

Prevalence and risk factors of renal tubular acidosis after kidney transplantation

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Abstract

Objective: To assess the prevalence of post-transplant renal tubular acidosis (RTA) and its associated risk factors.

Methods: A cross-sectional study was conducted on 100 live related renal transplant recipients, with a transplant duration of more than one year and an estimated GFR > 40 ml/min/1.73m². Patients with acute graft rejection within last 6 months, unstable graft function, acute urinary tract infection and diarrhoea were excluded. Renal Tubular Acidosis (RTA) was diagnosed on the basis of plasma bicarbonate, venous pH, urine and serum anion gap measurements.

Results: Out of 100 patients (74 male, 26 female) RTA was observed in 40 (29 male, 11 female). Patients with RTA had a lower GFR (65.87±12.35 versus 74.23±14.8 ml/min/1.73m², P= 0.004) and higher number of previous acute rejections. Lower bicarbonate was associated with higher serum chloride (108.2±3.19 versus 105.72±3.9 mEq/L, P= 0.001) and higher potassium concentration (3.95±0.53 vs 3.61±0.46 mg/dl, P= 0.001). Higher phosphorous level (3.46±0.71 in RTA vs 3.19±0.59 mg/dl in non-RTA, P= 0.045) but lower total serum calcium concentrations were found in patients with RTA. Intake of angiotensin converting enzyme inhibitors (ACE I) was associated with the development of RTA. Calcineurin inhibitor (CNI) therapy was not associated with an increased likelihood of RTA. While no difference was noted in sex, age, pre-transplant dialysis duration, post transplant period, body mass index and serum albumin levels.

Conclusion: There is a high prevalence of RTA in renal transplant recipients. In most of the patients, this is sub-clinical and does not require treatment.

Keywords: Kidney transplantation; immunosuppression; renal tubular acidosis (JPMA 61:23; 2011).

Introduction

Renal tubular acidosis (RTA) is a medical condition that involves accumulation of acid in the body due to failure of the kidneys to appropriately acidify the urine.¹ RTA is a hyperchloraemic metabolic acidosis with a normal anion gap. It is usually asymptomatic and subclinical in renal transplant recipients.² Different factors associated with post transplant RTA include ischaemic damage, acute tubular necrosis, graft rejection and the use of cyclosporine A (CsA) or tacrolimus.³ The acid base balance and level of certain blood electrolytes and minerals are changed by these factors. In this way, RTA that occurs early following transplantation disappears spontaneously and is predominantly a sequel to acute renal failure.⁴ On the other hand, defects that appear in the late post transplant period are results of chronic rejection or CsA-induced nephrotoxicity.³ Secondary hyperparathyroidism, urinary tract infection and obstructive uropathy may also play a contributory urinary role in the pathogenesis of RTA. Although successful renal transplantation restores glomerular filtration rate (GFR) to some degree but other functions of transplant kidney such as renal acid/base handling may not be normal with an otherwise good functioning graft.⁵ Patients manifest with overt or compensated metabolic acidosis with low serum bicarbonate with or without

acidic serum pH respectively, during early post transplant period and in the long term following transplantation.⁶ Renal electrolytes and metabolism of muscles, bone and red blood cells are affected by persistence of acidosis.⁵

The prevalence, risk factors and clinical importance of RTA are not well known in renal transplant recipients.^{7,8} In 1967, Massary et al⁹ reported the first case of post transplant RTA and later described by other authors.^{10,11} In Pakistan, although some cases of RTA associated with osteomalacia and stone disease have been reported,^{12,13} but so far, to the best of our knowledge, no study has been conducted in transplant recipients. We aimed to find the prevalence of RTA in our transplant population and detect risk factors associated with it in stable renal allograft recipients.

Patients and Methods

A cross sectional study was conducted in live related renal allograft adult recipients, being treated as out patient clinic in Department of Transplantation at Sindh Institute of Urology and Transplantation (SIUT), Karachi. A total number of 100 patients with an estimated GFR > 40 ml/min/m² and transplant duration of more than one year were asked to participate in the study. Patients with unstable graft function, acute graft rejection < 6 months prior to study, acute urinary tract infection and

diarrhoea were not included in the study. Informed consent was taken from all patients and study was approved by the Ethical Review Committee.

