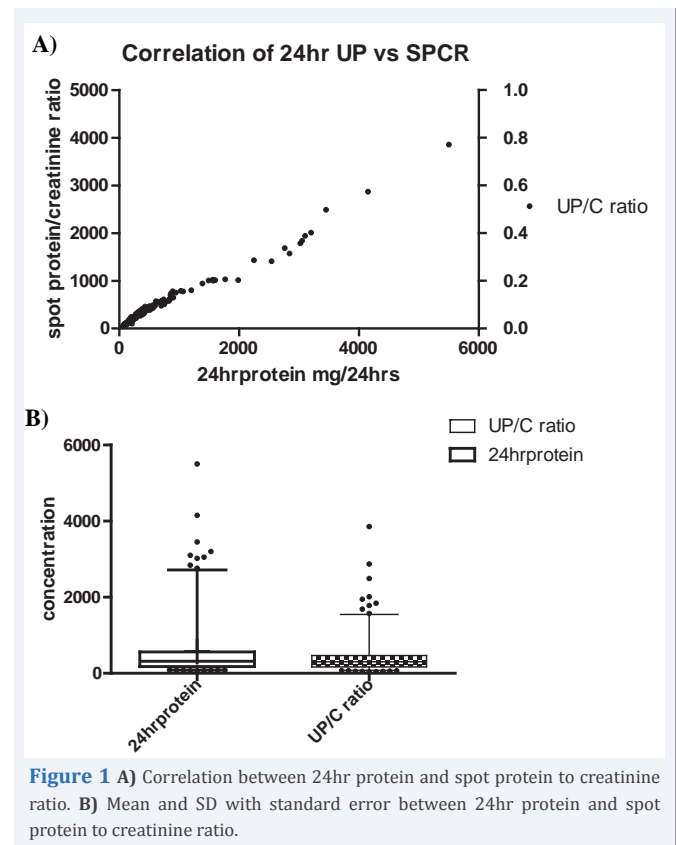
Data analysis was performed using SPSS version 18. The quantitative variables were expressed as mean and standard deviation. Spearman's correlation coefficient was used to find the correlation between 24UP and SPCR. A Bland-Altman assessment for agreement was used to compare the two methods [12] and ROC curve for agreement limits between the methods assessed using Prism Graph Pad 5.

RESULTS

From all the 183 patients urine was collected for both

Table 1: 24hr urine protein mg/day * spot protein/creatinine ratio Cross tabulation.

		spot protein/creatinine ratio			Total
		0 -500	501 -1000	>1000	
24hr urine protein mg/day	0 -500	125	0	0	125
	501 -1000	18	19	0	37
	>1000	0	4	17	21
Total		143	23	17	183



24hrsUP and spot protein to creatinine ratio. Protein levels were sub grouped into 1-500, 501-1000 and >1000mg/24hours (Table 1).

Spearman correlation with statistical significance observed between 24hour urinary protein and spot SPCR ($r=0.986$, $P=0.0001$) with 95% CI (0.981-0.989) Figure 1A, 1B. Using ordinal by ordinal the spearman correlation coefficient (SPSS) was 0.831 with a normal approximation of $P=0.0001$.

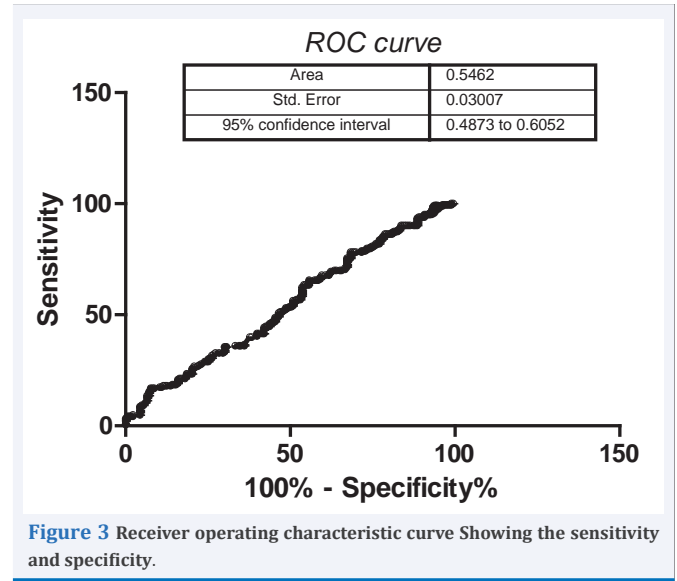
The degree of agreement in both the methods as shown in Bland -Altman plot (Figure 2), was poor at higher levels of excretion, while in the lower ranges the agreement was good with a Bias of 142.2mg/day with 298.49 SD of Bias and 95% CI limits of agreement from -442.8 to 727.3 mg/day. The inter-rater measurement of agreement Kappa was 0.721 ± 0.053 with an approximated ($P=0.0001$) indicating a strong agreement between the two methods Table 2.

