Fractional Excretion of Uric Acid as a Predictor for Saline Responsiveness in Long-Term Kidney Transplant Patients

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Key Words

Acute kidney injury • Kidney transplantation • Tubular transport • Uric acid

Abstract

Background/Aims: Subclinical hypovolemia may contribute to allograft dysfunction in long-term kidney transplant (KT) patients. In order to predict responsiveness to saline hydration, indices for tubular transport were investigated. **Methods:** Fifty-four clinically euvolemic long-term KT patients with recently aggravated azotemia were given intravenous hydration as follows: 0.9% saline 5 ml/kg over 1 h, followed by 0.9% saline 1 ml/kg/h over 12 h and 1 liter of 0.45% saline over the next 24 h. Serum and urine data were collected and analyzed to assess responses. **Results:** In all patients, saline hydration relieved azotemia, as shown by blood urea nitrogen (46.9 ± 17.2 vs. 39.3 ± 15.4 mg/dl; $p < 0.01$) and serum creatinine levels (2.9 ± 1.1 vs. 2.5 ± 1.1 mg/dl; $p < 0.01$) on day 0 versus day 2. In 38 patients, serum creatinine did not increase in the following month (70% responders). Compared with the nonresponders, the responders had a higher urine-to-plasma creatinine ratio and lower fractional excretion of sodium, uric acid and urea at admission. Multivariate logistic regression analysis revealed that responsiveness to

saline hydration was independently associated with lower fractional excretion of uric acid. **Conclusion:** Subclinical hypovolemia should be considered in long-term KT patients with azotemia of unexplainable causes. Fractional excretion of uric acid may predict responsiveness to saline hydration.

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Introduction

Kidney transplantation is the optimum treatment for many patients with end-stage renal disease [1]. Although 1-year transplant survival is excellent [2], most recipients experience chronic renal transplant dysfunction with time. Despite ever-improving immunosuppression, long-term renal allograft survival remains unchanged. Chronic allograft dysfunction in kidney transplant (KT) recipients is a clinically defined condition characterized by a slow, progressive decrease in the glomerular filtration rate, associated with de novo or aggravated hypertension and worsening proteinuria [3].

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Most late allograft failure is attributed to chronic allograft nephropathy (CAN), although that is a clinicopathological description not a specific diagnostic entity [4]. Its pathogenesis and treatment are largely unknown, and clinicians are frequently puzzled when they encounter unexplained azotemia in long-term KT patients. CAN is characterized histologically by interstitial fibrosis and tubular atrophy and is variably associated with fibrointimal thickening of the arteries within the transplanted kidney, as originally agreed in the Banff classification of 1997 [5]. This pathology is believed to be associated with tubular dysfunction such as salt wasting and defective urinary concentration.

In addition, sodium and water reabsorption in the proximal tubule may not be stimulated by renal sympathetic nerve activity when the kidney is denervated [6], and denervation of the donor kidney is inevitable in the transplantation procedure. Therefore, we postulated that patients with CAN may have defects in sodium and water conservation. Although volume depletion is a well-known reversible factor that interferes with renal function, it is difficult to assess volume status from the clinical setting and physical findings. Thus, intravenous fluid challenge is useful to test whether the patient is hypovolemic or not. In this study, intravenous saline was administered to long-term KT patients when their azotemia had been recently aggravated without any identifiable causes. In order to predict responsiveness to saline hydration, we investigated indices for tubular transport in long-term KT patients who are subclinically hypovolemic.

Methods

Patients

Patients with KT were enrolled between April 2007 and November 2010 at Hanyang University Hospital in Seoul, Korea. Eligibility criteria were as follows: time since KT >1 year, recently aggravated azotemia (serum creatinine increase $\geq 30\%$ during the last month), no signs of calcineurin inhibitor toxicity and no evidence of overt hypovolemia (including orthostatic hypotension). Patients were excluded if they were identified as having transplant renal artery stenosis, acute or chronic rejection, overt toxicity, systemic infectious disease, urinary tract obstruction or recurrent or de novo specific disease entities.

