Renal Tubular Acidosis

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Most conditions that affect the kidney cause a proportionate and simultaneous loss of glomerular and tubular function. The loss of glomerular function results in the retention of many products of metabolism, including the anions of various organic and inorganic acids, and urea. Loss of tubular function prevents the kidney from excreting hydrogen ions, thereby causing a metabolic acidosis. The parallel development of azotemia, anion retention, and acidosis is defined as uremic acidosis. When tubular damage develops uncoupled from glomerular damage, acidosis may occur without urea or anion retention; this is termed renal tubular acidosis. In uremic acidosis, the serum bicarbonate is replaced by phosphate, sulphate, and other anions not usually measured in standard electrolyte assays, whereas chloride replaces bicarbonate in the renal tubular acidosis, hence giving rise to the term hyperchloremic acidosis.

This review centers on those forms of renal acidosis that occur, at least initially, with a minimum of glomerular damage. After first defining the normal mechanism by which the kidney maintains acid-base balance we define the general pathophysiologic principles that underlie the development of the different forms of renal tubular acidosis. These principles set the foundation for the subsequent discussion of the clinical manifestations, diagnosis, and therapy of these disorders.

NORMAL ACID-BASE PHYSIOLOGY

The free hydrogen ion (H⁺) concentration in the extracellular fluid normally ranges from 35 to 45 nanomoles per liter (35–45 × 10⁻⁷mol/L).

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by taking the negative logarithm, or the pH, of the newly created the normal is maintained by closely regulating and integrating the processes of acid production, buffering, and excretion.

In normal steady-state conditions, 0.8 to 1.0 mg of nonvolatile acid per kilogram is generated daily, mostly as a byproduct of dietary protein, and is excreted in the urine. This is accomplished by the reclamation of filtered bicarbonate and excretion of protons with phosphate buffers (known as titratable acid) and ammonium. While anatomically distinct segments of the nephron carry out these processes by different mechanisms, hydrogen ion secretion remains the common link to all of them. Each of the 180 L of plasma filtered daily contains 26 mEq of sodium bicarbonate, resulting in cumulative daily filtration of 4500 mEq. The urinary loss of even a small percentage of this bicarbonate could rapidly deplete stores and cause severe acidosis.

The proximal tubule is the main site of renal reclamation of bicarbonate; 70% to 88% of it is reabsorbed. The membrane transport proteins responsible for acid-base handling in the proximal tubule are shown in Figure 1. The extrusion of H⁺ in the proximal tubule is dependent on a Na⁺-H⁺ exchanger. Thus, conditions that favor avid Na⁺ reabsorption in the proximal tubule, such as extracellular volume contraction, stimulate H⁺ secretion. The energy for H⁺ secretion is provided by basolateral sodium-potassium ATPase pumps, which maintain a low intracellular Na⁺ concentration and, thereby, provide a chemical gradient for passive sodium entry from the lumen.

![Figure 1. Proximal tubule transport mechanism.](image-url)

DISTAL TUBULE

The urine that reaches the distal nephron still contains 10% to 20% of the filtered bicarbonate, which is reclaimed by a similar mechanism to that of the proximal tubule. In a healthy subject, this will result in a urine virtually free of bicarbonate. After bicarbonate reclamation is complete, hydrogen secretion into the urine and bicarbonate addition to the blood continue. The dissociation of carbonic acid within the cell results in the production of hydrogen and bicarbonate ions. Bicarbonate diffuses into the blood, resulting in the generation of new bicarbonate ions. Hydrogen ions will diffuse into the tubular lumen where they are buffered by urinary buffers other than bicarbonate. The two most important buffers are phosphate and ammonia. At a pH < 6.8, the concentration of monohydron phosphate allows the buffering system to bind hydrogen ion and form dihydrogen phosphate.

Ammonia diffuses easily into the tubular lumen and binds hydrogen ion to form ammonium. Because both compounds, dihydrogen phosphate and ammonium, are poorly permeable across the renal tubule, they are trapped in the urine, thus trapping the hydrogen as well. The transport mechanisms in the distal tubule are depicted in Figure 2.

