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Original Article

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Renal tubular acidosis after kidney transplantation—incidence, risk factors and clinical implications

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Abstract

Background. Renal tubular acidosis (RTA) is a non-anion gap metabolic acidosis and is generally mild and asymptomatic in kidney recipients. Although calcineurin inhibitors, suboptimal allograft function, donor age and acute rejection have been associated with RTA, no detailed study has been conducted to investigate the prevalence and clinical implications of RTA in long-term kidney recipients.

Methods. In this cross-sectional study, we enrolled 109 patients (74 males, 35 females) for the study [patients with glomerular filtration rate (GFR) $<30\,ml/min/1.73\,m^2$, unstable allograft function, diarrhoea, and respiratory disease were excluded]. Thirty-six patients (33%) were found to have RTA on the basis of plasma bicarbonate, arterial pH, urine and serum anion gap measurements.

Results. Deceased donor transplantation [$P = 0.034$, 95% confidence interval (CI): 1.10–13.27], female gender ($P = 0.017$, 95% CI: 1.23–8.50), and lower GFR (55.8 ± 19.4 in RTA and $66.1 \pm 15.9\,ml/min/1.73\,m^2$ in non-RTA, $P = 0.002$, 95% CI: 1.10–13.27) were independent risk factors for RTA. Also, C-reactive protein was found to be higher in the RTA group (2.7 ± 1.5 *vs* $2.0 \pm 1.5\,mg/dl$, $P = 0.03$), while no difference was noticed in body mass index or serum albumin. Analysis of the prevalence of osteoporosis and osteopenia in patients with RTA and without RTA, respectively, revealed no difference in frequency of osteoporosis (33% *vs* 31%) or osteopenia (33% *vs* 47%).

Conclusion. Although long-term kidney recipients have a relatively high prevalence of RTA, it is usually mild and subclinical. Further studies are needed to clarify long-term effects of RTA in kidney recipients.

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Introduction

Metabolic acidosis is a common complication after kidney transplantation and it is mostly caused by renal tubular acidosis (RTA), especially in the early post-transplant period, due to suboptimal allograft function, calcineurin inhibitor (CNI) nephrotoxicity, acute rejection and ischaemic tubular dysfunction [1–13]. It is a non-anion gap metabolic acidosis and generally mild and asymptomatic. While RTA has not infrequently been reported in the early period of kidney transplantation, these were mostly case reports; there has been no detailed study defining risk factors and clinical implication of RTA in long-term kidney allograft recipients.

Osteoporosis, inflammation, negative protein balance and malnutrition seem to be associated with chronic acidosis in patients with chronic kidney disease [14–19]. National Kidney Foundation–Dialysis Outcome Quality Initiative (NKF–DOQI) guidelines have recommended routine measurement of serum total CO_2 in patients with stages 3–5 chronic kidney disease, and every 3 months up to 1 year after transplantation in kidney allograft recipients [20], with the aim of maintaining serum total CO_2 levels at $\geq 22\,mEq/l$. Though an overt acidosis due to uremia is generally expected to occur when the glomerular filtration rate (GFR) decreases below $30\,ml/min/1.73\,m^2$, RTA can occur in patients with a higher GFR level. In addition to lack of reliable information on the prevalence of RTA in long-term stable kidney allograft recipients, there has been a paucity of data regarding the clinical implication of RTA, including bone mineral density, inflammation markers and parathyroid function, in these subjects. Therefore, the aim of this study was to explore the prevalence, risk factors and clinical importance of RTA in long-term stable kidney allograft recipients.

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Patients and methods

This study is a cross-sectional study including adult kidney allograft recipients under the outpatient follow-up in our center who received first kidney transplantations between February 1993 and March 2005. We screened 135 patients and excluded 26 patients ($n=19$ due to poor graft function [GFR <30 ml/min/1.73 m^2], $n=6$ due to instable graft function, and $n=1$ due to chronic obstructive pulmonary disease). No patient was excluded due to diarrhea so that the final study population consists of 109 patients. The patients were on conventional maintenance immunosuppression including prednisolone + mycophenolate mofetil/azathioprine + cyclosporine (CsA)/tacrolimus (*n*, 101) or prednisolone + mycophenolate mofetil/azathioprine (*n*, 8). No patient was using any drug interfering with renal acid handling during the study (such as acetolazamide, sulfanilamide or amphotericin B). All patients gave written informed consent and the study was approved by the local ethics committee.