Study Protocol

On admission, all patients received 0.9% saline intravenously at a rate of 5 ml/kg over 1 h immediately after basal blood and urine sampling. This initial hydration was followed by 1 ml/kg/h of 0.9% saline over the next 12 h and 1 liter of 0.45% saline over the following 24 h. Other medication including immunosuppressants, antihypertensives and diuretics was maintained.

Table 1. Patient demographics

Patients	54
Age, years	48 $\pm$ 10
Males	33 (61%)
Time since transplant, months	145 $\pm$ 57
Underlying disease	
Diabetes mellitus	2
Hypertension	13
Chronic glomerulonephritis	18
Alport syndrome	1
Unknown	20

Data are means $\pm$ SDs or number of patients (percentage), as appropriate.

Serum and urine data were collected to examine allograft dysfunction on admission (day 0), day 1 and day 2 and at the 1-month follow-up. Blood urea nitrogen (BUN), serum creatinine, urine creatinine, uric acid and electrolytes were measured using an autoanalyzer (Hitachi 7600-210, Hitachi High-Technologies, Tokyo, Japan). A kinetic Jaffé method was used for creatinine measurement, and enzymatic methods were used to measure urea nitrogen and uric acid. Sodium, potassium and chloride concentrations were determined with ion-selective electrodes. As indices for tubular transport, the urine-to-plasma creatinine ratio (U/P_{Cr}) and fractional excretion of sodium (FE_{Na}), uric acid (FE_{UA}) and urea (FE_{urea}) were evaluated. They were calculated from the simultaneously obtained serum and urine samples. Because the goal of the saline hydration was to arrest the progression of azotemia, responders were defined as those whose serum creatinine did not increase in the following month.

Statistical Analysis

Results are expressed as means $\pm$ SDs or frequencies (and proportions), and data were analyzed with StatView 4.01 (SAS Institute Inc., Cary, N.C., USA). Groups were compared with the Wilcoxon signed-rank test for paired data or the Mann-Whitney U test for unpaired data. Differences were considered statistically significant at $p < 0.05$. Logistic regression was used to model odds ratios (ORs), and 95% confidence intervals (CIs) were employed as measures of the associations between responsiveness and basal parameters.

Results

A total of 54 patients completed the study and were included in the final analysis. The average age was 48 $\pm$ 10 years, and 33 of the patients (61%) were male. Other demographic characteristics including transplant duration and causes of native kidney disease are shown in table 1.

Figure 1 illustrates the changes in BUN and serum creatinine levels over the study period. On admission (day

Fig. 1. Changes in BUN and serum creatinine in the total patient population. Comparisons were performed using the Wilcoxon matched-pairs signed-ranks test. ^a $p < 0.01$ versus 1 month earlier; ^b $p < 0.01$ versus day 0; ^c $p < 0.05$ versus day 0. Cr = Serum creatinine.

0), the patients had significantly higher levels of BUN (46.9 ± 17.2 vs. 38.6 ± 14.2 mg/dl; $p < 0.01$) and serum creatinine (2.9 ± 1.1 vs. 2.3 ± 0.8 mg/dl; $p < 0.01$) than 1 month earlier. After saline hydration, BUN and serum creatinine decreased to 42.9 ± 17.0 mg/dl ($p < 0.01$) and 2.6 ± 1.1 mg/dl ($p < 0.01$), respectively, on day 1. This beneficial effect was maintained on the following day, with both BUN (39.3 ± 15.4 mg/dl) and serum creatinine (2.5 ± 1.1 mg/dl) remaining lower than at admission ($p < 0.01$ in each case). Although the relief of azotemia declined, levels of BUN (43.1 ± 18.7 mg/dl) and serum creatinine (2.7 ± 1.1 mg/dl) on day 30 were still lower than at admission ($p < 0.05$ for each).

However, the outcome on day 30 was not favorable in all patients. In 38 patients (70%), the serum creatinine level was not higher than at admission, whereas in 16 patients (30%) it had increased (fig. 2). If the former and the latter were defined as responders and nonresponders, respectively, responders had lower BUN (39.3 ± 17.3 vs. 52.1 ± 19.1 mg/dl; $p < 0.05$) and serum creatinine (2.4 ± 1.0 vs. 3.5 ± 1.1 mg/dl; $p < 0.01$) than nonresponders on day 30.

