Clinical Evaluation of Chinese Patients with Primary Distal Renal Tubular Acidosis

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Abstract

Objective Distal renal tubular acidosis (dRTA) is a hyperchloremic metabolic acidosis disorder characterized by a normal anion gap with abnormal urinary hydrogen (H^+) excretion. At present, there are few available reports regarding the clinical status of primary dRTA. The primary objective of this study was to analyze the clinical features and outcomes of primary dRTA.

Methods This was a retrospective study performed in patients with primary dRTA who were hospitalized at Ruijin Hospital between March 1996 and July 2009; the clinical features of these patients were analyzed.

Results This study included 95 consecutive inpatients: 40 men (42.11%) and 55 women (57.89%). Among them, 60 had hypokalemia (63.12%), 29 had complete dRTA and 66 had incomplete dRTA. The mean urine calcium levels of the patients with and without urinary lithiasis were 0.10 ± 0.04 and 0.07 ± 0.05 mmol/24 h·kg, respectively ($p=0.04$). The blood pH values of the patients with and those without bone disease were 7.37 ± 0.06 and 7.32 ± 0.06 , respectively ($p=0.01$). A total of 8.33% (8/27) of the patients had tubular proteinuria.

Conclusion Hypokalemia is the most common clinical manifestation of primary dRTA. Primary dRTA can also be accompanied by proximal tubular dysfunction. Controlling the urine calcium and citrate levels is crucial for the treatment of nephrocalcinosis and/or nephrolithiasis, while restoring the blood pH to the normal level is essential for controlling bone disease.

Key words: primary distal renal tubular acidosis, hypokalemia, kidney stones

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Introduction

Distal renal tubular acidosis (dRTA) is a hyperchloremic metabolic acidosis disorder characterized by a normal anion gap with abnormal urinary hydrogen (H^+) excretion. The pathogenesis of this disease is due to the dysfunction of α -intercalated cells located in collecting tubules that secrete protons into the tubular lumen (1). Patients with dRTA also present with alkaline urine, hypokalemia, nephrolithiasis and chronic acidosis. These conditions significantly impact the quality of life in untreated individuals and can lead to growth failure, osteoporosis, rickets and even renal insufficiency (2-5). Clinically, dRTA can occur as a primary or secondary disease (4). Primary dRTA often appears in inherited and sporadic forms (6); however, few published data are

available regarding the clinical manifestations of primary dRTA (7).

The objective of this study was to elucidate the clinical features of primary dRTA by analyzing the clinical data of 95 primary dRTA patients hospitalized at Shanghai Ruijin Hospital between March 1996 and July 2009.

Materials and Methods

The records of patients with primary dRTA treated at Shanghai Ruijin Hospital between March 1996 and July 2009 were reviewed.

Patients with hypokalemia or recurrent kidney stones were suspected to have dRTA. The diagnosis of dRTA was made primarily based on the clinical phenotype, history, hematological indices and results of urinary acidification

tests (4, 8-10). Information regarding sex, age at diagnosis, duration from onset to diagnosis, initial symptoms and symptoms correlated with hypokalemia, bone disease and manifestations of kidney injury was also referenced. In addition, data for family history, work history, previous disease records, medication history (i.e., herbs containing aristolochic acid, antibiotics, cotton-seed oil and analgesics), history of urinary tract infections and history of urinary lithiasis were collected.

The laboratory examinations included measurements of the red blood cell count, a urinalysis, liver and renal function parameters, an artery blood gas analysis, the levels of alkaline phosphatase, glucose, parathyroid hormone, blood and urine synchronic electrolytes (i.e., sodium, potassium, chlorine, calcium, phosphonium and carbon dioxide combining power) and urine protein electrophoresis. The urine titratable acid assay was performed to determine the renal acidification function by testing the urine pH, HCO_3^- , titratable acidity (TA) and NH_4^+ . Immunoassays for immunoglobulins (i.e., IgG, IgA and IgM), rheumatoid factor, anti-nuclear antibodies, anti-single strand DNA, anti-dsDNA, anti-SSA, anti-SSB, anti-ribonucleoprotein, anti-Smith antibodies, cryoglobulin, antimitochondrial antibodies and hepatitis B virus serum markers as well as a cold agglutination test were performed to exclude a diagnosis of secondary dRTA and/or other genetic diseases that could result in secondary dRTA.