PATHOGENESIS OF RENAL TUBULAR ACIDOSIS

The kidney maintains acid-base balance by bicarbonate reclamation and acid excretion. Acid excretion consists of ammonium and titratable acid
intraluminal electronegative potential difference. The responses to infusion of neutral phosphate, sodium sulfate, or furansidene have been used as discriminant tests that, however, carry no therapeutic implications. The administration of neutral sodium phosphate or sodium sulfate will stimulate distal H' secretion and prevent acid back-leak. Phosphate and sulfate are poorly reabsorbable anions that bind secreted H' in the tubule and increase the availability of Na' for distal nephron reabsorption. Their net effect is enhanced luminal electronegativity and increased H' secretion. The possibility of back-leak is prevented by the binding of H' to the anions. In normal patients, infusion of sodium phosphate or sodium sulfate will result in lowered urine pH (pH<5.5) and increased K' excretion, and a high urine carbon dioxide tension (P(O2)) with the differential between urine and blood (U-B) P(O2) greater than 20-30 mm Hg. When pH is maintained at 6.8 (the pK of the phosphate buffer at which phosphate is maximally effective in raising P(O2)), phosphate binds secreted H' to form diphosphoric acid, which in turn, donates H' to bind HCO3 to form H2CO3. In the distal nephron, there is delayed dehydration of carbonic acid because of the absence of intraluminal carbonic anhydrase. Dehydration continues within the renal papillae and pelvis, hence, the high P(O2). The isononnsidene test is analogous to the sodium sulfate infusion test, as furansidene will stimulate distal H' secretion by increasing Na' delivery to the collecting ducts.

Secretory dRTA. The existence of a secretory defect for H' in the collecting tubule has been well-documented. Pitts and Lutspschkel demonstrated that, in normal subjects, sodium bicarbonate loading will result in an (U-B)P(O2) > 30 mm Hg when the urine bicarbonate concentration is increased to values greater than 30 mEq/l. Patients with dRTA are unable to elevate P(O2) above that in blood. Halperin et al. have interpreted this as indicating an absence of or diminished H' secretion in the collecting ducts, because in alkaline urine, there is a favorable gradient for H' secretion. However, this does not exclude the possibility of back-diffusion of H' being responsible for this finding. Infusion of neutral sodium phosphate into patients with secretory dRTA results in a rise in titratable acid excretion but without a change in Urinary P(O2) (remains > 5.5). Infusion of sodium sulfate into the same patients gave similar results. These results were interpreted as being consistent with impaired H' secretion. It was also noted that the majority of these patients had no increase in P(O2) after sodium phosphate infusion.

Another study that lends support to the secretory hypothesis is the acidification defect observed in postobstructive nephropathy. In this condition,
sodium sulfate failed to lower UpH. Because sodium sulfate stimulates H+ secretion, the failure to lower UpH was attributed to a defect in H+ secretion, although a voltage-dependent mechanism also is operative in obstructive uropathy. Because sodium sulfate also stimulates K+ secretion, patients with secretory dRTA usually have a marked kaliuretic response to Na2SO4 infusion.

**Back-Diffusion dRTA.** Amphotericin B is a drug known to alter membrane permeability. In the late 1960s, it was found that this drug caused dRTA. It gave credence to the back-diffusion hypothesis. Experiments on turtle bladders have since shown that the impairment of urine acidification was a result of back-leak of H+ from lumen to cell and not impaired H+ secretion. From the bicarbonate loading experiments, it can be argued that the failure to elevate UPco2 in patients with dRTA may be secondary to either defective H+ secretion or increased back-diffusion of H+ or HCO3-. As mentioned earlier, the possibility of back-leak of H+ is restricted in the case of neutral phosphate or sodium sulfate loading because of binding of H+ to the nonionized anion. Thus, questions have been raised as to whether it is back-diffusion of H+ or of HCO3-. Sebastian et al.25 argued in favor of back-leak of HCO3-. The reason is that, if HCO3- is back-leaking, then the UPco2 cannot increase, as there will be no carbonate acid to be dehydrated. Another argument against H+ back-leaking was raised by Steinbaugh et al.26 They also reasoned that during urinary alkalization the tubular pH is higher than that of the peritubular blood; therefore, transfer of H+ from cell to lumen is favored, not vice versa. Conflicting results of UPco2 were obtained when amphotericin B was infused either acutely or chronically. Thus, the back-diffusion hypothesis still needs additional clarification in human studies.

