Renal Tubular Acidosis

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Cover Illustration by Andrew Grivas
The kidney normally acts to regulate serum bicarbonate ($\text{HCO}_3^-$), or the fixed, nonvolatile component of the acid-base status, at a level between 24 and 27 mEq/L.\textsuperscript{1} Renal regulation of the acid-base balance involves both the reabsorption of $\text{HCO}_3^-$ and the excretion of hydrogen ions (H'). In rare instances, defects in the renal mechanisms responsible for this regulatory system arise despite relatively normal rates of glomerular filtration; the clinical sequelae that result from these defects are termed renal tubular acidosis (RTA). This review presents an overview of the role of the kidney in regulating acid-base balance and discusses various forms of RTA with an emphasis on the underlying pathophysiology.

**RENAL REGULATION OF ACID-BASE BALANCE**

The kidney normally must carry out 2 functions vis-à-vis acid-base metabolism. First, it must accomplish the reabsorption of filtered $\text{HCO}_3^-$, which occurs in the proximal convoluted tubule. Second, it must accomplish the excretion of fixed (nonvolatile) acids through the titration of urinary buffers and the excretion of ammonium with secreted protons, which takes place primarily in the distal nephron.\textsuperscript{2,3} Reabsorption in the proximal tubule leads to the preservation of existing $\text{HCO}_3^-$, while the distal tubular process leads to the creation of new $\text{HCO}_3^-$ to replace $\text{HCO}_3^-$ lost in buffering the acid load of the normal diet and the incomplete metabolism of glucose and fat.

$\text{HCO}_3^-$ is used in the metabolism of components of the diet into end products that generate acid.\textsuperscript{4} The following reactions illustrate this phenomenon:

Methionine (component of meat) $\rightarrow$ glucose + urea + $\text{SO}_4^{2-}$ + 2 H'

Metabolism of cationic amino acids (arginine) $\rightarrow$ glucose (or $\text{CO}_2$) + urea + H'

Metabolism of phosphate esters in meat (R-$\text{H}_3\text{PO}_4$) + $\text{H}_2\text{O}$ $\rightarrow$ ROH + 0.8 HPO$_4^{2-}$/0.2 $\text{H}_2\text{PO}_4^-$ + 1.8 H'

Thereafter, the metabolism of these acids consumes $\text{HCO}_3^-$:

$$\text{H}_2\text{SO}_4 + 2 \text{NaHCO}_3 \rightarrow \text{Na}_2\text{SO}_4 + 2 \text{H}_2\text{O} + 2 \text{CO}_2$$

Thus, any circulating $\text{HCO}_3^-$ must be preserved, and because the normal diet generates H’ at a rate of approximately 1 mEq/kg of body weight daily, 50 to 100 mEq of $\text{HCO}_3^-$ must be created daily to maintain acid-base balance in a typical person.\textsuperscript{1}

**PROXIMAL TUBULE BICARBONATE REABSORPTION**

Approximately 80% to 90% of filtered $\text{HCO}_3^-$ is preserved through reabsorption in the proximal tubule. The mechanisms for proximal reabsorption involve H’ secretion at the luminal membrane of the proximal tubule via a protein termed the Na’/H’ exchanger and secondary $\text{HCO}_3^-$ transport at the basolateral membrane via a protein that couples sodium and $\text{HCO}_3^-$ cotransport.\textsuperscript{5} The sodium gradient across the luminal membrane drives sodium into the cell in exchange for H’ (Figure 1, site 1).\textsuperscript{6} This gradient is created by the action of Na’,K’-ATPase located on the basolateral or blood side of the epithelial cell. As H’ are secreted in exchange for sodium ions delivered via glomerular filtration, the H’ combine with filtered $\text{HCO}_3^-$ ions to produce the following reaction:

$$\text{H}^+ + \text{HCO}_3^- \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}_2\text{O} + \text{CO}_2$$

The carbon dioxide formed diffuses into the cell (Figure 1, site 2), where it combines with water to form carbonic acid ($\text{H}_2\text{CO}_3$). An equilibrium is formed between $\text{HCO}_3^-$ and H’ as illustrated in the equation. A key feature of this complex system is the presence of carbonic anhydrase, an enzyme located both at the luminal membrane and within the tubule cell.\textsuperscript{6} Carbonic anhydrase allows the rapid dissociation of carbonic acid into water and carbon dioxide in the lumen and also the rapid formation of carbonic acid from carbon dioxide and water within the cell. The $\text{HCO}_3^-$ that is formed enters the circulation via the Na’/$\text{HCO}_3^-$ cotransporter (Figure 1, site 3). Through the integrated set of transport systems and enzymatic reactions, the filtered $\text{HCO}_3^-$ is returned to the body.\textsuperscript{7} In addition,
approximately 20% of filtered HCO\textsubscript{3}– is reabsorbed by passive back-diffusion along the paracellular pathway.