Chronic kidney disease (CKD) was diagnosed and staged according to the K/DOQI guidelines. The kidney function of patients older than 16 years of age was evaluated using the Cock-Gault and simplified MDRD formulas, whereas that of patients younger than 16 years of age was evaluated using the Schwartz formula.

The imaging examinations consisted of kidney ultrasound, measurement of left-hand wrist bone age, chest, skull, pelvic, lumbar, vertebral and long bone X-ray and kidney, ureter, bladder and intravenous pyelography. If dilatation of the ureter or hydronephrosis without stones were found on kidney ultrasound, computed tomography was performed. If necessary, magnetic resonance imaging of the lumbar vertebrae and an examination of the bone mineral density (BMD) were performed. Patients with osteoporosis, pathological bone fractures or bone deformities and retardation of bone age in children were diagnosed with bone disease. EKG was also performed.

dRTA was diagnosed based on the following criteria: (1) hyperchloremic metabolic acidosis with a normal anion gap (AG)(blood $\text{AG} 12 \pm 2$ mmol/L, blood $\text{Cl}^- > 105$ mmol/L, blood $\text{pH} < 7.35$ or $\text{HCO}_3^- \leq 22$ mmol/L); (2) the inability to lower the urinary pH (urine $\text{pH} > 6$), even with severe metabolic acidosis; (3) a reduction in the levels of urine TA and NH_4^+ on urine acidification function tests (urine titratable acid assay)(urine TA < 10 mmol/L, urine $\text{NH}_4^+ < 25$ mmol/L); (4) results of ammonium chloride loading tests in patients with a blood pH of > 7.35 . Ammonium chloride (0.1 g/kg) was administered orally for three days. On the third day, the blood

carbon dioxide combining power (CO_2CP) and blood and urinary pH values were determined. A patient was defined as dRTA-positive if the blood pH and CO_2CP decreased while the urine pH exceeded 5.5 (11-13) and was diagnosed with incomplete dRTA. dRTA patients with a blood pH of < 7.35 were diagnosed with complete dRTA (5). Patients whose disease was considered to be a secondary form of dRTA, such as Sjögren's syndrome, obstructive uropathy, chronic active virus hepatitis or drug-induced nephropathy, were excluded (13). (6) Patients with a wide anion gap and high urine pH with a reduced eGFR were included when the Δ change in blood bicarbonate exceeded the Δ change in the blood anion gap.

The procedure for the urine titratable acid assay was as follows. Fresh urine was collected in the morning. The Urine pH, HCO_3^- , titratable acid and NH_4^+ values were tested within 30 minutes. The urine pH was measured at room temperature. A total of 5 mL of HCl of 0.1 molarity was added to 10 mL of urine, and the specimen was placed in boiling water for 15 minutes, after which it was cooled. The urine was titrated with 0.1 molarity NaOH to the original pH, and the amount of NaOH was recorded in order to calculate the level of HCO_3^- . The urine was then titrated with 0.1 molarity NaOH to a pH of 7.4, and the amount of NaOH was recorded in order to calculate the level of titratable acid. A total of 10 mL 8% methanol at a pH of 7.4 was added to the specimen, and the solution was mixed. The mixture was subsequently titrated with 0.1 molarity NaOH to a pH of 7.4, and the amount of NaOH was recorded in order to calculate the level of NH_4^+ .