**Voltage-Dependent dRTA.** Urinary acidification defect can result from an inability to generate enough negative transepithelial potential difference (PD) in the distal nephron. This voltage-dependent dRTA has been described in patients with obstructive uropathy3 and sickle cell nephropathy. The K+-sparing diuretic “amiloride” produces a similar type of defect in experimental animals. The lumina of the cortical collecting duct is electronegative compared to the peritubular capillary. This negative PD is dependent on Na+ transport and influences the secretory of H+ and K+. Therefore, factors that impair either distal delivery of Na+ or uptake of Na+ by the collecting duct will impair generation of adequate negative transepithelial PD; this holds true for amiloride (which inhibits Na+ channels), ureteral obstruction, and severe volume depletion wherein the dRTA is reversible. In urinary tract obstruction, structural damage may also result in back-leak or inhibition of proton pump secretion. A prominent feature of the voltage-dependent dRTA is the significant salt wasting (secondary to impaired Na+ reabsorption) and hyperkalemia. These features are similar to those seen in low aldosterone states, the difference being the elevated aldosterone level in voltage-dependent dRTA. Infusion of sodium phosphate or sodium sulfate in these patients results in failure to lower UpH below 5.5. Since there is increased Na+ delivery to the distal nephron, the inability to lower

**Rate-Dependent dRTA.** This is an ill-defined entity that has been described in some patients on chronic lithium therapy.6,24 Such patients have only a subtle acidification defect. They are unable to elevate UPco2 during alkali loading but can acidify urine normally. However, they demonstrated an elevated UPco2 on neutral phosphate infusion, which, in essence, rules out a secretory defect. The UPco2 is believed to be an accurate index of urinary acidification, and the failure to elevate UPco2 in alkaline urine may represent a defect in the rate of distal acidification (rate-dependent defect). This entity may represent an early manifestation of other forms of dRTA.

**Deficiency of Carbonic Anhydrase.** The other pathogenic mechanisms (Table I) have not been well-characterized clinically. Diminished intracellular generation of bicarbonate can result from deficiency of enzyme carbonic anhydrase. Bicarbonate reclamation is intimately related to the excretion of H+. Hence, an inability to generate intracellular bicarbonate will result in failure to excrete H+. Carbonic anhydrase deficiency itself may be responsible for some reported cases of juvenile RTA.24 Similarly, if generated bicarbonate is unable to exit the basolateral membrane as a result of impaired permeability, theoretically, an acidification defect can occur. It will be prudent to say that the various pathogenic mechanisms discussed so far are not mutually exclusive. A combination of mechanisms may exist in any particular patient.

**Pathogenesis of Type 2 (Proximal RTA)**

Proximal renal tubular acidosis (pRTA) is characterized by a reduced transport maximum (Tm) for bicarbonate reabsorption in the proximal tubules. It rarely occurs as an isolated defect of bicarbonate transport. It is usually associated with multiple proximal tubular transport defects, such that there is also increased urinary loss of glucose, phosphate, amino acids, uric acid, and other organic anions such as citrate (Fanconi syndrome). The role of the high urine citrate level in relation to urolithiasis will be discussed later. Phosphaturia can result in hypophosphatemia, which may cause bone disease and developmental abnormality in children. pRTA is self-limiting, as bicarbonaturia ceases as soon as serum bicarbonate is reduced to about 15 mEq/L. At this level of serum bicarbonate, a new Tm is established and the proximal tubule will be able to reabsorb all the filtered bicarbonate. Also, at this new Tm, the UpH can be lowered to < 5.5 with acid loading.