Using the receiver operating characteristic curve (ROC), the area under curve is 0.546 with 95%CI of 0.487-0.605 and 0.845

with 95%CI of 0.770 -0.919 (Figure 3).

DISCUSSION

Quantification of urinary protein is very important in the management of renal transplant patients. The collection of 24 hour sample is unwieldy. Hence an alternative method for the measurement of protein which is also recommended by NKF, KIDOQI guidelines is required and there should be good agreement between both the methods. Spot urinary protein to creatinine ratio is a simple and rapid method which will be useful in quantifying proteinuria. Earlier studies have assessed the correlation between these two methods in patients with diabetic nephropathy [7, 9-13], renal transplant [14]. Tornng.S.etal [14] in their study of urine protein to creatinine ratio as a predictor of 24-h urine protein excretion in renal transplant patients stated that urine P/C ratio is a useful and convenient with high sensitivity (74.4-90%) and specificity values (93-98%) for estimating proteinuria from 0.5 to 2 g/day. However,they observed that the precision of estimation decreased as the level of urinary protein excretion increased to >3 g/day. The positive predictive value decreased as proteinuria became >3 g/day. Antunes et al. also observed, the greater the proteinuria, the lesser the correlation and adjustment between the different methods (7).Morales et al found good correlation and agreement for both the methods in



all renal function levels, however stated that there was a marked difference, and decrease in correlation as increase in urinary protein excretion(8).

The present study showed a good correlation between 24UP and SPCR in the lower ranges while showing less correlation as increase in the protein excretion; with a sensitivity of (68.5 – 100%) and specificity of 77.0 - 91.9% at 500 to 1500 mg /day and a decrease in the specificity to 30% as the level of protein excretion increased to 2500mg/day. As shown by Bland-Altman the two methods do not consistently provide similar measures because there is a level of disagreement at higher levels. The measurement of agreement Kappa based on normal approximation was 0.721 indicating a strong correlation between both the methods. There was no difference between the two distributions, as predicted by the ROC area under curve of 0.546 with smaller values indicating stronger positive prediction. As the excretion of protein increased the positive predictive value decreased.

It is well known that there is 40% variation in daily excretion of protein in addition 15% variation in repeated 24hr protein excretion [15]. Agrawal in his study observed a variation of 10% in day to day 24hr protein excretion to that of 2% in protein to creatinine ratio [16]. In the present study we observed a variation of 12% in 24hr protein excretion (Repeated sampling) to that of 3.5% in protein to creatinine ratio. This variability could be one of the reasons for this poor correlation at higher levels between the methods. In the present study we observed cutoff values for SPCR in predicting protein threshold excretion 487,845mg/mg (By calculating averages) reliably predicted 500 and 1000 mg/day of 24UP with high sensitivity and specificity which was similar to the earlier studies [17].

The present observational study for assessing the correlation between 24hr protein and protein to creatinine ratio in spot urine showed a good correlation which will be very helpful even in screening the voluntary donors (Data not shown). In conclusion, protein to creatinine ratio in random spot urine is a reliable, simple and convenient method to measure proteinuria. However, it may not be helpful in finding the accurate protein excretion especially in the nephrotic range.

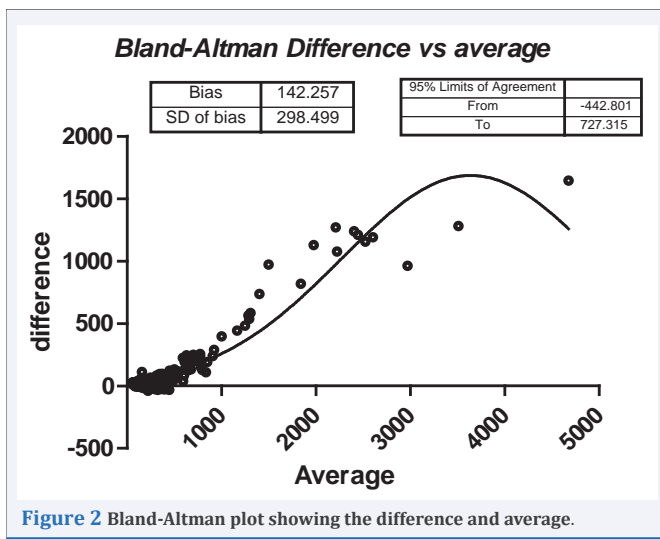


Table 2: Symmetric Measures of Correlation and Agreement.

		Value	Asymp. Std. Error ^a	Approx. T ^b	Approx. Sig.
Interval by Interval	Pearson's R	.882	.024	25.225	.000 ^c
Ordinal by Ordinal	Spearman Correlation	.831	.036	20.078	.000 ^c
Measure of Agreement	Kappa	.721	.053	13.109	.000
N of Valid Cases		183			

a. Not assuming the null hypothesis.
 b. Using the asymptotic standard error assuming the null hypothesis.
 c. Based on normal approximation.

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DISCLOSURE

Authors do not have conflict of interest to disclose and not funded by any commercial organization.

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