Statistical analyses

The SPSS version 11.5 software program was used for all the statistical analyses. The values are expressed as the mean $\pm$ standard deviation ($X \pm \text{SD}$). The level of statistical significance was set at $p < 0.05$.

Results

Between March 1996 and July 2009, a total of 380 patients were diagnosed with dRTA. Most cases were secondary dRTA (285/380, 75%), and the most common underlying cause was Sjögren's syndrome (118/285, 41.4%). Other common causes included aristolochic acid nephropathy, medullary sponge kidney, drug-induced dRTA, HBV infection, etc. A total of 95 cases were primary dRTA (95/380, 25%), most of which were sporadic (88/95, 92.6%).

Clinical manifestations

A total of 95 patients were enrolled in the present study. The mean age was 38.79 ± 20.32 years (2-82 years). There were 40 men (42.11%, mean age 37.55 ± 19.95 years) and 55 women (57.89%, mean age 42.87 ± 19.39 years). There were no significant statistical differences between the mean ages ($p = 0.19$). Among the 95 patients, 14 were children (< 18 years), including two patients from consanguineous families,

Table 1. Common Clinical Manifestation Analysis of 95 Cases

	manifestation	number	Percentage (%)
common clinical manifestation	muscle weakness	65	84.2
	overdrinking due to thirst and diuresis	22	23.16
	paralysis	30	32.00
	anorexia	13	13.68
	arthralgia	10	10.53
	dyspnea	11	11.58
	muscle ache	10	11.00
	acroanesthesia	18	18.95
	palpitation	11	12.00
	tic of limbs	9	9.47
	growth retardation in children	9/14	64.29
	increased nocturia	39	41.05
	urinary infection	6	6.32
	urinary lithiasis	11	11.58
renal involvement manifestation	kidney calcification	4	4.21
	eGFR<60ml/min/1.73m ²	28	29.47

Table 3. Analysis of Renal Tubular Function

	No.	%
complete RTA	29/95	30.5
incomplete RTA	66/95	69.5
Nephrogenic diabetes insipidus	1/95	1.05
tubular proteinuria	8/27	29.6
Increased urine β_2 microalbumin	12/28	42.9
Increased NAG	11/53	20.7
Increased RBP	15/39	38.5

both of whom were 17-year-old boys (one patient exhibited neural hearing loss in the right ear). The mean systolic pressure and diastolic pressure values were 121.33 ± 17.23 and 77.25 ± 11.96 mmHg, respectively.

The most common manifestations of dRTA included fatigue, increased nocturia, flaccidity and overdrinking due to thirst and diuresis. In this study, one patient had torsades de pointes. In addition to increased nocturia, the renal manifestations of dRTA included urinary lithiasis (Table 1).

Analysis of the renal function

The kidney function of the patients older than 16 years of age was evaluated using the Cock-Gault formula, whereas that of the patients younger than 16 years of age was evaluated using the Schwartz formula. The mean values of the glomerular filter rate according to the Cock-Gault and Schwartz formulas were 73.35 ± 35.41 mL/min and 77.12 ± 41.28 mL/min, respectively. Among the patients, 37 (38.95%), 33 (34.74%), 19 (20%), four (4.21%) and two (2.11%) had stage 1, 2, 3, 4 and 5 CKD, respectively.

Analysis of the tubular function

A total of 29 patients had complete distal RTA, while 66 had incomplete dRTA. The urine titratable tests revealed alkaline urine and abnormal urine acidification (Table 2). One patient exhibited dRTA complicated with nephrogenic diabetes insipidus with a low urine specific gravity and a volume

Table 2. Analysis of Urine Titratable Test

	$\bar{X} \pm SD$	complete dRTA $\bar{X} \pm SD$	incomplete dRTA $\bar{X} \pm SD$	p value
urine pH	6.86 ± 0.43	6.93 ± 0.67	7.06 ± 0.49	0.37
urine TA (mEq/L)	3.92 ± 4.64	3.40 ± 3.93	3.06 ± 4.13	0.74
urine NH_4^+ (mEq/L)	17.85 ± 9.23	17.01 ± 13.14	17.57 ± 10.07	0.84
urine HCO_3^- (mEq/L)	9.01 ± 4.67	8.85 ± 6.88	12.09 ± 7.08	0.03