The pathogenic mechanisms responsible for the proximal tubule defect are incompletely understood. Some of the postulated mechanisms are listed below.

1. Defect in pump secretion or function. The pumps involved in proximal tubule bicarbonate reclamation are the proton pump (H+ATPase), the Na+-H+ antiporter, and the Na+-K+ ATPase. Defects in these pumps will impair bicarbonate reabsorption. The Na+-K+ATPase located in the basolateral membrane provides the
energy for the Na⁺-H⁺ exchange, and hence, Na⁺ entry and water excretion.
A defect in this pump has been described.²²

2. Carbonic anhydrase (CA) plays a critical role in bicarbonate reclamation.
Thus, a deficiency of this enzyme either in the brush-border membrane in the
urinary collecting duct or in the proximal tubule will inhibit its action (such as acetazolamide or some
sulfur-containing topically used in burn patients) will result in bicarbonate
wasting. Inherited deficiency of CA has been reported in some children.²² It is
not clear if these children had pRTA or dRTA.

3. Structural damage to luminal membrane with possible increased bicarbonate
influx into lumen or basolateral membrane defect with failure of generated bicarbonate
to exit that membrane is a hypothetical postulate without any strong experimental
backing.²²

Prominent features of pRTA are hypokalemia and volume depletion.
The kaliuresis is secondary to the marked sodium bicarbonate wasting. The
loss of sodium bicarbonate results in volume depletion and secondary hyperaldosteronism, which will, in turn, stimulate K⁺ secretion. Volume
contraction also favors Na⁺-K⁺ exchange in the distal nephron. Of note is the
fact that the treatment of patients with jRTA or jRTA with alkali will worsen
the bicarbonaturia by increasing the filtered load of bicarbonate above the
new Tm, hence, aggravating the kaliuresis.

Pathogenesis of Type 4 RTA
This entity is often associated with some renal parenchymal disease. It is
most often seen in patients with diabetes mellitus and interstitial
nephritis. The exact pathogenesis is unclear. A prominent feature is the
hyperkalemic-hyperchloremic metabolic acidosis with deficiency of aldosterone
or other mineralocorticoid hormones. Some of the postulated mechanisms are:
(1) selective destruction of the juxtaglomerular cells, (2) decreased
sympathetic innervation of juxtaglomerular apparatus, (3) decreased
production of prostaglandins and subsequent decrease in renin-aldosterone
production, (4) primary hyperaldosteronism, and (5) secondary hyperaldosteronism
from chronic use of heparin.

The hyperkalemia is secondary to the low aldosterone level with
impairment of Na⁺ and K⁺ secretion in the collecting ducts. The acidosis is
maintained by hyperkalemia because hyperkalemia causes an intracellular
alkalinization with resultant impairment of Na⁺, K⁺ generation and excretion. The
ability to lower UpH below 5.5 is intact in these patients, but acid excretion
is reduced because of the deficiency of urinary buffers. Deficiency of
urinary buffers is also a feature seen in early renal failure with a reduced
glomerular filtration rate. In this case, it is caused by the reduction in renal
mass.

Aldosterone Resistance State. It is prudent to discuss this rare condition
at this state, which is a form of type 4 RTA. It is characterized by lack of
sensitivity to aldosterone action, hence, it is also known as pseudohypo-
aldosteronism. There are two subtypes. Type 1 is thought to be secondary
to a defect at the aldosterone receptor level. Type 2 (chloride shunt) is
thought to be a primary renal tubule secretory defect that results in
enhanced chloride resorption. This, in turn, causes a decreased electrical
gradient in the distal nephron.²³ It is separate from the voltage-dependent
dRTA because the UpH can be lowered to < 5.3.

RTA can be primary or secondary to a wide spectrum of ailments.
Some of the diseases that cause pRTA can also cause dRTA. The primary
form of both proximal and distal RTA is known to occur in relatives of
affected patients.