A number of physiologic and pathophysiologic factors can influence HCO\textsubscript{3}– reabsorption in the proximal tubule.\textsuperscript{5,8} These include the luminal HCO\textsubscript{3}– concentration and flow rate, extracellular fluid volume, peritubular HCO\textsubscript{3}– concentration, concentrations of PCO\textsubscript{2}, chloride, potassium, calcium, phosphate, and parathyroid hormone,\textsuperscript{8} use of glucocorticoids,\textsuperscript{9} α-adrenergic tone,\textsuperscript{10} and angiotensin II.\textsuperscript{11} In general, factors that lead to an increased rate of sodium reabsorption and factors that reduce the pH of proximal tubular cells tend to enhance bicarbonate reabsorption.

DISTAL FORMATION OF HCO\textsubscript{3}– AND URINARY ACIDIFICATION

After bicarbonate is reclaimed in the proximal tubule, “replacement” bicarbonate for that consumed by the buffering of dietary acids must be generated in the distal nephron.\textsuperscript{5} This process is accomplished by the formation of carbonic acid in the intercalated cell of the cortical collecting tubule; one type of intercalated cell, the α-cell, is capable of H\textsuperscript{+} secretion.\textsuperscript{3} Once formed, carbonic acid is dehydrated into H\textsuperscript{+} and HCO\textsubscript{3}–, and the H\textsuperscript{+} is then pumped out of the cell into the lumen by a vacuolar H\textsuperscript{+}-ATPase (Figure 2, site 1). Intracellularly formed HCO\textsubscript{3}– leaves the cell by an electroneutral mechanism involving Cl\textsuperscript{–}/HCO\textsubscript{3}– exchange, facilitated by an anion exchange protein.\textsuperscript{12} A second ATPase, the H\textsuperscript{+},K\textsuperscript{+}-ATPase, is also involved in H\textsuperscript{+} secretion as well as potassium absorption (Figure 2, site 2).\textsuperscript{13}

The exit of H\textsuperscript{+} is also highly influenced by the favorable electrochemical gradient from cell to lumen that results from luminal electronegativity created by active sodium transport taking place in a second cell type in the collecting tubule, the principal cells, which are responsible for sodium reabsorption and potassium secretion.\textsuperscript{14} The initiating event for H\textsuperscript{+} secretion is actually the uptake of sodium by the collecting duct cell. This uptake step occurs as sodium enters the cell through the sodium channel, termed the epithelial Na channel (ENaC). The production of this channel protein and its insertion into the cell membrane are both augmented by aldosterone.\textsuperscript{15} Once inside the cell, sodium ions are extruded to the peritubular side by the actions of the ubiquitous Na\textsuperscript{+},K\textsuperscript{+}-ATPase enzyme in exchange for potassium ions. Because sodium is more permeable than the accompanying anion, chloride, the lumen voltage becomes negative by 40 to 50 mV, thereby favoring H\textsuperscript{+} secretion (Figure 2, site 3). The net effect is a luminal milieu that favors the movement of H\textsuperscript{+} ions from the cell to the lumen down an electrochemical gradient. As the delivery of fluid and sodium increases past the collecting duct cell, more H\textsuperscript{+} may be secreted down the refreshed electrochemical gradient.

The kidney must generate 1 mEq of HCO\textsubscript{3}– for each mEq of acid added through diet, and thus each day 50 to 100 mEq of residual H\textsuperscript{+} resulting from the generation of HCO\textsubscript{3}– must be excreted in the urine. Since the maximal pH gradient between the distal tubular lumen and the cell is on the order of pH 4 lumen/pH 7 cell, only 10\textsuperscript{–4} Eq/L or 0.1 mEq of free H\textsuperscript{+} can exist in each liter of urine. Hence, to excrete 50 mEq of H\textsuperscript{+} per day, urinary buffers are needed to titrate the H\textsuperscript{+} and then be excreted.\textsuperscript{16} Urinary acidification, then, takes place in the distal nephron by the titration of the 2 major urinary buffers: ammonia and phosphate (Figure 2, site 4). Titration of divalent basic phosphate (HPO\textsubscript{4}\textsuperscript{2–}) to the monovalent acid form (H\textsubscript{2}PO\textsubscript{4}–) creates the so-called “titratable acid” of the urine.\textsuperscript{17} The second buffer involves the accumulation of ammonia (NH\textsubscript{3}) intraluminally, which then buffers H\textsuperscript{+} to form nondiffusible ammonium (NH\textsubscript{4}+).
sum total of these forms of acid excreted by the kidney is termed *net acid excretion* (NEA) and is equal to the amount of $\text{H}^+$ excreted as titratable acidity (TA) and $\text{NH}_4^+$ minus any $\text{H}^+$ added to the body because of urinary $\text{HCO}_3^-$ loss:

$$\text{NEA} = \text{TA} + \text{NH}_4^+ - \text{urinary } \text{HCO}_3^-$$

Ammonium production is the most important source of buffer in the urine because its production is a metabolic event under strict regulation and responsive to the specific amount of buffer needed by the kidney to excrete $\text{H}^+$. Urinary phosphate is primarily a function of dietary phosphate intake and hence its production is not responsive to acid-base status.