Table 4. Blood and Urine Biochemical and Renal Function Analysis of 95 Cases

	blood	urine
pH	7.36 ± 0.06	6.86 ± 0.43
sodium	140.75 ± 3.50 mmol/L	153.22 ± 78.83 mmol/24h
potassium	3.23 ± 0.64 mmol/L	47.24 ± 24.17 mmol/24h
chloride	107.59 ± 5.84 mmol/L	143.61 ± 83.02 mmol/24h
calcium	2.18 ± 0.18 mmol/L	4.29 ± 3.04 mmol/24h
phosphate	1.10 ± 0.34 mmol/L	15.48 ± 8.95 mmol/24h
urea nitrogen	5.51 ± 2.84 mmol/L	219.83 ± 93.21 mmol/24h
creatinine	88.86 ± 61.41 μ mol/L	8.00 ± 3.19 mmol/24h
uric acid	268.52 ± 90.09 μ mol/L	2.76 ± 1.05 mmol/24h

of daily urine of 7,600 mL, which persisted after water deprivation and the vasopressin assay, as well as a normal sella turcica according to a computed tomography scan. Moreover, 8.33% (8/27) of the patients presented with tubular proteinuria (urine protein <1 g/day) and low-molecular-weight proteinuria on urine protein electrophoresis (Table 3).

Laboratory data

A total of 10 patients had leukocytopenia (6.2%), while 33 had anemia (6.9%). Most patients (n=60, 63%) had hypokalemia. The mean urine pH of the patients was 6.86 ± 0.43 . The mean blood potassium, chloride, calcium and phosphate levels were 3.23 ± 0.64 , 107.59 ± 5.84 , 2.18 ± 0.18 and 1.10 ± 0.34 mmol/L, respectively. The mean urine potassium, chloride, calcium and phosphate levels were 47.24 ± 24.17 , 143.61 ± 83.02 , 4.29 ± 3.04 and 15.48 ± 8.95 mmol/L, respectively (Table 4). The mean urine calcium levels of the patients with and without urinary lithiasis were 0.10 ± 0.04 and 0.07 ± 0.05 mmol/24 h/kg, respectively, and they demonstrated statistical significance ($p=0.04$) (Table 5).

Bone diseases

Some patients were diagnosed with bone diseases, including osteoporosis (9/10), pathological bone fractures (6/95) and bone deformities (7/95), as well as retardation of bone age in children (3/14) (Table 6). The blood pH, calcium and phosphate levels in addition to the urine calcium and urine phosphate levels were compared between the patients with and without bone diseases. The blood pH values of the patients with and without bone diseases were significantly different (7.37 ± 0.06 and 7.32 ± 0.06 respectively, $p=0.01$, Table 5).

Outcomes

A total of 82 patients received treatment consisting of a

Table 5. Comparison of the Patients with and without Renal Lithiasis and/or Kidney Calcification, and Patients with and without Bone Disease

variables		with L and C n=11	without L and C n=84	p	p with BD n=22	without BD n=73	p
blood	pH	7.36±0.06	7.35±0.07	NS	7.32±0.06	7.37±0.06	0.01
blood	calcium	2.18±0.13	2.18±0.19	NS	2.17±0.23	2.12±0.26	NS
blood	phosphate	1.13±0.54	1.09±0.28	NS	2.06±8.12	1.14±0.56	NS
urine	pH	6.97±0.58	6.98±0.52	NS			
urine	calcium (mmol/24h/kg)	0.10±0.04	0.07±0.05	0.04	0.08±0.05	0.06±0.06	NS
urine	phosphate	13.87±6.69	15.61±9.43	NS	15.35±9.09	14.60±8.10	NS

L and C: renal lithiasis and/or kidney calcification

BD: bone disease, including osteoporosis, bone deformity and growth retardation in children.