The demographic data and previous history of biopsy-proven acute rejection were obtained from the patients' charts. All patients also gave fasting venous blood samples for biochemical analysis. Plasma bicarbonate and pH were obtained from arterial blood gas analysis (radiometer ABL 700 series). C-reactive protein (CRP) was measured by nephelometric method (Dade Behring). Blood lipids, uric acid, haemoglobin and electrolytes including potassium (K), sodium (Na), chloride (Cl), calcium (Ca) and phosphorus (P) were measured by autoanalyser (Beckman LX 20). All fresh urine samples were analysed by urine autoanalyser (IQ-200 Iris). Intact parathyroid hormone (iPTH) was measured by means of radioimmunoassay using a commercial kit (Gamma-BCT Intact PTH immunoradiometric assay; IDS, Boldon, UK). Estimated GFR was calculated using Modification of Diet in Renal Disease (MDRD) equation. Body mass index (BMI) was calculated as the ratio of weight to (height)^2 (kg/m^2).

The patients with a plasma bicarbonate level <22 mEq/l were further analysed for urine anion gap and serum anion gap. For urine anion gap, first morning urine was analysed for Na, K and Cl. Urine anion gap (UAG) $=([Na^+]+[K^+])-[Cl^-]$ and serum anion gap (SAG) $=[Na^+]-([Cl^-]+[HCO_3^-])$ were calculated. An anion gap between 7 and 14 was regarded as normal.

RTA was diagnosed on the basis of low arterial bicarbonate (<22 mEq/l) and pH (<7.37) together with normal SAG and positive UAG. The patients with RTA were further differentiated to type 1 distal RTA if urine pH was >5.5 and serum potassium was low or normal, to type 2 if urine pH was <5.5 and serum potassium was low or normal, and to type 4 if serum potassium was high, >5.4 mEq/l. All patients with RTA (36) and a randomly selected 32 patients without RTA were also evaluated for BMD, which was measured by dual energy X-ray absorptiometry (DEXA) of lumbar spine (L2-4) and hip (g/cm^2, Hologic Discovery A, S/N 81461). Osteoporosis and osteopenia were defined using the WHO definitions (*T*-score -2.5 or below, and *T*-score between -1 and -2.5, respectively).

Statistical analyses were done using SPSS for Windows (version 11.0, Chicago, IL, USA). Student *t*-test and Fishers' exact test were used as appropriate for the comparison of the groups. Logistic regression analysis was used for independent risk factor for RTA. A *P*-value <0.05 was taken to indicate statistical significance.

Results

The mean age of recipients at transplantation was 38 ± 11 years, the dialysis vintage was 17.9 ± 17.8 months, and the mean post-transplant follow-up period was 74.6 ± 57.9 months. The primary renal diseases were chronic glomerulonephritis including IgA nephropathy in 38, chronic tubulointerstitial disease in 13, polycystic kidney disease in 3, diabetes mellitus in 3, hypertension in 9 and amyloidosis in 7, and unknown cause in 36 patients. While there were 101 patients on CNI, 8 patients were on CNI-free maintenance immunosuppression.

RTA was diagnosed in 36 of 109 patients (33%). When RTA and non-RTA groups were compared, GFR and bicarbonate levels were significantly lower in the RTA group. While deceased donor transplantation and female gender were seen more frequently in the RTA group ($P<0.05$), previous acute rejection and high iPTH levels had borderline significance ($P=0.06$ and $P=0.07$, respectively) between the groups. Serum CRP was also found to be higher in the RTA group ($P=0.03$). No significant difference was found in age, blood lipids, BMI, serum albumin, dialysis vintage or post-transplant follow-up duration between the groups (Table 1). While only one of eight patients with CNI-free immunosuppression developed RTA (12.5%), there were 35 patients of 101 (34.7%) using CNI with RTA ($P>0.05$).

Multivariate analysis revealed that low GFR, deceased donor transplantation and female gender were the independent risk factors for RTA (Table 2).

The patients with RTA were further evaluated regarding the existence or not of a higher rate of prevalence of osteoporosis and osteopenia in comparison to the non-RTA group. Thirty-six RTA and 32 non-RTA subjects underwent DEXA for BMD and there was no difference between the groups regarding either osteoporosis or osteopenia (Table 3). The control subjects with ($n=32$) and without ($n=41$) BMD evaluation showed no significant differences in GFR, age, sex, type of transplantation, duration of dialysis and transplantation, dose and use of CsA and tacrolimus, acute rejection, lipid levels, iPTH, BMI, serum bicarbonate, albumin and CRP (data not shown).

When urine pH and blood K levels were considered for differential diagnosis of RTA, 24 patients had type 1 RTA, 9 had type 2 RTA and 3 had type 4 RTA. Mean serum K levels were 5.5 ± 0.2, 3.9 ± 0.3 and 4.4 ± 0.4 mEq/l in type 4, type 1 and type 2 RTA, respectively. Urine pH levels were 6.0 ± 0.5 in type 1, 5.2 ± 0.4 in type 4 and 5.0 ± 0.2 in type 2 RTA. However, we did not perform further loading tests for more definite differentiation of types 1 and 2 RTA.