Interestingly, there were no significant differences in BUN and serum creatinine between responders and nonresponders on day 1 (BUN: 43.7 ± 18.5 vs. 40.8 ± 12.8 mg/dl; serum creatinine: 2.49 ± 1.12 vs. 2.87 ± 0.92 mg/dl) or day 2 (BUN: 39.5 ± 16.8 vs. 38.8 ± 11.5 mg/dl; serum creatinine: 2.35 ± 1.05 vs. 2.85 ± 1.00 mg/dl), or even 1 month prior to admission (BUN: 37.8 ± 15.3 vs. 40.5 ± 11.3 mg/dl; serum creatinine: 2.22 ± 0.88 vs. 2.50 ± 0.66 mg/dl).

Fig. 2. Distribution of patients by response to saline hydration, measured by the change in serum creatinine as follows: ΔCr = Serum creatinine at 1 month – serum creatinine on day 0.

We compared basal characteristics at admission between responders and nonresponders (tables 2–4). The two groups did not differ significantly with regard to age, gender, body mass index, transplant duration or proportions of immunosuppressant, antihypertensive and diuretic users (table 2). Our patients used small doses of prednisolone at admission, and BUN levels were not significantly different between responders and nonresponders (table 3). Interestingly, FE_{Na} was not significantly affected by the use of diuretics (diuretic users: $2.4 \pm 3.8\%$; diuretic nonusers: $2.9 \pm 2.6\%$). In contrast, FE_{UA} was lower in diuretic users than in diuretic nonusers (10.2 ± 9.1 vs. $15.4 \pm 10.3\%$; $p < 0.05$). FE_{urea} was also lower in diuretic users than in nonusers (29.7 ± 14.9 vs. $46.3 \pm 31.2\%$; $p < 0.01$). FE_{UA} was not significantly different between angiotensin receptor blockade users and nonusers (13.4 ± 7.7 vs. $13.6 \pm 11.5\%$).

Whereas BUN and serum creatinine did not differ significantly between the two groups at admission (table 3), serum albumin was higher in the responders than in the nonresponders (4.12 ± 0.44 vs. 3.80 ± 0.56 g/dl; $p < 0.05$). Table 4 presents a comparison of urinary indices at admission in responders and nonresponders. Responders had lower values of FE_{Na} (1.9 ± 1.8 vs. $4.3 \pm 4.5\%$; $p < 0.01$), FE_{UA} (11.0 ± 9.0 vs. $20.1 \pm 10.3\%$; $p < 0.01$) and FE_{urea} (33.8 ± 13.1 vs. $54.9 \pm 43.0\%$; $p < 0.05$) and higher U/P_{Cr} (41.1 ± 26.6 vs. 21.2 ± 13.8 ; $p < 0.01$) than nonresponders.

In agreement with these findings, some laboratory parameters at admission were associated with responsiveness to saline hydration (table 5). Univariate logistic re-

Table 2. Comparison of the profiles of responders and nonresponders

	Responders (n = 38)	Nonresponders (n = 16)	p value
Age, years	47 ± 11	50 ± 9	NS
Males/females	24/14	9/7	NS
BMI	23.0 ± 3.9	22.6 ± 3.2	NS
Diabetics	2	0	NS
Time since transplant, months	145 ± 58	145 ± 56	NS
Medication			
Prednisolone dose, mg/day	5.2 ± 1.2	5.6 ± 1.4	NS
Cyclosporine	33 (87)	15 (94)	NS
Calcium channel blockers	29 (76)	14 (87)	NS
Angiotensin receptor blockers	13 (34)	4 (25)	NS
Diuretics	14 (37)	6 (38)	NS

Continuous data are presented as means ± SDs. Other values represent number of patients (percentages). BMI = Body mass index; NS = not significant.