Table 6. Bone Disease of 95 Cases of dRTA

presentations	number	Percentage (%)
osteoporosis	9/10	90
bone pain	7/95	7.37
bone fracture	6/95	6.32
bone deformity	7/95	7.14
retardation of bone age in children	3/14	21.43%

mixture of sodium and potassium citrate. Sodium bicarbonate, oral calcium and 25-hydroxyvitamin D3 were also prescribed according to the recovery status. The follow-up period ranged from two to seven years. One patient died of rectal cancer, while two received renal transplantation and the others had good prognoses.

Discussion

dRTA constitutes a group of disorders characterized by hyperchloremic metabolic acidosis with a normal anion gap. This condition is caused by distal tubular dysfunction in the excretion of protons and/or reabsorption of HCO_3^- . Primary dRTA consists of sporadic and inherited types. Both autosomal-dominant and autosomal-recessive patterns have been reported in cases of primary dRTA. The presently reported genes associated with dRTA include SLC4A1, ATP6V1B1 and ATP6V0A4 (10). dRTA is caused by the defective acidification of the distal renal tubules, which makes it impossible to maintain a strong hydrogen concentration gradient between luminal and tubular cells and thus acidify urine under the circumstances of systemic acidosis, resulting in abnormally alkaline urine. The net urinary elimination of hydrogen depends on its buffering and excretion as TA (mainly $\text{HPO}_4^{2-} + \text{H}^+ \leftrightarrow \text{H}_2\text{PO}_4^+$), and H^+ is excreted as NH_4Cl in the urine, simultaneously generating 'new' bicarbonate, which is added to the plasma (2, 14).

In this study, we found the most predominant manifestations to include muscle weakness, increased nocturia, paralysis and over drinking due to thirsty and diuresis. The most common laboratory abnormality was hypokalemia. Moreover, one patient had *torsade de pointes*. Dysfunction of contraction and dilution of the distal tubules can cause overdrinking due to thirst and increased nocturia. Moreover,

previous authors have report that dRTA can be accompanied by nephrogenic diabetes insipidus (15, 16), which was diagnosed in one patient in our study.

Some patients have both distal and proximal tubular dysfunction. Low-molecular-weight (LWW) proteinuria, including that involving urine β_2 microalbumin, NAG (N-acetyl-beta-D-glucosaminidase) and RBP (retinol binding protein), was detected. Although the mechanism underlying the proximal dysfunction observed in dRTA patients remains unclear, there are two possible explanations: endosomal dysfunction of proximal renal tubular cells and hypokalemic nephropathy (17-20). LMW proteins are filtered by glomeruli, reabsorbed via a receptor-mediated (i.e., megalin and cubilin) endocytic pathway and catabolized by proximal renal tubular cells. H^+ -ATPase participates in this process at the level of proximal renal tubular cells, which is why mutations of the subunits of H^+ -ATPase can induce proximal tubular dysfunction. Furthermore, there is evidence that the proximal tubular dysfunction noted in primary dRTA is reversible in association with relief of RTA following the administration of alkali therapy. Because our study is based on retrospective data, there is a lack of follow-up data in these patients.

In contrast with reports in the literature regarding the incidence of symptomatic nephrolithiasis (23%) and nephrocalcinosis (77%), hypokalemia (46.88%) and bone disease (33%) (21), we found a higher frequency of hypokalemia (63.16%) and lower frequencies of nephrolithiasis (11.58%), nephrocalcinosis (4.21%) and bone disease (23.16%). As for the low frequency of nephrolithiasis and nephrocalcinosis, we believe this finding is due to the low sensitivity of kidney ultrasound.