The initial step in ammonium excretion is the generation of $\text{NH}_4^+$ within the tubular cells from the metabolism of glutamine. A series of pH-dependent enzymatic steps in the proximal tubule govern ammonium production:

Glutamine $\leftrightarrow$ $\text{NH}_4^+$ + glutamate $\leftrightarrow$ $\text{NH}_4^+$ + $\alpha$-ketoglutarate

The first step in the pathway is regulated by glutaminase and the second by glutamate dehydrogenase. Glutamate dehydrogenase acts to form $\alpha$-ketoglutarate. The subsequent metabolism of $\alpha$-ketoglutarate in the Krebs cycle results in the generation of $2 \text{ HCO}_3^-$ ions that enter the systemic circulation via the basolateral membrane. This pathway is pH-dependent so that intracellular acidosis stimulates the production of ammonia in a teleologically beneficial fashion. While it is primarily ammonium, not ammonia, that is produced by these reactions, ammonia can freely diffuse out of the cell across both the luminal and basolateral membranes. Because it is a charged moiety, ammonium ($\text{NH}_4^+$) requires transmembrane transporters to leave the cell, and these are present only in the luminal membrane. There is a complex countercurrent multiplier system that leads to an accumulation of $\text{NH}_4^+/\text{NH}_3$ within the renal medulla. The $\text{NH}_4^+/\text{NH}_3$ pair has an equilibrium pH (PK) of 9.0, so that at pH 7.0, 99% of the $\text{NH}_4^+/\text{NH}_3$ is in the charged form; however, the 1% that exists as ammonia is available for diffusion into the luminal fluid of the collecting tubule to buffer secreted $\text{H}^+$ ions. As ammonia leaves the cell, equilibrium of the buffer pair $\text{NH}_4^+/\text{NH}_3$ is re-established, and ammonia is available for further buffering.

In addition to being responsible for the specific localization of the ENaC in the apical membrane of principal cells of distal tubules and cortical collecting tubules, aldosterone enhances $\text{H}^+$-ATPase activity in cortical and medullary collecting tubules, an effect that is independent of plasma potassium levels. Aldosterone also has an effect on ammonium excretion by increasing ammonia synthesis, both as a direct action and as a consequence of simultaneous changes in potassium homeostasis (hypokalemia stimulates ammoniagenesis and hyperkalemia inhibits it).

### CLASSIFICATION OF RENAL ACIDIFICATION DEFECTS

RTA has been separated into 3 main categories based on clinical and pathophysiologic grounds: proximal RTA (type 2); distal RTA (type 1); and hyperkalemic RTA (type 4). Each may occur in a number of hereditary or acquired etiologies (Table 1).
Renal Tubular Acidosis

DISTAL RTA (TYPE 1)

CASE PATIENT 1
Initial Presentation and Evaluation
A 25-year-old man presents to the emergency department complaining of muscle weakness and increased urination over the past few weeks. He had 2 episodes of a similar nature in the past and was told it was likely related to recent episodes of diarrhea. At this time, he has had no diarrhea. The weakness is diffuse, but he has no symptoms of paresthesias or dysesthesias. His hearing is normal. He denies using any medications nor has he experienced any nausea and vomiting. He has a past medical history of 2 episodes of kidney stones. There is a strong family history of episodes of muscle weakness and of kidney stones occurring in his father and in his twin brother. Physical examination is normal except for mild diffuse muscle weakness.

The following laboratory data are obtained: blood urea nitrogen (BUN), 18 mg/dL; creatinine, 1.2 mg/dL; arterial pH, 7.30; PCO₂, 34 mm Hg; PO₂, 100 mm Hg; sodium, 138 mEq/L; potassium, 2.7 mEq/L; chloride, 110 mEq/L; and HCO₃⁻, 16 mEq/L. Urinary electrolyte values are as follows: sodium, 110 mEq/day; potassium, 65 mEq/day; and chloride, 145 mEq/day. Urinalysis shows a pH of 6.0, specific gravity of 1.005, and normal sediment.

• What is the most likely diagnosis?

The hypokalemia and hyperchloremic metabolic acidosis suggest either lower gastrointestinal or renal losses of potassium and HCO₃⁻. The absence of a history of diarrhea, the high rate of urine potassium excretion in the face of hypokalemia, and the elevated urine pH in the face of acidemia suggest renal potassium wasting, making RTA a distinct possibility. Distal (classic or type 1) RTA is caused by impaired distal acidification and is characterized by an inability to lower urinary pH maximally (< 5.5) under the stimulus of systemic acidemia. The impaired excretion of ammonium is secondary to this defect. In distal RTA, HCO₃⁻ reabsorption by the proximal tubule and by the loop of Henle generally is normal; however, a minor degree of bicarbonaturia may be present.

Distal RTA arises when there is an innate failure of the distal nephron to secrete H⁺ or when the transport systems are intact but inhibited by an extrinsic condition (discussed below). A number of genes that encode transport proteins that control H⁺ secretion have been identified, and distal RTA can occur as a result of mutations in these genes. The molecular basis of some of the acquired cases of distal RTA is not as well understood but probably involves damage to or antibodies against key transport proteins, such as the H⁺-ATPase in the α-type intercalated cells of the collecting duct.