Table 3. Comparison of blood data at admission in responders and nonresponders

	Responders (n = 38)	Nonresponders (n = 16)	p value
BUN, mg/dl	47.8 ± 18.8	44.6 ± 12.7	NS
Creatinine, mg/dl	2.76 ± 1.13	3.05 ± 0.93	NS
Uric acid, mg/dl	8.09 ± 2.08	8.39 ± 2.22	NS
Hemoglobin, g/dl	10.7 ± 2.0	10.7 ± 2.0	NS
Protein, g/dl	6.87 ± 0.65	6.49 ± 0.83	NS
Albumin, g/dl	4.12 ± 0.44	3.80 ± 0.56	<0.05
Corrected calcium ^a , mg/dl	8.9 ± 0.5	8.7 ± 0.9	NS
Sodium, mEq/l	137 ± 5	139 ± 3	NS
Potassium, mEq/l	4.80 ± 0.69	4.36 ± 0.79	NS
Chloride, mEq/l	105 ± 4	106 ± 4	NS
Total CO ₂ , mEq/l	19.7 ± 4.9	21.1 ± 4.6	NS
Anion gap, mEq/l	12.9 ± 3.1	12.0 ± 4.4	NS
Cystatin C, mg/l	2.53 ± 0.77	2.82 ± 0.93	NS

Data are means ± SDs. NS = Not significant.

^a Corrected calcium = 0.8 × (4 – albumin) + serum calcium.

gression analysis revealed that responsiveness was associated with higher levels of serum albumin (OR 4.016, 95% CI 1.037–15.55) and U/P_{Cr} (OR 1.050, 95% CI 1.009–1.093) and lower levels of FE_{Na} (OR 0.755, 95% CI 0.578–0.985), FE_{UA} (OR 0.911, 95% CI 0.845–0.982) and FE_{urea} (OR 0.941, 95% CI 0.893–0.992). However, in multivariate logistic regression analysis, only the association between FE_{UA} and responsiveness was significant (OR 0.925, 95% CI 0.857–0.998). Thus, measurement of FE_{UA} could be useful for predicting whether unexplained progressing azotemia would be stabilized by saline hydration.

Discussion

In spite of all the improvements in immunosuppressive therapy, human leukocyte antigen matching and prevention and careful management of many of the risk factors for CAN, it remains the major cause of renal allograft failure [7, 8]. Allograft function in KT patients is routinely assessed by serum creatinine, urinary sediment analysis and routine biopsy [9]. However, renal tubule function is not usually evaluated in transplant patients, although the extent of tubulointerstitial lesions correlates with

Table 4. Comparison of urinary indices at admission in responders and nonresponders

	Responders (n = 38)	Nonresponders (n = 16)	p value
Urine Na ⁺ , mEq/l	66.9 ± 27.9	71.6 ± 23.5	NS
Urine K ⁺ , mEq/l	31.8 ± 14.0	23.7 ± 12.1	<0.05
Urine Cl ⁻ , mEq/l	55.8 ± 22.4	64.5 ± 23.0	NS
FE _{Na} , %	1.9 ± 1.8	4.3 ± 4.5	<0.01
FE _K , %	21.9 ± 16.0	39.8 ± 35.3	NS
FE _{Cl} , %	2.45 ± 0.88	2.9 ± 1.0	NS
FE _{UA} , %	11.0 ± 9.0	20.1 ± 10.3	<0.01
FE _{urea} , %	33.8 ± 13.1	54.9 ± 43.0	<0.05
U/P _{Cr}	41.1 ± 26.6	21.2 ± 13.8	<0.01

Data are means ± SDs. FE = Fractional excretion; NS = not significant.

Table 5. Logistic regression analysis for predictors of responsiveness to saline hydration

Predictor	Univariate analysis		Multivariate analysis	
	OR	p value	OR	p value
Serum albumin	4.016 (1.037–15.55)	0.044		
Urine K ⁺	1.052 (0.998–1.109)	0.058		
U/P _{Cr}	1.050 (1.009–1.093)	0.015		
FE _{Na}	0.755 (0.578–0.985)	0.038		
FE _{UA}	0.911 (0.845–0.982)	0.015	0.925 (0.857–0.998)	0.045
FE _{urea}	0.941 (0.893–0.992)	0.024		

Figures in parentheses represent 95% CIs.

long-term prognosis of organ function in many progressive renal diseases [10]. Tubulointerstitial damage begins soon after kidney transplantation due to ischemia-reperfusion injury, and resolution of this process is crucial for kidney outcome [11]. The present study suggests that subtle hypovolemia contributes to allograft dysfunction in a subset of long-term KT patients because a brief course of saline hydration induced a small but significant improvement in azotemia in our patients without overt aggravating factors.

