Is the Safety of Urıne Proteın to Urıne Creatınıne Ratıo ın Kıdney Transplant Receıvers as ın other Patıents wıth Kıdney Dıseases for Estımatıon of Daıly Proteınurıa?

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ABSTRACT

Background and aim: Quantitative 24 hour urinary protein excretion is the gold standard for the evaluation of proteinuria. However there are some problems in urine collection. An alternative to time urine collection is the use of spot samples for the calculation of the protein: creatinine ratio (Upr/Ucr) or the albumin: creatinine ratio (Ua/Ucr) . The aim of this study is to evaluate the Upr/Ucr ratio for 24 hours urinary protein excretion in patients with kidney transplantation receivers (KTrs), diabetic nephropathy (DN) and chronic glomerulonephritis (CGN).

Patients and Methods: Study group was consisted of one hundred ninety cases (90 females, 100 males, mean age 41.8 ±12.9 years). Upr and Ucr were measured in morning spot urine samples and SUpr/Ucr was calculated for each patient. Daily urinary protein excretion was measured in 24 hour urine samples. Glomeular filtration rate (GFR) was calculated by Cockroft Gault Formula.

Results: The spot morning Upr/Ucr was significantly correlated with 24 hours Upr excretion rate in all groups: p values were 0.92, 0.97 and 0.96 for DN, KTrs and CGN, respectively. The correlation in different levels of proteinuria: <1 g/day, 1-3 g/day and > 3 g/day were statistically significant ($p<0.001$). Similar correlations were found in different threshold for GFR: <30 ml/min, 30-60 ml/min and >60 ml/min.

Conclusion: Significant correlation was found between Upr/Ucr in spot urine and daily protein excretion. Daily proteinuria can be calculated as y= 1,09x + 0,095 (y= daily proteinuria, x= Spot Upr to Ucr ratio). We found that Upr/Ucr is a simple and valid method and can be used easily to detect daily proteinuria both in different degrees of proteinuria and also in different GFR levels in KTrs as in DN and CGN.

Keywords: 24 hoururine protein, chronic kidney disease, protein-creatinine ratio

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INTRODUCTION

Proteinuria is an important diagnostic and prognostic marker in patients with different renal disease as well as renal transplant receivers. It is used as both diagnostic and prognostic values in detection and confirmation of renal diseases or response to therapy. For renal transplant recipients, the assessment of protein and albumin excretion can indicate early disease such as transplant glomerulopathy or recurrent glomerulonephritis.(1) Because of protein excretion varies in the course of the day, 24-hours proteinuria (Up/24 h) has been accepted as the classic reference method to determine daily proteinuria (2). Urine collection is a problematic procedure for different reasons. 24 hour urine collection is cumbersome for patients and it is often collected incorrectly. Upr/Ucr in spot urine seems to be a reliable and simple diagnostic test to detect the urinary protein excretion. The Upr/Ucr is easy for patients and it is correlated with daily protein excretion. However the Upr/Ucr correlates well with 24-hour urine protein excretion there are two major limitations to the performance of this test. These include 1) the Upr/Ucr is heavily influenced by the urine creatinine concentration (the denominator of the ratio) and therefore by the total daily creatinine production, 2) urine protein excretion can vary throughout the day (especially resulting from exercise and posture) and from day to day. (3)

Urine albumin or protein-to-creatinine ratio in an untimed urine sample should replace the 24 h collection method to detect protein excretion according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines of the US National Kidney Foundation.

The aim of this study is to explore the diagnostic value of Upr/Ucr in spot urine sample to measure the daily proteinuria and to compare with 24 hours samples in KTrs and in patients with DN and CGN.

PATIENTS AND METHODS

One hundred ninety outpatients with proteinuria attending to nephrology outpatient clinic Cukurova University Hospital were included in this study. The mean age of patients was 41,8±12,9 years and female/male ratio was 100/90. Detailed history and clinical examination was carried out by physician. Patients were grouped into DN (n: 38), CGN (n: 47) and kidney transplantation receivers (n: 105). Patients were followed in outpatient clinic and they were trained to collect 24 hours urine and spot urine.

Urinary protein and urinary creatinine values were measured in spot and 24 h urine samples. A random urine sample was collected on next morning and after completion of 24 hour collection. Up/UCr ratio in spot urine was calculated by dividing the urinary protein concentration to urinary creatinine concentration. KTrs had been treated with steroid, tacrolimus or cyclosporine, and azathioprine or mycophenolate mofetil. The patients were stratified for GFR as >60, 30-59 and <30ml/min/1.73 m2.

The Spearman's correlation between the spot urine P/C ratio and 24 h urine total protein were performed by the Statistical Package for Social Science. $p<0.05$ was considered statistically significant.

RESULTS

The basic characteristics of the study population were shown in Table 1. The Up/UCr was significantly correlated with 24 hours Up excretion rate in all three groups: DN, KTrs and CGN and p values were 0.92, 0.97 and 0.96, respectively. As shown in table 1, direct and statistically significant correlation was observed between Up/24 h and Up/UCr in whole group (n=190).