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Table 1. Clinical and laboratory findings of patients with or without RTA

	All patients ($n=109$)	RTA (+) ($n=36$)	RTA (−) ($n=73$)	*P*
Age	38 ± 11	36 ± 11	39 ± 11	0.15
Sex (F/M)	35/74	19/17	16/57	0.002
Tx type (DD/L)	21/88	11/25	10/63	0.04
GFR (ml/min/1.73 m^2)	62.7 ± 17.7	55.8 ± 19.4	66.1 ± 15.9	0.004
Post Tx time (month)	74.6 ± 57.9	76.8 ± 62.5	73.5 ± 55.9	0.78
Previous AR (+/−)	14/95	8/28	6/67	0.06
iPTH (pg/ml)	120.2 ± 75.6	146.2 ± 105.9	106.0 ± 47.6	0.07
Plasma HCO_3^- (mEq/l)	23.0 ± 2.5	19.5 ± 1.3	24.3 ± 1.4	<0.0001
Arterial pH	7.37 ± 0.03	7.34 ± 0.04	7.38 ± 0.02	<0.0001
Plasma chloride	106 ± 3	108 ± 3	104 ± 3	<0.0001
BMI (kg/m^2)	24 ± 4	23 ± 4	24 ± 5	0.49
Albumin (g/dl)	4.5 ± 0.3	4.4 ± 0.4	4.6 ± 0.3	0.24
CRP (mg/dl)	2.3 ± 1.5	2.7 ± 1.5	2.0 ± 1.5	0.03
CsA (+/−)	66/43	21/15	45/28	0.83
Tacrolimus (+/−)	35/74	15/21	20/53	0.19
Triglyceride (mg/dl)	163 ± 67	156 ± 73	166 ± 64	0.52
LDL-cholesterol (mg/dl)	103 ± 32	102 ± 36	104 ± 31	0.85
HDL-cholesterol (mg/dl)	58 ± 15	57 ± 13	58 ± 16	0.67
Uric acid (mg/dl)	6.7 ± 1.6	6.8 ± 1.7	6.7 ± 1.6	0.88
Systolic BP	131 ± 17	132 ± 16	131 ± 17	0.73
Diastolic BP	82 ± 10	82 ± 10	81 ± 9	0.60

RTA, renal tubular acidosis; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone; BMI, body mass index; CRP, c-reactive protein; AR, acute rejection; DD/L, deceased donor/living related; CsA, cyclosporine; BP, blood pressure.

Table 2. Risk factors in multivariate analysis for RTA

Variable	*P*	Exp (*B*)	95% CI
GFR (ml/min/1.73 m^2)	0.002	0.957	0.93–0.98
Female sex	0.017	3.239	1.23–8.50
Deceased donor Tx	0.034	3.834	1.10–13.27

Table 3. Osteoporosis and osteopenia in RTA and non-RTA patients

	RTA (+) ($n=36$)	RTA (−) ($n=32$)	
Osteoporosis	12 (33%)	10 (31%)	NS
Osteopenia	12 (33%)	15 (47%)	NS

While types of RTA were taken into consideration for osteoporosis and osteopenia, there were 9 and 8 (17 of 24 patients) patients in distal type 1 RTA, 3 and 2 (5 of 9 patients) in type 2 RTA and 1 and 1 (2 of 3) in type 4 RTA had osteoporosis and osteopenia, respectively. The difference was not significant.

Discussion

RTA is not an uncommon disorder in the early period after kidney transplantation, but information about its prevalence, clinical importance and risk factors in long-term allograft recipients is scarce. In the present cross-sectional study, prevalence of RTA was 33% in long-term stable kidney allograft recipients. GFR, female gender and deceased donor transplantation were found to be independent risk factors for RTA. While CRP level was significantly higher in the RTA group, there was no difference in osteoporosis/osteopenia between the groups.

Metabolic acidosis is a frequent complication after kidney transplantation and a major cause is RTA, which has been reported to be associated with early allograft dysfunction and CNI nephrotoxicity [1–13]. With dose reduction of CNI and functioning allograft, RTA appears to be resolved in the later post-transplant period. Although type 1 classic distal RTA has been reported more frequently in kidney recipients, type 2 and 4 were also seen in these patients [9,10]. Type 4 RTA can be related with diabetes mellitus (none of our patients), drugs which cause mineralocorticoid deficiency (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, CNI) and abnormal cortical collecting duct due to chronic tubulointerstitial damage. Tubulointerstitial injury due to rejection or CNI can also result in both type 1 and type 2 RTA in these subjects. It was demonstrated in pathological studies that chronic CNI nephrotoxicity can be seen as early as 3 months after kidney transplantation and it increases 60–70% in 2 years [21]. While almost two-thirds of interstitial fibrosis develops in the first year, subsequent fibrosis comes largely from CNI nephrotoxicity which can cause further long-term histological damage. Furthermore, chronic CNI nephrotoxicity is largely non-correlated with the renal functional change in early period and it becomes irreversible by the time an elevated serum creatinine was observed [21]. Therefore, chronic CNI nephrotoxicity may have an important role in the pathogenesis of RTA in long-term kidney allograft recipients. In our study,

