

Renal Tubular Acidosis

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ABSTRACT

Renal tubular acidosis (RTA) refers to a group of disorders characterised by impaired renal acid excretion, resulting in normal anion gap (hyperchloremic) metabolic acidosis with either hypokalaemia or hyperkalaemia and a relatively well-preserved GFR. Proximal RTA (type 2 RTA) is caused by reduced ability to reabsorb HCO_3^- in the proximal tubules, while distal RTA (type 1 RTA) is caused by a defect in distal H^+ ion excretion. Type 1 RTA is characteristically associated with urinary pH more than 5.5, while the urine pH is less than 5.5 in type 2 RTA. Sjogren's syndrome has a strong association with type 1 RTA. One must always consider myeloma in the differential in patients presenting with type 2 RTA.

While both conditions are treated with alkali and potassium replacement, type 2 RTA often needs larger doses of alkali, which can cause worsening of the hypokalaemia. In these patients, and the type 1 RTA patients who are recurrent renal calcium stone formers, one can use potassium citrate for alkali replacement.

Type 4 RTA is most commonly caused by aldosterone deficiency or tubular resistance to the action of aldosterone. It is common in those with diabetes and is also associated with drugs which interfere with the RAAS pathway, i.e., ACEI or ARB, as well as aldosterone antagonists such as spironolactone. While synthetic mineralocorticoids such as fludrocortisone are effective, in patients with hypertension or fluid overload, thiazide or loop diuretics may be helpful.

INTRODUCTION

Renal tubular acidosis (RTA) refers to a group of disorders characterised by normal anion gap (hyperchloremic) metabolic acidosis with either hypokalaemia or hyperkalaemia.

Both proximal and distal RTAs (types 2 and 1 RTA respectively) present with hypokalaemia, while type 4 RTA presents with hyperkalaemia. Type 2 RTA is caused by reduced proximal tubular ability to reabsorb bicarbonate (HCO_3^-) leading to HCO_3^- wasting in the urine with the resultant metabolic acidosis, while type 1 RTA is caused by defects in distal tubular hydrogen (H^+) excretion leading to H^+ retention and metabolic acidosis.

Type 4 RTA is due to either aldosterone deficiency or tubular resistance to the action of aldosterone. Less commonly, this condition is caused by inherited or acquired defects in sodium (Na^+) transport in the principal cells in the collecting duct.

While type 1 RTA occurs more frequently than type 2 RTA, type 4 RTA is the commonest among the RTAs.

KIDNEY'S ROLE IN MAINTAINING ACID-BASE AND POTASSIUM BALANCE.

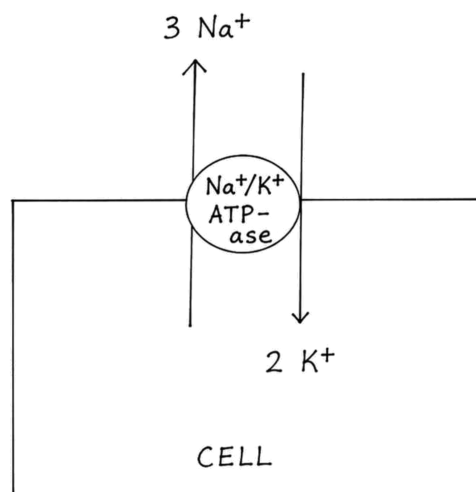
The normal acid-base balance of the body depends on the removal of carbon dioxide (CO_2) by the lungs via alveolar ventilation and renal proximal tubular reabsorption of filtered HCO_3^- and distal tubular excretion of H^+ ions.

While the glomeruli freely filter HCO_3^- , 85-90 % of this HCO_3^- is reabsorbed in the proximal convoluted tubules (PCT); the remaining 10-15% is reabsorbed in the distal nephron by the intercalated cells.

An average healthy adult generates 50 to 70 mEq of acid per day from diet, most of which is excreted in the urine by tubular secretion. Excretion of this acid load in the form of H^+ requires urinary buffers, as otherwise the urine would become supersaturated with excessive H^+ and the pH would drop severely, inhibiting further H^+ secretion. The chief urinary buffers are ammonia-ammonium (NH_3 and NH_4^+) and phosphate (HPO_4^{2-} and $\text{H}_2\text{PO}_4^{-1}$).