When patients stratified according to GFR calculated as (>60, 30-59 and <30ml/min/1.73 m2) there were no differences between Up/24 h and Up/Ucr ratio in spot urine in all subgroups (table 2). Also we found similar important correlations between daily proteinuria and urine spot Up/ UCr ratio in 3 tertiles for proteinuria as < 1 g/day, 1-3 g/day, > 3 g/day, (table 3)

There were correlations with regression equation and line Rsq= r2= determination coefficient between spot Up/UCr ratio and Up/24 h in total 190 patients, and 3 groups which, KTrs, CGN and DN and these has been shown in figure 1. We found that daily proteinuria can be calculated with y= 1,09x + 0,095 in all patients (y= daily proteinuria, x= Spot Upr to Ucr ratio) formula.

DISCUSSION

The detection and quantification of proteinuria is of great importance in the management of patients with kidney disease. Proteinuria is an important risk factor not only for progression of renal failure but also for the development of cardiovascular disease in patients with chronic kidney disease (CKD) (4).

The collection of 24h urine is a complicated procedure and it is not always performed correctly. An easy and reliable method is the spot urine sample for the measurement of the Up/UCr ratio. Several studies have analyzed the correlation between Up/24 h and the Up/Ucr ratio in spot urine (2,5-12). The NKF K/KDOQI guidelines suggest that untimed spot urine samples should be used to detect and to monitor proteinuria in children and adults. The Up/UCr ratio in a random urine sample is a simple test, which is low-cost and easy to perform. We found a good correlation between the spot Up/ UCr ratio and daily proteinuria in KTrs as well as in patients with DN, CGN in our study.

Proteinuria is a predictor of progressive renal failure, graft loss and increased mortality in KTrs (13,14,15,16). In a retrospective multivariate analysis performed in over 450 KTrs, the degree of proteinuria was the most powerful predictor of the decline of creatinine clearance (17). On the other hand Biradar reported a positive correlation between the spot Up/ UCr ratio and Up/24h in patients with diabetic nephropathy ($r = 0.925$, $p < 0.0001$)(17). Ayman also showed the similar results as in our study in patients with DN, CGN and nephrotic syndrome (18). However Torng et al found positive predictive value of Up/UCr ratio in cases with daily proteinuria >3 g/day (19). In contrast to Torng's study we showed similar important correlations between all daily proteinuria levels between 24 h protein excretion and Up/ Ucr in spot urine. When we looked the similar studies in KTrs, sensitivity and specificity of the Up/UCr were between 74% and 99% and 73% and 99%, respectively (18,19,20,21,22). Cohall et al showed that significant correlations of protein to creatinine ratio in the Up/24 h, spot Up/Cr and Up/ 12 h AM- U/p 12 h PM samples on healthy populations. (23)

Spot urine albumin to creatinine ratio (Ualb/ UCr) and spot Up/UCr ratio have been found to be predictive for subsequent progression of renal disease in some studies (24,25,26). Up/UCr has been found to be more sensitive than Ualb/ Ucr ratio by Methven (27). However Ualb/ UCr ratio has been found to be more sensitive than spot Up/ UCr in diabetic patients in other studies (25, 26).

Albuminuria has been found to be associated with increased risk for cardiovascular mortality and morbidity and end stage renal disease in nontransplant patients. Similarly albuminuria has been found to be associated with declining kidney function, graft loss, and mortality in KTrs (28). Panek et al. (29) showed an association between Up/ UCr ratio and Ualb/ UCr ratio and outcome of graft loss, doubling serum creatinine and death in 500 KTrs. Both microalbuminuria and macroalbuminuria have been found to be independent predictors

of end-stage renal disease and death in KTrs in some studies (30) In our study we did not evaluated Ualb/ Ucr.

We found 8 studies in KTrs. Among these studies [9] both Up/UCr and Ualb/UCr have been evaluated in one (15, 31-35), Up/UCr in six and , [10] Ualb/UCr alone has been studied in one study. We used only Up/UCr.

The clinical significance of Up/UCr ratio has been shown in various disorders such as type 1 diabetes mellitus, non-diabetic renal failure, pregnancy, pre-eclampsia, renal transplantation and lupus nephritis. Although random Up/UCr ratio has been found as a reliable and practical way to measure and follow the proteinuria by some authors, its precision and accuracy may be affected by physical activity of the patient (32-36).

In our study, when stratifying by kidney function calculated by Cockcroft-Gault method, both determinations showed a very strong correlation with the different models divided into three tertiles (>60, 59-30 and <30ml/min/1.73 m2). Morales et al also found a similar association (36). We also found important correlations between daily proteinuria and urine spot Up/ UCr ratio in 3 tertiles for proteinuria as < 1 g/day, 1-3 g/day, and > 3 g/day as reported by Steinhäuslin et al (22)

In summary, daily proteinuria can be estimated as urine protein to urine creatinine ratio in spot urine sample in KTrs as in DN and CGN. Daily proteinuria can be calculated by fomula y= 1,09x + 0,095 (y= daily proteinuria, x= Spot Upr to Ucr ratio).