• What are the mechanisms responsible for distal RTA?

The key to the pathogenesis of distal RTA is the inability to maintain a pH gradient of at least pH 7:pH 5.2 between the interior of the collecting tubule cell and the tubular fluid (urine). In the absence of this gradient, ammonia diffuses into the tubular lumen but does not

<table>
<thead>
<tr>
<th>Table 1. Hypokalemic Forms of Renal Tubular Acidosis (RTA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal RTA (type 2)</td>
</tr>
<tr>
<td>Primary/hereditary</td>
</tr>
<tr>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Autosomal recessive associated with mental retardation and ocular abnormalities</td>
</tr>
<tr>
<td>Sporadic</td>
</tr>
<tr>
<td>Secondary</td>
</tr>
<tr>
<td>Associated with the Fanconi syndrome (cystinosis, galactosemia, Wilson disease, Lowe syndrome, multiple myeloma, light chain disease)</td>
</tr>
<tr>
<td>Drugs and toxins (acetazolamide, outdated tetracycline, aminoglycoside antibiotics, valproate, 6-mercaptopurine, ifosfamide, lead, cadmium, mercury)</td>
</tr>
<tr>
<td>Distal RTA (type 1)</td>
</tr>
<tr>
<td>Primary chronic form</td>
</tr>
<tr>
<td>Sporadic or inherited as autosomal dominant or autosomal recessive</td>
</tr>
<tr>
<td>Autosomal recessive associated with deafness</td>
</tr>
<tr>
<td>Incomplete distal RTA</td>
</tr>
<tr>
<td>Secondary</td>
</tr>
<tr>
<td>Autoimmune diseases (systemic lupus erythematosus, Sjögren’s syndrome, autoimmune hepatitis, primary biliary cirrhosis, thyroiditis)</td>
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<tr>
<td>Drugs and toxins (amphotericin B, toluene)</td>
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<tr>
<td>Renal transplant rejection</td>
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<tr>
<td>Dysproteinemia syndromes</td>
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<tr>
<td>Multiple myeloma</td>
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<tr>
<td>Hypergammaglobulinemic conditions</td>
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<tr>
<td>Cryoglobulinemia</td>
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<tr>
<td>Amyloid</td>
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Renal Tubular Acidosis

undergo conversion to the charged ammonium moiety. Ammonia then back-diffuses into the interstitium and the principle urinary buffer is lost. Since the kidney must excrete 50 to 100 mEq of H+ per day in order to generate an equal amount of H+, overall acid excretion (and H+ production) fails to match acid generation and systemic acidosis ensues. Thus, while glomerular filtration is intact and all other synthetic functions of the kidney such as ammoniagenesis are intact, the failure to secrete H+ into the terminal portions of the nephron, and thus to maintain a steep pH gradient, proves to be a rate-limiting step in renal acid-base homeostasis.

There are 3 basic abnormalities that may underlie the abnormal H+ secretion of distal RTA: decreased activity of the H+-ATPase in the intercalated cells of the collecting tubule;25 abnormal permeability of the luminal membrane of the collecting tubule cells;26 and reduction in sodium reabsorption in principal cells, which secondarily depresses H+ secretion.27 Decreased H+-ATPase is a common basis for the inability to secrete H+ and therefore to generate new HCO3− in the distal nephron. The molecular basis for this abnormality may lie in immunologically-mediated damage to the pump, as may be seen in Sjögren’s syndrome, in mutations in the genes encoding subunits of the ATPase, or mutations in genes responsible for transport of HCO3− from the cell to the blood.28,29 An example of the latter mutation involves the gene encoding the Cl−/HCO3− exchange protein in the basolateral surface of the intercalated cell. If this protein is defective or absent, HCO3− would accumulate in the cell and reduce the cellular production of H+ for secretion and ammonia buffering.30

The inability of the distal nephron to maintain a steep pH gradient between cell and lumen also could be due to increased back-leak of secreted H+ (gradient defect) or an inability to generate or maintain a negative transepithelial voltage difference (voltage defect).31 A clear example of the permeability-based defect is amphotericin-induced RTA. Amphotericin is known to produce nonspecific “holes” in the luminal membrane of renal distal tubules, among other forms of renal injury. In the distal nephron, these structural defects lead to back-leak of H+ into the distal tubular cells and H+ secretion fails to occur.26 An example of the voltage form of RTA is obstructive uropathy.32 The failure to reabsorb sodium leads to a failure to maintain a highly negative voltage at the luminal membranes; hence, there is less of a driving force for secretion of the positively charged H+. Other conditions in which a voltage type of defect is seen include treatment with amiloride, trimethoprim, and pentamidine.1,33,34 The 3 agents bind to and interfere with the function of the ENaC.

It should be noted that any form of renal disease in which there is reduced buffer capacity of the urine at the site of H+ secretion would present a superficial clinical picture resembling distal RTA with a hyperchloremic metabolic acidosis. However, the inability to maintain the urine pH below 5.2 in the face of systemic acidosis implies that the defect involves H+ secretion or maintenance of a gradient and thereby defines such a case as an underlying RTA of the distal type.