Volume depletion is one of the major reversible causes of deteriorating serum creatinine concentrations in KT patients [1]. However, clinical assessment (e.g. physical examination) of dehydration is neither sensitive nor accurate. Although some urinary indices can be indicative of dehydration, there are no data on the appropriate values of urinary indices to allow one to determine what is abnormally low or high in KT patients. Thus, responsive-

ness to fluid challenge would be more useful for diagnosing volume depletion.

Our patients responded immediately to fluid challenge, suggesting that they were in a subclinical state of volume depletion. When we classified the patients as responders or nonresponders according to whether or not their azotemia was stabilized for the following month, 70% of them were found to be responders. It is possible that responsiveness to saline hydration lasts longer in patients with lesser degrees of tubular damage. Thus, we believe that our nonresponders may have suffered from more severe tubular dysfunction than the responders. It is notable that the use of diuretics was not significantly associated with the responsiveness to saline hydration in this study.

In agreement with this idea, nonresponders had lower U/P_{Cr} and higher FE_{Na}, FE_{UA} and FE_{urea} values than responders. In contrast, the degree of azotemia at admis-

sion did not differ in the two groups. It is interesting that tubular dysfunction may be dissociated from a decline in glomerular filtration rate in a subgroup of KT patients.

Many urinary indices indicative of tubular dysfunction have been used for differential diagnosis of acute kidney injury [12, 13]. For instance, FE_{Na} is useful to distinguish prerenal azotemia from acute tubular necrosis [14]. However, few data on the fractional excretion of solutes have been reported from KT patients, although FE_{Na} and FE_{urea} values have been evaluated in acute renal allograft rejection [15]. To the best of our knowledge, we report the significance of FE_{UA} in KT patients for the first time.

Many drugs and medical conditions can interfere with the accuracy of FE_{Na} [14]. In particular, diuretics inhibit the active transport of NaCl along the tubule and alter FE_{Na} . Likewise, drugs or disease entities that inhibit the active transport of urea will alter FE_{urea} . Cyclosporine, one of the most important immunosuppressants used in KT patients, has been suggested to interfere with the active transport of urea in the kidney [16]. Some of our patients were using diuretics at admission, and most were using cyclosporine. FE_{Na} was not significantly affected by the use of diuretics, probably because of associated tubulointerstitial lesions, whereas FE_{urea} and FE_{UA} were significantly lowered by diuretic use in this study. However, saline responsiveness was not associated with previous diuretic use. We investigated the independent roles of urinary indices, including FE_{Na} , FE_{urea} and FE_{UA} , in predicting saline responsiveness.

Although FE_{Na} and FE_{urea} were significantly different in responders versus nonresponders, neither FE_{Na} nor FE_{urea} were independently associated with responsive-

ness to saline hydration. Instead, responsiveness to saline hydration was independently associated with FE_{UA} . Uric acid has traditionally been used as a marker of proximal tubule reabsorption of sodium, and FE_{UA} decreases during volume contraction and increases during expansion [17, 18]. Serum uric acid increases by 1.0–1.4 mg/dl from subjects on a strict low-salt diet (approx. 20–50 mEq/day) to subjects on a high-salt diet (approx. 170–214 mEq/day) [19–23]. This short-term change is induced by altered renal uric acid excretion [21].

Changes in renal hemodynamics influence the tubular handling of uric acid by decreasing the flow rate or the uric acid concentration in the proximal tubular fluid [24]. Urea transport also occurs in the thin descending limb and inner medullary collecting duct as well as the proximal tubule [25]. These physiologic considerations seem to be compatible with our conclusion that measurement of FE_{UA} in long-term KT patients may be the most suitable method of predicting whether unexplained progressing azotemia will be stabilized by saline hydration. The combined use of FE_{Na} , FE_{UA} and FE_{urea} may increase the accuracy of assessment of volume status in the differential diagnosis of acute kidney injury [26]. We believe that the use of these urinary indices is an important means of assessing the reversibility of accelerated allograft dysfunction. Clinicians should take seriously subclinical volume depletion in long-term KT patients.

Disclosure Statement

No conflicts of interest declared.

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