Proximal RTA (Type 2)
This is probably the least common form of RTA found in adults. As
with the other forms of RTA, an essential component of the diagnostic
evaluation includes consideration of the many diseases capable of producing
impaired renal handling of acid (Table 2). The most common forms are
those associated with hypokalemia and secondary hyperparathyroidism, as
occur in malabsorption syndromes with inadequate vitamin D absorption
and the drug toxicities.

pRTA associated with the Fanconi syndrome has been reported in
recipients of renal transplants. In general, the occurrence of bicarbonate
wasting in the absence of glucose, phosphate, amino acid, or uric acid
wasting is rare. Because acid does not progressively accumulate with pRTA,
systemic buffers are not continually consumed, and therefore, hyperkalemia,
nephrocalcinosis, and nephrolithiasis are rare.²⁶ As was discussed
previously, the relative acid UpH and normal urinary citrate levels of
untreated patients also protect against renal stone formation. However,
morphologic bone disease is a common complication in pRTA and is generally
attributed to the frequently deranged vitamin D metabolism and hypo-
phosphatemia. Other than bone disease, the principal symptoms related to
pRTA include those related to acidemia (malnutrition and growth retardation)
and hypokalemia (polyuria, polydipsia, nocturnal enuresis, and muscular
weakness).

Hypokalemic Distal RTA (Type 1)
The hereditary form of dRTA is inherited in an autosomal dominant manner.²⁷ In
addition to the inherited and drug-induced forms, dRTA has been reported to occur mostly in association with hyperparathyroidenic and autoimmune disorders,²⁸ tubulointerstitial infiltration of inflammatory cells being the cause of tubular dysfunction/RTA (Table 3).

The known association between liver disorders, such as chronic active
hepatitis and hepatic cirrhosis, and dRTA is most likely caused by the
exaggerated sodium resorption in the proximal segments of the nephron
that limits the amount delivered to the distal nephron, thereby decreasing
distal hydrogen ion secretion. This mechanism is also responsible for the
impaired distal acidification seen in patients with nephrotic syndrome.²⁹

Classic dRTA is found frequently in association with tubulointerstitial
nephropathies such as sickle cell disease, obstructive uropathy, and chronic
rejection of renal transplants.³⁰ Symptoms of classic dRTA also relate to
acidemia and hypokalemia. In addition, nephrocalcinosis, hypocitraturia,
and nephrolithiasis are common, either as a cause or as a consequence.
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- sickle cell anemia
- obstructive enopathy
- renal transplantation

**Hyperkalemic Distal RTA (Type 4)**

Hyperkalemic dRTA occurs in disease states associated either with aldosterone deficiency or entities associated with distal tubular dysfunction (Table 4). Patients with aldosterone deficiency are capable of achieving normal minimum UrH values, and systemic acidosis is usually mild, not requiring therapy. These patients may have mild renal insufficiency, but do not have the hypercalcemia or nephrocalcinosis seen in patients with classic distal RTA. Patients with Type 4 RTA who have adequate to supranormal levels of circulating aldosterone usually cannot achieve a normal minimum UrH, suggesting that they may have a more severe hydrogen secretory defect than those with aldosterone deficiency. Clinical manifestations of acidemia, hyperkalemic (arrhythmias and muscle weakness), or renal salt wasting (orthostatic hypotension, azotemia) may predominate. In patients with hyporeninemic hypaldosteronism or mineralocorticoid-resistant states, hypertension may be present.

**Nephrolithiasis in RTA**

Nephrolithiasis is rare in patients with pRTA. Only one study from Sweden had found a high incidence of stone disease in their patients: 57 of 389 (15%) with pRTA and 26 of 389 (7%) with dRTA. However, the review of 92 patients with RTA by Brenner et al. found that only 3 of 43 (7%) patients with dRTA had nephrolithiasis, but none of the pRTA patients
had nephrolithiasis. Several other studies have shown a higher incidence of nephrolithiasis and nephrocalcinosis in dRTA.\textsuperscript{12,14}