The case patient likely has a familial form of RTA based on the positive family history and lack of obvious secondary causes. If the RTA is hereditary, the patient likely has a mutation in the gene encoding the α4 subunits of the H+-ATPase pump given the fact that he has no hearing deficits.

• What laboratory findings are used in the diagnosis of distal RTA?

URINE pH

The measurement of urine pH is a basic step in evaluating distal urinary acidification. As noted, the free H+ content of the urine represents only a tiny fraction of the H+ that must be secreted each day to maintain acid-base balance. However, the maintenance of a low urine pH is crucial to allowing the excretion of adequate amounts of ammonium to allow HCO3− production to proceed and H+ to be secreted.1

The urine pH should be measured electrometrically in a fresh random morning urinary sample collected under oil, since escape of the dissolved, carbonic-acid–producing carbon dioxide will allow the urine pH to rise artifically. The measurement must be done at a time when there is a clear-cut systemic acidemia.35 A low urine pH does not ensure a normal distal urinary acidification mechanism if production of ammonium is low due to defects in synthesis. Moreover, a patient may have a urine pH between 5.6 and 5.9 without necessarily having a deficiency of HCO3− generation if ammoniagenesis occurs at a very high rate.35 It also should be remembered that a high urine pH might be secondary to urinary infection with urea-splitting organisms such as Proteus species.36 Hence, urine pH is an important component of diagnosing renal acidification defects, but it must be interpreted using other relevant data.

URINE ANION GAP

The urine anion gap is an indirect index of urinary ammonium excretion in patients with non-anion gap metabolic acidosis.37 The urine anion gap is calculated using the following formula:
AG = ([urinary Na⁺] + [urinary K⁺]) – [urinary Cl⁻]

The urine anion gap is virtually equal to the concentration of ammonium minus the concentration of unmeasured anions such as phosphate, sulfate, and organic anions. The excretion of these anions remains relatively constant as they generally reflect dietary intake. In the normal kidney, as ammoniagenesis increases during metabolic acidosis and urinary ammonium excretion increases, there is a parallel increase in the excretion of chloride. The urine anion gap becomes progressively more “negative,” reflecting a stable sodium and potassium excretion but a rising chloride excretion to maintain electroneutrality of the urine. In distal RTA, as urinary acidification fails, the excretion of ammonium becomes minimal and the urine anion gap becomes positive or close to 0. The finding of a minimal or positive urine anion gap in the face of metabolic acidosis is a very strong indicator of distal RTA.48

HYPOCITRATURIA

Normal daily urinary excretion of citrate is approximately 300 to 900 mg; values are substantially higher in premenopausal women, especially pregnant women, than in men. Hypocitraturia usually occurs in all forms of metabolic acidosis but is particularly profound in distal RTA. Hypocitraturia is perhaps the most important risk factor for calcium stone formation and nephrocalcinosis in patients with distal RTA because citrate is the principal chelator of calcium in the urine and its absence allows the precipitation of calcium crystals into kidney stones or into the renal interstitium where nephrocalcinosis occurs.39 Nephrocalcinosis leads to renal inflammation and ultimately interstitial fibrosis and renal insufficiency.40 Other causes of hypocitraturia include potassium depletion, presumably because of intracellular acidosis;41 bacteriuria, because the infecting organisms may metabolize the urinary citrate; and acidifying conditions, such as renal insufficiency and chronic diarrhea.42 An idiopathic variety of hypocitraturia may be associated with recurrent nephrolithiasis in many patients, partly because of excessive dietary protein intake, which leads to increased endogenous acid production and excretion.43 Recent studies have shown an important role for the enzyme citrate lyase in the hypocitraturia of metabolic acidosis.44 Low intracellular pH in the proximal tubule activates this enzyme and leads to increased intracellular citrate utilization, thereby enhancing citrate absorption and lowering urinary citrate in metabolic acidosis. This response is teleologically beneficial as the reabsorbed citrate enters the TCA metabolic cycle and is metabolized to HCO₃⁻, thus mitigating metabolic acidosis.

• What is the basis of hypokalemia seen in this patient?

Potassium depletion is common in patients with metabolic acidosis due to gastrointestinal and/or renal losses of potassium.45 In acute metabolic acidosis, the initial serum potassium concentration is frequently normal as a result of cellular buffering of H⁺ with shifts of potassium out of cells. Indeed, when hypokalemia initially presents with metabolic acidosis, there is a very severe potassium deficit, and correction of the acidosis results in further reduction in serum potassium concentrations. Hypokalemia is present in most cases of distal RTA because the impairment in the H⁺-ATPase pump results in more potassium secretion in the cortical collecting duct as K⁺/Na⁺ exchange becomes a dominant mechanism for sodium reabsorption to maintain electroneutrality.46 In addition, metabolic acidosis will diminish net proximal fluid reabsorption, leading to increased distal salt delivery and secondary hyperaldosteronism, further augmenting potassium losses. In addition, if the mechanism of the distal RTA is a form of increased luminal permeability in the collecting duct cells, this may also lead to enhanced potassium losses into the urine. Finally, if the defect is in the H⁺,K⁺-ATPase pump, potassium reabsorption will fall, leading to increased potassium excretion.47

• What therapy should be used in this patient?

