Incomplete Distal Renal Tubular Acidosis and Kidney Stones

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Renal tubular acidosis (RTA) is comprised of a diverse group of congenital or acquired diseases with the common denominator of defective renal acid excretion with protean manifestation, but in adults, recurrent kidney stones and nephrocalcinosis are mainly found in presentation. Calcium phosphate (CaP) stones and nephrocalcinosis are frequently encountered in distal hypokalemic RTA type I. Alkaline urinary pH, hypocitraturia, and, less frequently, hypercalciuria are the tripartite lithogenic factors in distal RTA (dRTA) predisposing to CaP stone formation; the latter 2 are also commonly encountered in other causes of urolithiasis. Although the full blown syndrome is easily diagnosed by conventional clinical criteria, an attenuated *forme fruste* called incomplete dRTA typically evades clinical testing and is only uncovered by provocative acid-loading challenges. Stone formers (SFs) that cannot acidify urine of pH $<$ 5.3 during acid loading are considered to have incomplete dRTA. However, urinary acidification capacity is not a dichotomous but rather a continuous trait, so incomplete dRTA is not a distinct entity but may be one end of a spectrum. Recent findings suggest that incomplete dRTA can be attributed to heterozygous carriers of hypofunctional V-ATPase. The value of incomplete dRTA diagnosis by provocative testing and genotyping candidate genes is a valuable research tool, but it remains unclear at the moment whether they alter clinical practice and needs further clarification. No randomized controlled trials have been performed in SFs with dRTA or CaP stones, and until such data are available, treatment of CaP stones are centered on reversing the biochemical abnormalities encountered in the metabolic workup. SFs with type I dRTA should receive alkali therapy, preferentially in the form of K-citrate delivered judiciously to treat the chronic acid retention that drives both stone formation and bone disease.

Key Words: Kidney stones, Renal tubular acidosis, Acidification test, Alkali therapy

INTRODUCTION

Homeostasis or fixité du milieu intérieur, as first described by the pioneering French physiologist Claude Bernard, is a prerequisite for multicellular life and ensured by multiple organs, including the kidney. In addition to numerous other homeostatic tasks, the kidney plays a pivotal role in maintaining body acid-base balance and body fluid pH by the reclamation of bicarbonate from the glomerular filtrate and excretion of net acid. Renal net acid excretion regenerates bicarbonate decomposed by nonvolatile acids. If renal excretion is defective or overwhelmed as in the case of nonvolatile acid overproduction, metabolic acidosis ensues. In contrast, renal tubular acidosis (RTA) is a group of congenital or acquired disorders characterized not by nonvolatile acid overproduction but by defective renal acid excretion in the setting of preserved glomerular filtration rate (GFR). Traditionally, RTA is classified as "proximal" or "distal," depending on the site of the tubular lesion. There is also a popular but less informative numeric classification separating RTA into 4 types (Table 1). Clinically, all forms of RTAs—with the exception of the incomplete form of distal RTA—present as normal anion gap metabolic acidosis. To secure the diagnosis of RTA, other forms of normal anion gap acidosis need to be excluded; which includes nonrenal alkali-losing states and overproduction acidosis with successful renal excretion of the conjugate anion of the acid. Depending on the type of RTA, serum K and urinary pH are either high or low and allow further separation (Table 1).[1] Low urine ammonium and its surrogate of highly positive urinary anion gap are present in distal RTAs (dRTAs) but typically not in proximal RTA (pRTA).

The clinical presentation of RTA ranges from completely asymptomatic to increasingly dire outcomes such as recurrent kidney stones, nephrocalcinosis, end-stage renal disease, and sudden death from hypokalemic dysrhythmias. The main focus of this review lies on kidney stone formation in incomplete dRTA (idRTA), but we provide a briefly account of the association of all RTA forms with renal stone disease.

PROXIMAL RTA (TYPE II)

Impaired tubular bicarbonate reclamation, either isolated or generalized in the form of a Fanconi syndrome, is the hallmark of pRTA.[2] Isolated forms of pRTA are mostly congenital with either autosomal-recessive or autosomal-dominant inheritance. The former is due to bi-allelic mutations in the basolateral sodium/bicarbonate cotransporter NBCe1, encoded by the *SLC4A4* gene, whereas the cause of the latter remains elusive.[2,3] Although patients with pRTA are acidemic (low blood pH), accruing nonvolatile acid equivalents daily can be eliminated by the distal nephron, and no net acid retention occurs under steady-state conditions.[3,4] As a

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result, the classical promoters of calcium phosphate (CaP) stone formation encountered in type I dRTA and idRTA (hypercalciuria, hypocitraturia, and alkalinuria) are not present in pRTA. Thus, with the exception of some specific rare scenarios (eg, Fanconi syndrome associated with Dent's disease), nephrocalcinosis and nephrolithiasis are not common features of pRTA.