Hypercalcuria, hyperphosphaturia, hypocalciaturia, and high UpH are the main features that predispose patients to kidney stone disease. A high UpH promotes precipitation of calcium and phosphate stones (mostly brushite). The high urine calcium is related to the chronic acidosis and bone buffering of the excess H\textsuperscript{+}. Patients with pRTA have lower urine calcium concentration and, at steady state, have no H\textsuperscript{+} retention. Hence, there is insignificant bone buffering and less calcium release into the blood. Acidosis per se will suppress distal calcium reabsorption (but high distal delivery of bicarbonate will increase Ca\textsuperscript{2+} reabsorption).\textsuperscript{15} It has also been reported that a primary disorder of Ca\textsuperscript{2+} metabolism with hypercalcuria can give rise to dRTA.\textsuperscript{16} It also is possible that there is a blunting of parathyroid hormone effect in metabolic acidosis with loss of its anticalcic effect.\textsuperscript{6}

Urinary citrate is an important inhibitor of crystal aggregation and precipitation. Patients with pRTA have high urinary citrate levels as opposed to the low levels observed in patients with dRTA and incomplete dRTA. Citrate complexes with calcium to form soluble salts of higher solubility than calcium oxalate or calcium phosphates. Metabolic acidosis and hypo-

mutes citrate uptake from renal luminal and its metabolism in renal cell mitochondria. The net effect is less citrate available for urinary excretion.\textsuperscript{17} Hypokalemia causes an intracellular acidosis by transcellular K\textsuperscript{+}/H\textsuperscript{+} exchange, thus aggravating the hypokalemia.\textsuperscript{17} In addition to pH, plasma calcium also seems to be an important regulator of citrate oxidation in the kidney, as an increase in plasma calcium decreases oxidation by the kidney. Thus, the conditions associated with hypercalcemia should be associated with an increased level of citrate in the tissue and enhanced excretion by the kidney.

Patients with incomplete dRTA who may present with recurrent nephrolithiasis comprise a special group. The only clue to the presence of a metabolic disorder will be the high UpH.\textsuperscript{18} Such patients may have an essentially normal biochemical profile but will be unable to lower UpH to < 5.5 with ammonium chloride loading. These patients are hypokalemic, and the stone problem is easily corrected by supplementation with potassium citrate. Therefore the treatment of choice for patients with dRTA or incomplete dRTA with stone disease is potassium citrate. Correction of the hypokalemia also will help improve the urine citrate level. Patients with hereditary dRTA whose major metabolic abnormality is hypercalcemia may benefit more from use of thiazide diuretics.\textsuperscript{6}

**RENEAL TUBULAR ACIDOSIS AND BONE DISEASE**

dRTA (Type I) of the idiopathic type is associated with nephrocalcinosis and osteomalacia. It is more prevalent in children in whom osteomalacia leads to growth retardation. dRTA is not commonly associated with significant bone disease because the positive H\textsuperscript{+} balance and resultant hypercalcemia are not present. In dRTA, a continuous hypercalcemia is produced by bone resorption.

In Brenner et al's review,\textsuperscript{19} radiographic evidence of osteodystrophy was present in 17% of patients. Bone disease was more frequent in the azotemic patients and in patients with RTA. In a previous series,\textsuperscript{13} bone disease was twice as common as Brenner et al's description, but the patient population was not divided into the various types, and thus it is impossible to determine if the real prevalence of bone disease was any higher. Contrary to the previous series, the Brenner et al study\textsuperscript{18} showed that pRTA is the type most frequently associated with bone disease; there were no bone biopsy procedures done to corroborate the radiologic diagnosis, and thus, it is impossible to determine the true incidence of skeletal disease in pRTA.

In clinical states of vitamin D deficiency, a Fanconi-type syndrome may develop. Although the mechanisms of Fanconi syndrome have not been completely studied, it is possible that vitamin D deficiency, phosphate depletion, PTH excess, and hypocalcemia may all depress proximal tubular reabsorption of bicarbonate, glucose, and amino acids, in addition to directly contributing to abnormal skeletal modeling or remodeling. Administration of 1,25(OH)\textsubscript{2} vitamin D corrects both the rickets and the Fanconi syndrome. Similarly, in patients with idiopathic Fanconi syndrome, the administration
development of rickets may be related to impaired vitamin D metabolism. It is quite possible that injury to the proximal tubule may impair the conversion of 25(OH)D to 1,25(OH)2, vitamin D. Still, in the few patients that have been tested, 1,25(OH)2 vitamin D levels were normal in most instances, raising the question of tissue resistance to action of 1,25(OH)2 vitamin D in the presence of metabolic acidosis. The complex relationship between vitamin D and metabolic acidosis in the Fanconi syndrome requires further study to unravel their interactions.