For distal RTA, the goal of therapy is to provide HCO₃⁻ or HCO₃⁻ equivalents to balance the loss of HCO₃⁻ that arises from buffering of daily H⁺ generation.48 Sufficient alkali should be provided to maintain urinary citrate excretion in the normal range (> 300 mg/day). This strategy uses the fact that any degree of intracellular acidosis will result in a fall in urinary citrate excretion. Normalizing citrate excretion with alkali repairs the underlying acidosis completely and provides the key factor to prevent the major complication of acidosis, nephrocalcinosis. Because H⁺ release from bone occurs during the process of skeletal growth, the daily amount of alkali required per kilogram of body weight decreases from infancy to adulthood.49 In young infants, daily alkali amounts are between 5 and 8 mmol/kg, while 3 to 4 mmol/kg and 1 to 2 mmol/kg are required in children and adults, respectively. Potassium citrate is the preferred form of alkali therapy as it produces far less gastrointestinal distress than equivalent doses of sodium or potassium bicarbonate. An appropriate dosage should correct most of the urinary abnormalities, including hypercalciuria.

Correction of the hypercalciuria should also be a goal of therapy. Hypercalciuria results from acidosis, which is mediated by a direct effect of acidosis to inhibit urinary calcium reabsorption as well as an effect on bone to increase calcium release.50
Monitoring the urinary calcium-to-creatinine ratio and the citrate-to-creatinine ratio is a valuable tool to calculate an adequate amount of alkali supplementation. It is important to avoid overcorrection of the acidosis because this produces expansion of extracellular fluid volume and an unintended increase in the urinary calcium excretion.

Primary distal RTA is a permanent disease, and therapy should be maintained throughout life. Nevertheless, prognosis is excellent if the diagnosis has been made early in life and appropriate amounts of alkali supplements are continuously administered. Alkali therapy restores growth in children and prevents the progression of nephrocalcinosis at all ages. However, if therapy is delayed to late childhood or adulthood, progression to end-stage renal insufficiency, as a result of nephrocalcinosis, may not be avoided.

PROXIMAL RTA (TYPE 2)

CASE PATIENT 2
Initial Presentation and Evaluation

A 68-year-old man with a history of back pain and weakness enters the outpatient department. He is not taking any medications, and there is no family history of weakness. Physical examination is normal except for mild diffuse muscle weakness and pallor.

The following laboratory data are obtained: BUN, 24 mg/dL; creatinine, 1.3 mg/dL; sodium, 138 mEq/L; potassium, 2.7 mEq/L; chloride, 122 mEq/L; total CO₂, 16 mmoles/L; uric acid, 2.1 mg/dL; hemoglobin, 8.6 mg/dL; arterial pH, 7.30; Pco₂, 34 mm Hg; Po₂, 100 mm Hg; HCO₃⁻, 16 mEq/L. Urine electrolyte values are as follows: sodium, 110 mEq/day; potassium, 65 mEq/day; and chloride, 145 mEq/day. Urinalysis reveals 1+ protein, 2+ glucose, pH of 5.3, specific gravity of 1.005, and normal sediment.

What is the likely diagnosis?

The hyperchloremic metabolic acidosis, the hypokalemia, and the presence of glycosuria in the face of normal blood glucose suggest that this patient has proximal (type 2) RTA. The etiology is likely proximal tubular damage secondary to a nephrotoxic myeloma paraprotein. Anemia due to bone marrow invasion and a low plasma anion gap due to a large amount of cationic immunoglobulin G are clues to the presence of multiple myeloma.

Proximal RTA may occur as a primary, isolated entity or be accompanied by other proximal tubular defects; in the latter instance, it is considered to be part of the Fanconi syndrome. Proximal RTA may also have a hereditary origin, be secondary to administration of drugs and toxins, or be associated with a number of varied diseases (Table 1). Nephrocalcinosis and urolithiasis occur infrequently, even in situations in which hypercalciuria is present.

What pathophysiologic features of proximal RTA differentiate it from distal RTA?

Type 2 RTA is characterized by HCO₃⁻ wasting only when the plasma HCO₃⁻ concentration is above the HCO₃⁻ reabsorptive threshold. This threshold is a function of a number of factors, including the activity of the Na⁺/H⁺ exchanger in the proximal tubule, the activity of the carbonic anhydrase enzyme both within the cell and at the luminal membrane, the activity of the Na⁺/HCO₃⁻ cotransport system at the basolateral cell membrane, the overall rate of proximal tubular sodium reabsorption, and the intracellular pH (and therefore the availability of H⁺ ions for secretion) (Figure 1). Since the more distal segments of the nephron such as the loop of Henle and the distal convoluted tubule have HCO₃⁻ reabsorptive capacity, not all filtered HCO₃⁻ is lost into the urine, and the plasma HCO₃⁻ concentration is usually maintained between 12 and 20 mEq/L in this disorder. When the serum HCO₃⁻ is at or below the reabsorptive threshold, most of the disturbances in urine acidification cannot be detected. Thus, urine pH is below 5.3, urine ammonia production may be normal, and urinary potassium wasting may not be seen. However, if the patient is given HCO₃⁻ in an attempt to correct the ongoing acidosis, the distal nephron is not capable of handling the large, incremental delivery of HCO₃⁻. The urine then becomes highly alkaline and contains a great fraction of the filtered load (10% to 15%), potassium wasting begins, and ammonium excretion falls. This HCO₃⁻ wasting is a transient phenomenon, and a steady state is again maintained when plasma HCO₃⁻ concentration stabilizes in the acidemic range. Citrate excretion is usually not reduced in proximal RTA, likely because citrate reabsorption is defective in the proximal tubule. Hence, there is little nephro lithiasis or nephrocalcinosis in this condition. In distal (type 1) RTA, there is an inability to excrete the daily acid load; in the absence of alkali therapy, this defect results in progressive H⁺ retention, and plasma HCO₃⁻ concentration that may fall below 10 mEq/L.