Venous blood samples were processed to measure haemoglobin and electrolytes including sodium, potassium, calcium, phosphorus and chloride. Plasma bicarbonate and pH were obtained by venous blood gas analysis. Fresh urine samples were used for estimation of urinary pH and spot urinary electrolytes including sodium, potassium and chloride. Urine anion gap (UAG) = (Na+ + K+) - (Cl-) and serum anion gap (SAG) = (Na+) - (Cl- + HCO₃⁻) were calculated; and anion gap between 7 and 14 was regarded as normal. Estimated GFR was calculated using Modification of Diet in Renal Disease (MDRD) equation.¹⁴ Patient's medical records were looked to collect data regarding age, sex, post-transplant period, number of transplants, previous graft rejections, primary disease and drug intake (prednisolone, azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, rapamycin and ACE inhibitors).

Patients having normal plasma anion gap with serum pH less than 7.37 and bicarbonate less than 22 mmol/L together with positive urinary anion gap (UAG) were considered to have RTA. On the basis of serum potassium and urine pH, RTA was further differentiated to type I if urine pH was > 5.5 and serum potassium was low or normal, to type II if urine pH was < 5.5 and serum potassium was low or normal, and to type IV if serum potassium was high > 5.4 mEq/L.¹⁵ Statistical

calculations were performed using SPSS for Windows software version 10. Data are expressed as Mean ± standard deviation or percentage as appropriate. Categorical variables were confirmed using Chi-square test and continuous variables were confirmed using Student t-test. A p value less than 0.05 was considered to have statistical significance.

Results

Hundred renal transplant recipients were enrolled in the study, 74 male and 26 female. The underlying causes of primary renal diseases were stone disease in 14, hypertension in 8, glomerulonephritis in 5, Alport's syndrome in 1, APKD in 4, diabetes mellitus in 1 and unknown cause in 67 patients. Six patients had developed post transplant diabetes mellitus (PTDM). The mean age at time of transplant was 34.6±9.03 years, post transplant follow up period was 61.97±48.55 months and pre-transplant dialysis duration was 8.86±8.62 months. Five patients had more than one renal transplant. Immunosuppressive medicines being used are shown in Table-1. All of the patients were on maintenance prednisolone therapy. RTA was diagnosed in 40 (male 29; female 11) of 100 patients. When RTA and non-RTA groups were compared (Table-2), it was noted that patients with RTA had lower GFR (65.87±12.35 in RTA vs 74.23±14.8 ml/min/1.73m² in non-RTA, P= 0.004) and bicarbonate (17.7±2.73 in RTA vs 21.85±3.66 mmol/L, P < 0.0001) levels. Lower bicarbonate was associated with higher serum chloride (108.2±3.19 in RTA vs 105.72±3.9 mEq/L in non-RTA, P= 0.001) and higher potassium concentration

Table-1: Demographic Data and Immunosuppression protocol of RTA and Non-RTA group.

	All Patients (n= 100)	RTA (n= 40)	Non-RTA (n= 60)	P
Mean Age (years)	34.65 ± 9.03	35.58±9.37	34.03±8.82	0.406
Sex (Male/Female)	74 / 26	35.58±9.37	45 /15	0.819
Mean Transplant age (months)	61.97±48.55	29 /11	57.53±49	0.265
No. of Transplants (1/2)	95 / 5	68.62±47.70	58 / 2	0.349
Azathioprine	62	23	39	0.449
Cyclosporine A	66	28	38	0.491
Mycophenolate Mofetil	36	16	20	0.496
Tacrolimus	5	2	3	1.000
Rapamycin	6	2	4	0.731

Table-2: Laboratory findings of patients with and without RTA.

	All Patients (n= 100)	RTA (n= 40)	Non-RTA (n= 60)	P
Creatinine (mg/dl)	1.20±0.22	1.27±0.24	1.16±0.19	0.020
MDRD-GFR (ml/min/1.72m ²)	70.89±14.41	65.87±12.35	74.23±14.8	0.004
Plasma chloride (mEq/L)	106.68 ±3.83	108.20±3.19	105.72±3.9	0.001
Plasma bicarbonate (mmol/L)	20.22±3.92	17.70±2.73	21.85±3.66	0.000
Blood pH	7.35±0.037	7.32±0.029	7.36±0.03	0.000
Serum potassium (mg/dl)	3.75±0.51	3.95±0.53	3.61±0.46	0.001
Serum albumin (mg/dl)	4.03±0.40	4.06±0.42	4.01±0.38	0.600
Serum phosphorus (mg/dl)	3.30±0.66	3.46±0.71	3.19±0.59	0.045
Serum calcium (mg/dl)	9.36±0.55	9.27±0.44	9.41±0.60	0.220

Table-3: Comparison of characteristic features of RTA and Non-RTA groups.