**NEPHROCALCINOSIS**

Brenner et al.
reviewed the prevalence of nephrocalcinosis according to the localization and type of calcification in the kidney. Examination of radiographs without prior knowledge of the type of RTA, for either parenchymal (nephrocalcinosis) or pelvic calcifications (nephrolithiasis), showed that nephrocalcinosis was present in 29% of all patients, and it occurred only with dRTA. When the dRTA group was analyzed, it was found that 56% of patients had nephrocalcinosis, 5% had nephrolithiasis, and 2% had both. The finding of nephrocalcinosis in dRTA was more frequent in adults than in children (58% versus 10%).

The relationship between nephrocalcinosis and dRTA is complex. In some cases, the acidification defect is the consequence of nephrocalcinosis, whereas in others, the nephrocalcinosis is the consequence of the dRTA. There is experimental and clinical evidence to suggest that some conditions associated with chronic hypercalcemia or hypercalciuria may lead to dRTA. These conditions include hyperparathyroidism, vitamin D-related hypercalcemia, and medullary sponge kidney. There are also familial cases in which the hypercalciuria leads to an acidification defect.

In other subjects, especially those with idiopathic dRTA, the nephrocalcinosis seems to be the consequence of the distal acidification defect, because correction of the metabolic acidosis leads to a decrease in the hypercalciuria and regression of the nephrocalcinosis.

In patients with dRTA, the increased excretion of amino acids and other organic anions binds calcium and, thus, prevents precipitation of calcium and nephrocalcinosis. In dRTA, the decrease in citrate execution prevents binding of calcium and leads to precipitation of calcium and nephrocalcinosis.

**DIAGNOSTIC APPROACH AND TREATMENT**

The presence of a hyperchloremic metabolic acidosis with no obvious gastrointestinal bicarbonate loss of base or exogenous acid intake produces the suspicion of a renal acidification defect. As described in Figure 3, the algorithm summarizes the steps in the diagnosis of renal tubular acidosis. The first step in subjects with normal-to-low potassium levels is the determination of UpH under oil, using a pH meter rather than a dipstick.
The diagnosis of pRTA can be made by a bicarbonate infusion with a high fractional excretion of bicarbonate as the serum bicarbonate normalizes (FE_{Bic} > 15%). Urine tests for amino acids, glucose, phosphate and uric acid, in cases of multiple urinary leaks, will point towards the Fanconi syndrome, frequently associated with pRTA. Because urinary citrate is usually low in classic dRTA, but not in the proximal types, this is also a useful ancillary test. The measurement of the U-BPCO₂ during a bicarbonate loading also strengthens the diagnosis of dRTA, as it will be decreased in these patients.

When overt acidosis is not present but suspicion of such arises in patients with nephrolithiasis of unknown cause, calcium phosphate stones, medullary sponge kidney, nephrocalcinosis or familial history of RTA, evaluation for incomplete dRTA is warranted. A first, early morning urine specimen with a pH of < 5.5 rules out this condition. A second test involves the determination of the value of the urinary acidification test. This is accomplished by the measurement of U-BPCO₂ in urine obtained immediately after ingestion of an oral load of 100 mg ammonium chloride per kilogram of body weight. A thin layer of mineral oil is layered over the collected urine sample immediately and measured. Under these circumstances, a pH of < 5.5 is diagnostic of dRTA. As mentioned previously, the measurement of U-BPCO₂ in urine is also a sensitive indicator of incomplete proximal dRTA, and its normalization also verifies therapeutic success in patients with no obvious systemic acidosis.