Chronic acidosis can cause growth retardation, osteoporosis, bone deformities and even bone fractures (22, 23). The present results revealed a significant difference in blood pH between the patients with and without bone disease. Unfortunately, we have no follow-up data regarding the relationship between improvements in bone disease and corrections in blood pH.

The present study identified a significant difference in the urine calcium levels between the patients with and without nephrocalcinosis and/or nephrolithiasis (2.18 ± 0.20 mmol/L and 0.07 ± 0.05 mmol/24 h/kg, respectively). This result is

concordant with the findings of a previous study (7). In addition, there were no significant differences between the groups with respect to any other variables, including the blood and urine levels of phosphate and pH. Hypercalciuria, which is always accompanied by hypocitraturia, is one of the most common manifestations of dRTA. However, the mechanism of hypercalciuria in dRTA patients remains unclear, although it may be due to increased calcium release from bone due to metabolic acidosis (24) or the downregulation of renal calcium transport proteins as a result of acidosis (25). Our laboratory examination method has some limitation in testing urine citrate; therefore, we have no data for the levels of urine citrate. Meanwhile, the differences in urine calcium between the patients with and without nephrocalcinosis emphasize the need to control the urine calcium and citrate levels. Several studies have demonstrated that an increased intake of potassium citrate decreases the risk of metabolic acidosis and citrate oxalate stones (26-28). In the present study, the patients received a mixture of sodium and potassium citrate administered orally. However, owing to the limited nature of this respective study, we were unable to determine the effects of the oral intake of citrate on nephrolithiasis.

The present results demonstrated that the most frequent clinical manifestations of dRTA include muscle weakness, increased nocturia, paralysis and growth retardation in children. We noted that approximately 40% of the patients exhibited proximal tubular dysfunction, primarily LWW proteinuria and reduced urine β_2 microalbumin, NAG and RBP levels. In addition, we found that hypercalciuria was correlated with the existence of nephrolithiasis and that correcting blood pH is important for the prevention and treatment of bone diseases caused by dRTA.

The authors state that they have no Conflict of Interest (COI).