How can the diagnosis of proximal RTA be made?

The diagnosis of proximal (type 2) RTA disorder can be made simply by infusing sodium bicarbonate intravenously at a rate of 0.5 to 1.0 mEq/kg/hr in order to
Renal Tubular Acidosis

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raise the serum HCO₃⁻ level to a value above the threshold, usually to 20 mEq/L. Once the proximal tubular threshold for HCO₃⁻ reabsorption is exceeded, the urine pH will rise rapidly.⁵⁵ The urine pH will be above 7.5, and the fraction of filtered HCO₃⁻ excreted (FE HCO₃⁻) will exceed 10% to 15%. FE HCO₃⁻ may be calculated from the following equation:

\[ \text{FE HCO}_3^- = \frac{\text{urinary HCO}_3^- / \text{plasma HCO}_3^-}{\text{urinary creatinine} / \text{plasma creatinine}} \]

**HYPERKALEMIC RTA (TYPE 4)**

**CASE PATIENT 3**

**Initial Presentation and Evaluation**

A 60-year-old obese man with a 14-year history of type 2 diabetes mellitus and degenerative arthritis of his knees is admitted to the hospital with chest pain. His only medication is glipizide 5 mg/day. Blood pressure is 180/100 mm Hg supine. His lungs are clear, and he has 1+ lower extremity edema.

The patient is placed on a low sodium diet and fluid restriction and started on nitrates and furosemide 20 mg/day. Electrocardiography and cardiac enzymes rule out myocardial infarction. He is placed on ibuprofen (a nonsteroidal anti-inflammatory drug) 400 mg 3 times daily because of pain in his knees. A chemistry profile on the fourth hospital day reveals the following pattern:

<table>
<thead>
<tr>
<th>Hospital Day 4</th>
<th>Admission</th>
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<tbody>
<tr>
<td>BUN (mg/dL)</td>
<td>27</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.9</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>260</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>140</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.8</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>110</td>
</tr>
<tr>
<td>Total CO₂ (mMoles/L)</td>
<td>18</td>
</tr>
</tbody>
</table>

Urinalysis reveals 4+ glucose, trace ketones, 3+ protein, and pH of 5.

- What is the likely cause of RTA in this patient?
- What are the pathogenic mechanisms of acquired hyperkalemic RTA?

Hyperkalemic RTA (type 4) is characterized by hyperkalemia, hyperchloremic acidosis, and an acid urine pH (< 5.2). The basic defect in this condition is a failure of potassium secretion and resultant hyperkalemia.⁵⁵,⁵⁶ The pathophysiology of type 4 RTA is complex but involves an acquired mineralocorticoid deficiency, either a primary defect in mineralocorticoid production at the level of the adrenal gland or secondary to hyporeninemia in patients with mild to moderate renal insufficiency, often due to diabetic nephropathy, systemic lupus erythematosus, or AIDS nephropathy (Table 2).⁵⁷ It is also a common characteristic of a number of tubulointerstitial renal diseases that demonstrate reduced responsiveness to aldosterone and defective tubular potassium secretion. Type 4 RTA may also result from the side effects of a number of drugs.⁵⁸ In this patient, it is likely secondary to diabetic nephropathy.

The acidification defect is mainly caused by impaired ammoniagenesis and is characterized by a normal ability to acidify the urine after an acid load but a subnormal net acid excretion due to very low rates of ammonium excretion. Hyperkalemia impairs ammoniagenesis since it is associated with a paradoxical rise in intracellular pH, the mirror image of the intracellular acidosis that characterizes hypokalemia.⁵⁹ The mechanism of the