For type 4 RTA, when metabolic acidosis is usually not the main problem, the diagnostic search for the cause of the hyperkalemia takes priority. In these patients, measurement of the aldosterone level becomes the first step in the evaluation. Subjects with a pH of < 5.5 are likely to be aldosterone or cortisol deficient, except in the rare cases of aldosterone resistance. In the hyperkalemic patient with a pH > 5.5, aldosterone is usually normal or high, and a specific cause of renal distal tubular dysfunction, like obstructive uropathy, should be sought.

THERAPY

Once an underlying disease entity has been identified, specific therapy is needed to control the primary problem. Still, therapy for the renal tubular acidosis is usually needed. Depending on the type of RTA, the goals of therapy are to decrease the rate of progressive renal insufficiency by preventing nephrocalcinosis and nephrolithiasis, neutralize metabolic bone disease, and improve growth in children.

In the case of pRTA, multitherapy with large quantities of alkali (approximately 5 mEq/kg/day), vitamin D, and potassium supplementation is required. In dRTA, the amount of bicarbonate administered is usually 1 to 2 mEq/kg/day in adults. Provision of bicarbonate by using citrate salts that are metabolized in the liver to bicarbonate provides the additional advantage of exogenous citrate from the portion escaping hepatic metabo-

cases of hyperkalemic dRTA, entities amenable to intervention, such as obstructive uropathy, should be identified. In general, distal sodium delivery should be encouraged by ingestion of increased dietary salt, taking into account that many of these patients also have coexisting cardiac disease or compromise. Fluid overload can be overcome by the addition of furosemide to the high-salt diet. Beta-blockade encourages distal delivery of sodium by rendering the collecting tubule impermeable to chloride, and decrease exchange of sodium for hydrogen or potassium.

Mineralocorticoid therapy is sometimes useful when aldosterone deficiency is present, taking care to combine it with sodium loading and diuretics to avoid heart failure. Refractory hyperkalemia may require periodic intake of K⁺ exchange resins (kayexalate). In many cases, careful evaluation of potential iatrogenic offenders (beta blockers, ACE-inhibitors) would explain persistent high potassium in the absence of moderate-to-severe renal failure.

SUMMARY

Renal tubular acidosis refers to a group of disorders that result from pure tubular damage without concomitant glomerular damage. They could be hereditary (primary) or acquired (secondary to various disease states like sickle cell disease, obstructive uropathy, postrenal transplant, autoimmune disease, or drugs). The hallmark of the disorder is the presence of hyperchloremic metabolic acidosis with, or without, associated defects in potassium homeostasis, a pH > 5.5 in the presence of systemic acidemia, and absence of an easily identifiable cause of the acidemia.

There are three physiologic types whose basic defects are impairment of or a decrease in acid excretion, i.e., type 1 (dRTA); failure in bicarbonate reabsorption, i.e., type 2 (pRTA); and deficiency of tubular or impaired generation of NH₄⁺, i.e., type 4 RTA. Several pathophysiologic mechanisms have been postulated for these various types.

pRTA is the least common of all in the adult population. It rarely occurs as an isolated defect. It is frequently accompanied by diffuse proximal tubule transport defects with aminoaciduria, glycosuria, hyperphosphatemia, and so forth (Fanconi syndrome).

dRTA is associated with a high incidence of nephrolithiasis, nephrocalcinosis, osteodystrophy, and growth retardation (in children). Osteodystrophy also occurs in pRTA to a lesser degree and is believed to be secondary to hypophosphatemia. Patients with type 4 RTA usually have mild renal insufficiency from either diabetes mellitus or interstitial nephritis.

Acute bicarbonate loading will result in a high fractional excretion of bicarbonate greater than 15% (FE_{Bic} > 15%) in patients with pRTA, but FE_{Bic} < 3% in patients with dRTA. Type 1 patients will also have a low (U - B) PCO₂ with bicarbonate loading. They are also unable to lower their urine pH to < 5.5 with NH₄Cl loading.

The treatment of these patients involves avoidance of precipitating