	All Patients (n= 100)	RTA (n= 40)	Non-RTA (n= 60)	P
Pre-Tx HD Period (months)	8.86±8.62	7.68±6.16	9.65±9.90	0.432
Body mass index (kg/m ²)	22.93±4.41	23.47±5.51	22.56 ±3.50	0.315
Previous rejection	12	8	4	0.044
CAN	11	6	5	0.297
CsA dosage (mg/kg/day)	1.21±1.18	1.31±1.24	1.15±1.5	0.491
ACE I	27	16	11	0.017
Diabetes mellitus	7	4	3	0.337

Pre-Tx HD= Pretransplant haemodialysis. CAN: Chronic Allograft Nephropathy. CSA: Cyclosporine A. ACEI= Angiotensin converting enzyme inhibitor.

(3.95±0.53 in RTA vs 3.61±0.46 mg/dl non-RTA, P= 0.001). Higher phosphorous (3.46±0.71 in RTA vs 3.19±0.59 mg/dl, P= 0.045) but lower total serum calcium (9.27±0.44 in RTA vs 9.41±0.60 mg/dl in non-RTA) concentrations were found in patients with RTA. RTA group showed high rate of previous acute rejections (20% vs 6.66%, P= 0.044) with comparison to non-RTA group (Table-3). ACE inhibitors were being used more frequently in patients with RTA (40% in RTA vs 18.3% in non-RTA, P= 0.017). Sixty six percent of patients were on CsA therapy with mean dosage of 1.21±1.18 mg/kg/day. It was noted that CNI therapy was not associated with development of RTA. No significant difference was found in sex, age, BMI, serum albumin, pre-transplant dialysis duration or post-transplant follow up period between the groups. On the basis of urinary pH and serum potassium; 26 patients had type 1 RTA, 15 had type 2 RTA and 1 had type 4 RTA.

Discussion

In our study, prevalence of RTA was found to be 40% in long term stable allograft recipients, that is comparable with the observation of some other authors.^{7,10,15} In a study done by Keven et al,¹⁵ 33% of transplant recipients were found to have RTA. In another study by Schwarz et al⁷ RTA was present in only 13% of the transplant recipients, which differs significantly from our study. The pH value set to define RTA was 7.35 in the study by Schwarz et al, so a smaller number of patients were found to have RTA. We used a higher cutoff pH 7.37, which was also used by Keven et al and nearly similar prevalence of RTA was observed by us. By using a cutoff value of pH <7.35, prevalence of RTA in our study was 28%. Several factors associated with post transplant RTA include ischaemic tubular damage, reduced renal mass for few months post transplant, chronic transplant rejection and CNI nephrotoxicity.¹⁶⁻¹⁸ It has also been suggested that alloantigens trigger direct immune mediated mechanism leading to RTA, by means of specific interference with molecules involved in tubular acid handling or resulting in global damage of tubulointerstitial structures.⁵ A defect in proximal tubule ammonia synthesis due to insulin resistance may lead to metabolic acidosis secondary to immunosuppressive drugs such as corticosteroids and CNI.^{5,19} Patients with secondary hyperparathyroidism before

transplantation, tend to develop post transplant RTA because high PTH activity causes leak of bicarbonate from the proximal tubules that affects urine acidification.^{8,10}

Several immunosuppressive drugs have been implicated into the pathogenesis of post transplant RTA mainly CNI, such as cyclosporine A and tacrolimus.^{16,17} The immunosuppressive effect of CsA is mediated by a calcineurin-inhibitory complex with its cytosolic receptor, cyclophilin A. CsA also inhibits peptidyl prolyl cis-trans isomerase (PPIase) activity of cyclophilin A, which is required for its nephrotoxic effects. In intercalated cortical collecting duct cells, PPIase of cyclophilins is required for hensin polymerization which is also inhibited by CsA.¹⁸ The transformation of intercalated cells from bicarbonate secretion (β -type intercalated cells) to acid secretion (α -type intercalated cells) is regulated by hensin depending on the acid/base status.²⁰ By this mechanism the indirect inhibition of hensin by CsA via above mentioned mechanism may lead to distal RTA during acidosis. Chronic CNI nephrotoxicity leads to long-term histological damage which is not exactly estimated by the change in renal function and that becomes mostly irreversible by the time an elevated serum creatinine is noted.³

In the present study, 30 (75%) of 40 patients with RTA were on CNI therapy while 10 (25%) were on CNI free immunosuppressive therapy. It was found that CNI therapy was not associated with an increased likelihood of RTA. This can be explained by the fact that due to better HLA match and living donor; mean CsA dosage being used in our transplant population was low which could have been a factor in preventing CNI nephrotoxicity. Schwarz et al⁷ and Yakupoglu et al¹⁹ have also found no association between CsA therapy and development of RTA. These authors have described some association of tacrolimus with RTA in comparison to CsA. We were unable to find such an association as number of patients on tacrolimus therapy in our study population was very small (5%).