One of the limitations of the present study were not evaluated of Ualb/UCr ratio. Urine protein to urine creatinine ratio has also found to be safe for estimating daily proteinuria in patients with different levels of GFR and proteinuria. In kidney transplant receivers as in other renal disease the urine protein to urine creatinine ratio can be useful and safety screening test for proteinuria.

There is no conflict of interest

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Table 1: The mean age and the levels of blood urea nitrogen (BUN), serum creatinine (SCr), glomerular filtration rate (GFR), daily proteinuria (24h Up) and the ratio of urine protein to urine creatinine (Up/UCr) in kidney transplant receivers (KTrs), patients with diabetic nephropathy (DN) and chronic glomerulonephritis (CGN).

	KTrs Mean±SD Med (Min-Max)	DN Mean±SD Med (Min-Max)	CGN Mean±SD Med (Min-Max)	P	Totally Mean±SD Med (Min-Max)
Age	40,5±10,6 38 (21-66)	49,8±12,9 56 (21-70)	40,7±14,9 35 (18-83)	0,003	41,8±12,9 42 (18-83)
BUN (mg/dl)	17,3±6,8 17(6-45)	23,7±14,8 19,5(7-57)	20,6±16,2 15,5(2-73)	0,231	19,4±12,4 17(2-73)
Cr (mg/dl)	1,2±0,44 1,1 (0,57-3)	1,7±1,3 1,2 (0,49-4,6)	1,2±1,0 0,90 (0,48-5,5)	0,003	1,3±0,84 1,1 (0,48-5,5)
GFR (ml/min)	76,4±28,8 74,8 (26,7-203,5)	78,5±54,5 56,4 (16,9-219)	90,1±45,6 90,9 (14,7-204,3)	0,096	81,7±40,0 79,5 (14,7-219)
24h Up g/day	0,67±1,1 0,29 (0,02-6,1)	1,9±2,1 1,1 (0,06-8,3)	2,5±3,0 1,1 (0,06-11,3)	0,001	1,5±2,3 0,47 (0,02-11,3)
Uprot/Ucr	0,59±1,1 0,21 (0,05-6,6)	1,5±1,6 0,72 (0,04-5,8)	2,1±2,5 0,99 (0,08-8,9)	0,001	1,3±1,9 0,37 (0,04-8,9)

Table 2:The mean value and correlations between the ratio of urine protein to urine creatinine (Up/UCr) and daily proteinuria ın 24 hours urine (24h Up) in different values of glomerular filtration rate (GFR).

	Up/Ucr		24 hours Up (g/day)			
	Mean±SS	Med (Min-Max)	Mean±SS	Med (Min-Max)	**Cronbach Alfa değeri**	**p**
GFR <30 (n=20)	4,4±4,4	3,2(0,2-14,3)	3,8±3,3	3,2(0,2-10,3)	0,970	0,050
30-60 (n=40)	1,8±1,9	0,9(0,1-7,1)	2,2±2,7	2,7(0,1-10,6)	0,904	0,048
>60 (n=130)	0,8±1,6	0,2(0,0-10,8)	1,5±2,3	0,9(0,3-10,2)	0,988	0,0001

Table 3:The correlations between daily proteinuria and the ratio of spot urine protein to urine creatinine in 3 tertiles for proteinuria as < 1 g/day, 1-3 g/day, > 3 g/day

Proteinuria 24h (mg)	All	< 1 g/day	1-3 g/day	>3 g/day
N	190	125	32	33
SCC (r)	0,772	0,771	0,778	0,773

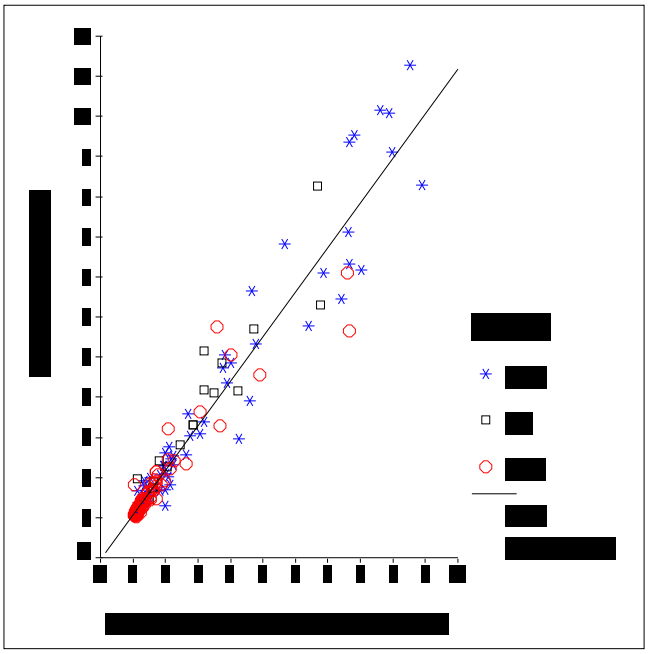

Figure 1: The correlations between daily proteinuria and the ratio of spot urine protein to urine creatinine in patients with chronic glomerulonephritis (CGN) and diabetic nephopathy (DN) and kidney transplant receivers (KTrs).