HYPERKALEMIC FORMS OF RTA: LOW URINARY pH AND URIC ACID STONES

In contrast to pRTA, all forms of dRTA maybe associated with recurrent kidney stones. The pathogenic mechanisms of stone formation are similar for hypokalemic type I, combined type III and incomplete dRTA. In hyperkalemic forms of dRTA, however, the mechanism is different. Hyperkalemic dRTA associated with aldosterone deficiency, also known as type IV RTA, is the most frequent form of RTA encountered clinically and is characterized by low urine pH and decreased acid excretion. This is in contrast to other forms of hyperkalemic dRTA in which aldosterone is not decreased and urine pH always fails to decrease as discussed elsewhere in this issue. Calcareous stone formation is uncommon in patients with hyperkalemic forms of dRTA.[5-8] A main reason for that is that patients with hyperkalemic RTA have typically some degree of CKD with marked reduction in urinary calcium excretion. Type IV dRTA can potentially be a cause of uric acid calculi, especially if associated with low urine pH (<5.5), type II diabetes, or high body mass index.[9-11] Note that the majority of classic uric acid stone formers (SFs) have unduly aciduria but rarely have hyperkalemic RTA.[12] The fundamental pathophysiology in idiopathic uric acid nephrolithiasis is an increased acid load to the kidney and inadequate ammonia production/excretion.[13] The solubility of undissociated uric acid is low, ~0.5 mM in human urine at 37°C. Thus, at a urine pH of 5.35 (pK_a of uric acid), only ~1 mM of uric acid (sum of dissociated and undissociated forms of uric acid) can be solubilized. Physiological concentrations of uric acid in the urine are typically >1mM, and as such, uric acid stone formation is a simple consequence of a low urinary pH. Low urinary pH in type IV RTA is due to a shortage of the urinary buffer ammonium, which is caused by hyperkalemia-induced impaired ammoniagenesis in the proximal tubule.[9,11,14] Treatment of uric acid calculi associated with hyperkalemic type IV RTA should be targeted at eliminating the underlying cause (eg, cessation of offending drugs or treatment of obstructive uropathy). If this is not feasible, increase of urinary pH by alkali supplementation effectively prevents stone formation.

CLINICAL SUMMARY

- Distal RTA (dRTA), which can be caused by a variety of congenital or acquired conditions, predisposes to calcium phosphate stones via pathophysiologic intermediates of alkalinuria, hypocitraturia, and, to a lesser extent, hypercalciuria.
- Incomplete distal RTA (idRTA) usually escapes routine clinical detection, and its diagnosis requires the demonstration of inadequate urinary acidification from provocative acid-loading testing. Such traits are not "normal vs abnormal," but in fact, they are a continuum, and at the present momentum, it is unclear whether these tests should extend from the human research laboratory into clinical practice.
- The mainstream therapy of complete and incomplete distal RTA (idRTA) is still alkali supplement such as potassium citrate, to render the urine less lithogenic by raising citrate and to prevent bone loss, but the citraturic effect can be offset by worsening alkalinuria. So, cautious dose titration is of critical importance.

HYPOKALEMIC DISTAL RTA (TYPE I): HIGH URINARY pH AND CALCIUM PHOSPHATE STONES

The first description of type I dRTA in an autopsy series with 6 children was presented by Lightwood in 1935.[15] Albright and associates recognized the tubular origin of the entity in 1946, and the term "renal tubular acidosis" was coined by Pines and Mudge in 1951.[16,17] Type I dRTA can be acquired or inherited (Table 2). A myriad of acquired causes are known to cause type I dRTA, the most classical one being Sjögren's syndrome with autoantibodies directed at α-intercalated cells.[18] For familial cases, autosomal-recessive and autosomal-dominant mutations in the anion exchanger 1 (AE1; encoded by *SLC4A1* gene), autosomal-recessive mutations in the B1 and a4 subunits of the V-ATPase (encoded by *ATP6V1B1* and *ATP6V0A4* genes, respectively), and recent autosomal-recessive mutations in the transcription factor Foxi1 (encoded by the *FOXI1* gene) have been identified as the underlying monogenic causes.[19-22] Overall, type I dRTA is considered a rare cause of calcareous nephrolithiasis.[23,24] Mechanistically, rate- or capacity-limited distal tubular H^+ secretion is the reason for reduced urinary net acid excretion and alkaline urinary pH.[25] Unlike in pRTA, there is systemic H^+ retention in patients with type I dRTA.[3,4] As a consequence of H^+ retention, intestinal calcium absorption and release of calcium from bone increase and renal calcium reabsorption decreases, resulting in hypercalciuria.[26-28] Hypocitraturia due to avid reclamation of citrate by proximal tubular cells in the setting of systemic acidosis is another hallmark of type I dRTA.

The sequelae of type I dRTA are recurrent nephrolithiasis, nephrocalcinosis, and bone disease. The 3 key prolithogenic factors in type I dRTA (hypercalciuria, hypocitraturia, and relatively alkaline to very alkaline urinary pH) favor CaP precipitation (Fig 1). The typical calculus in type I dRTA consists of carbonate apatite (95.7%) with only minute brushite admixture (1.4%) and has a characteristic morphology with a smooth aspect and a glazed brown-yellow appearance with tiny cracks.[29,30] Stone composition similar to dRTA is observed in patients with carbonic anhydrase inhibitor treatment (acetazolamide and topiramate). In contrast,