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we found that only one patient developed RTA in patients with CNI-free protocol (12.5%), however, lack of sufficient patients with CNI-free protocol in our study precludes us to find any association between CNI and RTA. In the early period, with high doses of CNI, although type 4 RTA can be expected more frequently due to suppression of renin–angiotensin–aldosteron axis, in long-term, distal type 1 RTA can be more prevalent due to chronic CNI nephrotoxicity as we demonstrated more patients with distal classic type 1 RTA in long-term kidney recipients.

The clinical and experimental studies have demonstrated that chronic metabolic acidosis produces change in bone mineral composition, protein metabolism and insulin resistance [14–19]. Domrongkitchaiporn *et al*. [22], demonstrated that low bone mass is common among patients with distal RTA and that chronic metabolic acidosis results in suppression of bone formation and resorption, which in turn may contribute to the development of low bone mass in the non-transplant population. While major clinical manifestations are hyperchloremic acidosis, nephrocalcinosis, nephrolithiasis, growth retardation, bone disease in the primary form, the clinical nature, impact and behaviour of RTA after kidney transplantation are not precisely known.

Inhibition of osteoblastic activity, increased osteoclastic activity and blunted the response to growth hormone on bone, are well-known effects of chronic metabolic acidosis. It is recommended to screen for serum CO_2 or bicarbonate among patients with stages 3–5 chronic kidney disease, as well as in patients on maintenance dialysis [20]. Chronic metabolic acidosis contributes to renal osteodystrophy, and lower survival has been reported in these patients when compared to patients without acidosis [23]. Negative protein metabolism and decreased synthesis of amino acids associated with low pH have been shown. Increased insulin resistance also appears to be associated with chronic metabolic acidosis [14]. NKF–DOQI guidelines recommend measurement of plasma CO_2 every 3 months until 1 year post-transplant and maintenance of serum total CO_2 level, as a marker for metabolic acidosis, at >22 mmol/l. Plasma bicarbonate and plasma total CO_2 can be interpreted almost identically. In the present study, plasma bicarbonate was measured by blood gas analysis in stable long-term kidney allograft recipients in whom GFR was higher than $30\,ml/min/1.73\,m^2$. Measurement of BMD, which is recommended to be followed with DEXA, indicated that a majority of allograft recipients had osteopenia or osteoporosis in the late post-transplant period. BMD decreases in the early post-transplant period due to glucocorticoids, CsA/tacrolimus, immobilization, hyperparathyroidism and previous renal osteodystrophy; however, further worsening of osteopenia occurs up to 2 years post-transplant [19,20]. In our study, the majority of our patients had osteopenia/osteoporosis, as was shown in previous studies; however, we failed to show any association between osteopenia/osteoporosis and RTA. We have also shown that our patients with RTA had higher CRP levels in comparison to the non-RTA group; this association merits further consideration in long-term complications.

In this study, deceased donor transplantation, female recipient and lower GFR were found to be independent risk factors for RTA. It is obvious that renal tubular dysfunction is an essential mechanism in the pathogenesis of RTA, and patients with lower GFR and deceased donor transplantation naturally should have more tubular injury, which causes renal bicarbonate wasting or decrease in hydrogen ion secretion. In our analyses, female sex was an independent risk factor for RTA; however, we did not have any explanation for this association.

Limitations of this study include its cross-sectional nature, no previous detailed history of renal osteodystrophy, and lack of pre-transplant or early post-transplant BMD. Furthermore, it should be considered that many significant factors play a part in the development of osteopenia/osteoporosis in the post-transplant period. While RTA also contributes to this process, we could not show an important role in the cross-sectional evaluation. In a recent report of Pongchaiyakul *et al*. [18], no association between incomplete distal RTA and lower bone mass was found in healthy adults, which is compatible with our study including kidney allograft recipients. However, considering the difference in study population, it is difficult to extrapolate their findings to kidney allograft recipients. Another limitation of the study could be the lack of further differentiation of types 1 and 2 RTA on the basis of HCO_3 or acid loading tests (e.g. with NH_4Cl); however, we did not perform these tests.

In conclusion, RTA is a prevalent condition following kidney transplantation even in the late post-transplant period. Although there was no increased frequency in osteopenia/osteoporosis in those patients, long-term effects of acidosis and higher CRP levels should be considered.

Conflict of interest statement. None declared.

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