**Table 2. Causes of Hyperkalemic RTA (Type 4)**

<table>
<thead>
<tr>
<th>Primary mineralocorticoid deficiency</th>
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<tbody>
<tr>
<td>Addison’s disease</td>
</tr>
<tr>
<td>Isolated hypoaldosteronism</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>Secondary/hyporeninemic hypoaldosteronism</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>AIDS nephropathy</td>
</tr>
<tr>
<td>Mineralocorticoid resistance (genetic disorders)</td>
</tr>
<tr>
<td>Primary pseudohypoaldosteronism type 1</td>
</tr>
<tr>
<td>Primary pseudohypoaldosteronism type 2 (Gordon syndrome)</td>
</tr>
<tr>
<td>Associated with chronic interstitial nephropathies</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
</tr>
<tr>
<td>Medullary cystic disease</td>
</tr>
<tr>
<td>Various forms of acute interstitial nephritis</td>
</tr>
<tr>
<td>Acute renal transplant rejection</td>
</tr>
<tr>
<td>Analgesic abuse nephropathy</td>
</tr>
<tr>
<td>Drug-induced hyperkalemia</td>
</tr>
<tr>
<td>Inhibition of renin-aldosterone axis</td>
</tr>
<tr>
<td>(cyclo-oxygenase inhibitors, converting enzyme inhibitors, heparin, spironolactone)</td>
</tr>
<tr>
<td>Inhibitors of renal potassium secretion (potassium-retaining diuretics, trimethoprim, pentamidine, cyclosporin A)</td>
</tr>
</tbody>
</table>

intracellular alkalosis is felt to be a rise in cellular potassium in the face of hyperkalemia and a subsequent egress of $\text{H}^+$ from the cell interior in order to maintain electroneutrality in the cell. The enzymatic pathways responsible for ammoniagenesis are $\text{pH}$ dependent and are inhibited by the higher cell $\text{pH}$. This defect is reversible if hyperkalemia is corrected, for example, by the use of cation exchange resins such as Kayexalate or the use of kaliuretic diuretics.

The cause of hyporeninemia in this condition is also complex in origin. It may be the result of chronic suppression of renin secretion through chronic extracellular fluid volume overload or through some neurohumoral consequence of chronic volume overload conditions such as congestive heart failure. Studies have documented that chronic diuretic administration can reverse the hyporeninemia and the type 4 RTA, suggesting that hyporeninemia is a functional disorder.

Type 4 RTA has similarities to the voltage-dependent form of distal RTA, particularly the finding of hyperkalemia, although unlike in the distal condition, the ability to lower urinary $\text{pH}$ in response to systemic acidosis is maintained. Although the decrease in ammonia production is mainly caused by the hyperkalemia itself, aldosterone deficiency or resistance may also play a contributory role.

### What are the mechanisms of genetic forms of hyperkalemic RTA?

An interesting genetic form of hyperkalemic RTA is primary pseudohypoaldosteronism type 2, or Gordon syndrome. This condition is inherited as an autosomal dominant syndrome consisting of arterial hypertension, hyperkalemia, metabolic acidosis, and hyporeninemia. The mechanism of this inherited disorder is a series of gain-of-function mutations in the genes encoding the WNK4 kinase, which probably plays an important role in electrolyte homeostasis by increasing the transcellular and paracellular conductance to chloride. The name “chloride-shunt syndrome” also has been proposed due to the existence of a tubular hyperreabsorption of sodium chloride in the thick ascending Henle’s loop and early distal tubule, leading to impaired potassium and $\text{H}^+$ secretion in the collecting duct because of reduced sodium delivery to those sites for the $\text{Na}^+/\text{K}^+$ and $\text{Na}^+/\text{H}^+$ exchange pathways found in the distal nephron.

Type I pseudohypoaldosteronism (PHA-1) is a rare salt wasting syndrome that occurs soon after birth and is characterized by apathy and severe dehydration accompanied by hyponatremia, hyperkalemia, and metabolic acidosis despite high plasma aldosterone concentrations. It is only seen in children. The molecular defect involved in the systemic autosomal recessive form of the syndrome has been identified. Mutations in all 3 genes encoding the ENaC lead to a decrease in the channel function, resulting in the disease. This syndrome is similar to the effects of amiloride, where absence of entry of sodium into the sodium channel leads to loss of the lumen negative potential voltage in the distal nephron, secondary reduction in the electrochemical gradient for potassium and $\text{H}^+$ secretion, and limitation of the availability of sodium to drive cell potassium entry via the $\text{Na}^+\text{K}^+\text{ATPase}$ at the basolateral membrane (Figure 2).

### How is acquired hyperkalemic RTA treated?

Treatment and prognosis of acquired hyperkalemic type 4 RTA depends on the underlying cause. Agents such as spironolactone or drugs of the amiloride class that interfere with sodium uptake in the distal nephron should be withdrawn. Dietary potassium should be reduced and severe sodium restrictions should be loosened, as an extremely low sodium diet usually contains large quantities of potassium and impairs potassium excretion by limiting sodium delivery to the distal nephron. Hyopaldosteronism due to adrenal failure may respond adequately to replacement doses of fludrocortisone. Fludrocortisone therapy may also be useful in hyporeninemic hypoaldosteronism, preferably in combination with a loop diuretic such as furosemide to reduce the risk of extracellular fluid volume expansion. In some cases, alkali supplements (1.5 to 2 mmol/kg daily) are also required.

### REFERENCES

1134–45; discussion 1134–9.


38. Streather CP, Phillips AO, Goodman FR, Scoble JE. How often should we measure the urinary anion gap for cases of suspected renal tubular acidosis? Nephrol Dial
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