Past episodes of renal allograft rejections have also been associated with RTA.² In our study 25% of patients with RTA had previous acute rejections, while in non-RTA group it was 7% patients. Keven et al¹⁵ have shown that previous acute

rejection was marginally different between RTA and non-RTA patients, while Schwarz et al⁷ found that 50% of the patients in RTA group had history of past acute rejections.

In renal transplant recipients, classic distal RTA has been described as a predominant form, but type 2 and 4 were also seen in these patients.^{7,10,16} We also observed similar results which coincide with findings of Keven et al.¹⁵ Type 4 RTA is associated with diabetes mellitus, drugs causing mineralocorticoid deficiency like ACE I, angiotensin receptor blockers (ARBs); and cyclosporine A. Schwarz et al⁷ showed that treatment with RAAB (renin angiotensin aldosterone blocker) is responsible for RTA in approximately 25% of the patients. We also observed that intake of ACE I had a significant association with the presence of RTA. ACE I and ARBs can induce type 4 RTA. In this condition impaired ammoniogenesis leads to acidification defect and is characterized by a normal ability to acidify the urine after an acid load associated to a subnormal net acid excretion due to very low rates of NH₄ excretion. At normal plasma HCO₃⁻ concentration there is reduced reabsorption of renal bicarbonate. Although hyperkalemia itself mainly causes the decrease in NH₃ production, important contributory roles may also be played by aldosterone deficiency or resistance.²¹

Patients with end stage renal disease (ESRD) have a broad spectrum of bone disorders and osteopenia, which may worsen after renal transplantation secondary to immunosuppression with corticosteroids or CNI. Bone mineral density can be lost after successful renal transplant and there is an increased risk of fracture in this group of population.²² Metabolic acidosis has got a contributing effect in the pathogenesis of post transplant bone disease.¹⁹ It induces calcium excretion and reduces renal synthesis of 1,25(OH)₂D₃ which causes PTH release. In this way homeostatic relationship between blood ionized calcium, PTH and 1,25(OH)₂D₃ is disturbed leading to exaggerated bone dissolution. Yakupoglu et al¹⁹ has reported that lower serum bicarbonate was related with higher serum phosphate and PTH concentration and lower serum calcium. Similar results were obtained in our study, where it was found that lower serum bicarbonate was associated with higher serum phosphorus and lower calcium concentration although we did not measure serum PTH levels in our study population.

In the presented study, GFR was found to be lower in RTA group as compared to non-RTA group, which is consistent with the findings of Keven et al¹⁵ and Schwarz et al.⁷ Patients with lower GFR have got tubular dysfunction which is an essential mechanism for the development of RTA, leading to renal bicarbonate wasting or decrease in hydrogen ion secretion.¹⁵ In a study done by de Brito-Ashurst et al,²³ was observed that oral sodium bicarbonate supplementation in patients of chronic kidney disease (CKD) with low plasma HCO₃⁻ levels slows the rate of decline of renal function and the

development of ESRD. Another study has shown that patients of CKD with persistent uncorrected low bicarbonate levels between 16 and 21 mmol/L experienced an annual decline in their estimated GFR of >3 ml/min compared with 1 ml/min in those with bicarbonate levels >22 mmol/min.²⁴ In our study, plasma bicarbonate was found to be <18 mmol/L and <15 mmol/L in 32% and 12% respectively in patients of RTA group. For assessment of the effect of base supplementation, renal transplant patients should be followed by the NKF-K/DOQI guidelines for maintenance of serum bicarbonate levels at 22 mmol/L or greater.^{19,25}

Conclusion

It is concluded that a considerable number of renal transplant recipients with stable graft function have RTA, however a smaller number of patients with RTA require treatment. Previous acute graft rejection and use of ACE I was associated with the development of RTA, while CNI therapy was found to have no such association. Further studies are needed to demonstrate the effect of bicarbonate therapy in renal transplant recipients with RTA.

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