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References

- Schwartz GJ. Diagnosis of distal renal tubular acidosis: use of furosemide plus fludrocortisone versus ammonium chloride. *Nat Clin Pract Nephrol* 3: 590-591, 2007.
- Pereira PC, Miranda DM, Oliveira EA, Silva AC. Molecular pathophysiology of renal tubular acidosis. *Curr Genomics* 10: 51-59, 2009.
- Rodriguez Soriano J. Renal tubular acidosis: the clinical entity. *J Am Soc Nephrol* 13: 2160-2170, 2002.
- Ring T, Frische S, Nielsen S. Clinical review: Renal tubular acidosis: a physicochemical approach. *Crit Care* 9: 573-580, 2005.
- Gregory MJ, Schwartz GJ. Diagnosis and treatment of renal tubular disorders. *Semin Nephrol* 18: 317-329, 1998.
- Stover EH, Borthwick KJ, Bavalua C, et al. Novel ATP6V1B1 and ATP6V0A4 mutations in autosomal recessive distal renal tubular acidosis with new evidence for hearing loss. *J Med Genet* 39: 796-803, 2002.
- Bajpai A, Bagga A, Hari P, Bardia A, Mantan M. Long-term outcome in children with primary distal renal tubular acidosis. *Indian Pediatr* 42: 321-328, 2005.
- Brown AS. Renal tubular acidosis. *Dimens Crit Care Nurs* 29: 112-119, 2010.
- Nikali K, Vanegas JJ, Burley MW, et al. Extensive founder effect for distal renal tubular acidosis (dRTA) with sensorineural deafness in an isolated South American population. *Am J Med Genet A* 146A: 2709-2712, 2008.
- Fry AC, Karet FE. Inherited renal acidoses. *Physiology (Bethesda)* 22: 202-211, 2007.
- Bossini N, Savoldi S, Franceschini F, et al. Clinical and morphological features of kidney involvement in primary Sjögren's syndrome. *Nephrol Dial Transplant* 16: 2328-2336, 2001.
- Oduwale AO, Giwa OS, Arogundade RA. Relationship between rickets and incomplete distal renal tubular acidosis in children. *Ital J Pediatr* 36: 54, 2010.
- Ren H, Wang WM, Chen XN, et al. Renal involvement and followup of 130 patients with primary Sjögren's syndrome. *J Rheumatol* 35: 278-284, 2008.
- Laing CM, Toye AM, Capasso G, Unwin RJ. Renal tubular acidosis: developments in our understanding of the molecular basis. *Int J Biochem Cell Biol* 37: 1151-1161, 2005.
- Liu H, Tomoda F, Koike T, et al. A case of distal renal tubular acidosis complicated with renal diabetes insipidus, showing aggravation of symptoms with occurrence of diabetes mellitus. *Nihon Jinzo Gakkai Shi (Japanese Journal of Nephrology)* 53: 726-731, 2011 (in Japanese, Abstract in English).
- Folami AO, Balfe JW, Robson WL, Halperin ML, Stinebaugh BJ. Coexistence of distal renal tubular acidosis and nephrogenic diabetes insipidus in two patients: implications for the pathogenesis of distal renal tubular acidosis. *Clin Invest Med* 1: 105-109, 1978.
- Watanabe T. Proximal renal tubular dysfunction in primary distal renal tubular acidosis. *Pediatr Nephrol* 20: 86-88, 2005.
- Yamamoto K, Cox JP, Friedrich T, et al. Characterization of renal chloride channel (CLCN5) mutations in Dent's disease. *J Am Soc Nephrol* 11: 1460-1468, 2000.
- Norden AG, Lapsley M, Igarashi T, et al. Urinary megalin deficiency implicates abnormal tubular endocytic function in Fanconi syndrome. *J Am Soc Nephrol* 13: 125-133, 2002.
- Igarashi T, Kawato H, Kamoshita S. Reversible low-molecular-weight proteinuria in patients with distal renal tubular acidosis. *Pediatr Nephrol* 4: 593-596, 1990.
- Caruana RJ, Buckalew VM Jr. The syndrome of distal (type 1) renal tubular acidosis. Clinical and laboratory findings in 58 cases. *Medicine (Baltimore)* 67: 84-99, 1988.
- Sharma AP, Singh RN, Sharma RK, Kapoor R, Filler G. Bicarbonate therapy improves growth in children with incomplete distal renal tubular acidosis. *Pediatr Nephrol* 24: 1509-1516, 2009.
- Domrongkitchaiporn S, Pongsakul C, Stitchantrakul W, et al. Bone mineral density and histology in distal renal tubular acidosis. *Kidney Int* 59: 1086-1093, 2001.
- Rocher LL, Tannen RL. The clinical spectrum of renal tubular acidosis. *Annu Rev Med* 37: 319-331, 1986.
- Nijenhuis T, Renkema KY, Hoenderop JG, Bindels RJ. Acid-base status determines the renal expression of Ca^{2+} and Mg^{2+} transport proteins. *J Am Soc Nephrol* 17: 617-626, 2006.
- Tapaneya-Olarn W, Khositseth S, Tapaneya-Olarn C, et al. The optimal dose of potassium citrate in the treatment of children with distal renal tubular acidosis. *J Med Assoc Thai* 85(Suppl 4): S1143-S1149, 2002.

27. Domrongkitchaiporn S, Khositseth S, Stitachtrakul W, Tapaneya-olarn W, Radinahamed P. Dosage of potassium citrate in the correction of urinary abnormalities in pediatric distal renal tubular acidosis patients. *Am J Kidney Dis* **39**: 383-391, 2002.
28. Preminger GM, Sakhaee K, Skurla C, Pak CY. Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. *J Urol* **134**: 20-23, 1985.

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