TYPE 2 RTA

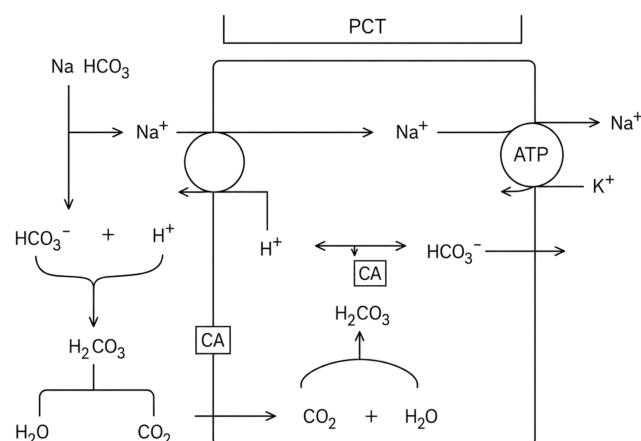
Type 2 RTA is characterised by the reduction in proximal tubular capacity to reabsorb HCO_3^- . Like every other cell in the body, in the renal tubular cells, basolateral Na^+-K^+ -ATPase creates a low intracellular Na^+ concentration by extruding three Na^+ ions from the cell in exchange for two K^+ ions (diagram 1). This creates the electrochemical gradient that drives tubular Na^+ reabsorption.



Diag 1- The Na^+-K^+ -ATPase extrudes 3 Na^+ and pulls in 2 K^+ into cells, leading to the cells being low in Na^+ and high in K^+ and also electronegative.

Sodium bicarbonate (NaHCO_3) is freely filtered across the glomerular capillaries and dissociates in the lumen of PCT into Na^+ and HCO_3^- . As the tubular cell reabsorbs the Na^+ (leaving behind HCO_3^- in the tubular lumen), it secretes an H^+ into the tubular lumen. In the tubular lumen, H^+ combines with HCO_3^- to form carbonic acid (H_2CO_3), which is converted by luminal carbonic anhydrase to CO_2 and H_2O . CO_2 readily diffuses into the tubular cell, where it is reconverted to H_2CO_3 and subsequently dissociates into H^+ and HCO_3^- under the influence of intracellular carbonic anhydrase.

The H^+ is secreted into the PCT lumen as described above, while the HCO_3^- diffuses into the peritubular capillaries (diagram 2). The net result is that both Na^+ and HCO_3^- (derived from the filtered NaHCO_3) are reabsorbed in the PCT cells. Also, as Na^+ is reabsorbed, it helps to co-transport glucose, phosphate, uric acid and amino acids.



Diag 2- Action of carbonic anhydrase (CA) in reclaiming HCO_3^- in the Proximal Convoluted Tubule (PCT).

Under normal circumstances, urine does not have any NaHCO_3 , and so, one would expect the urinary pH to be high in type 2 RTA due to the presence of NaHCO_3 in urine. However, this does not occur because the distal tubules compensate for the metabolic acidosis by secreting extra H^+ , resulting in urinary pH below 5.5. On the other hand, in type 1 RTA, the urine pH is higher than 5.5 due to the inability of the distal tubules to secrete H^+ . Thus, while both types 1 and 2 RTA present with metabolic acidosis and hypokalaemia, one can distinguish between the two with the aid of urinary pH, being >5.5 in type 1 and <5.5 in type 2 RTA. Importantly, in patients with type 1 RTA who receive alkali therapy, the increased filtered bicarbonate load overwhelms the tubular capacity to secrete additional acid, and the urine pH is frequently above 5.5 in this scenario.

As Na^+ and HCO_3^- reabsorption is coupled in the proximal tubule, impaired HCO_3^- reabsorption in type 2 RTA results in urinary wasting of both HCO_3^- and Na^+ . The increased delivery of Na^+ to the collecting duct enhances distal Na^+ reabsorption through epithelial sodium channels (ENaC). This generates a negative luminal potential, which promotes K^+ secretion into the tubular lumen leading to increased urinary K^+ losses and hypokalaemia.

Also, Na^+ reabsorption in the PCT helps to co-transport amino acids, glucose, uric acid, and phosphate. Type 2 RTA can occur as an isolated defect in HCO_3^- reabsorption or as a generalised defect in proximal tubular reabsorption with amino aciduria, phosphaturia, glycosuria, and uric aciduria. This condition is termed Fanconi syndrome and presents with normal anion gap metabolic acidosis with hypokalaemia, urine pH < 5.5 , glycosuria, proteinuria, and low plasma phosphate and uric acid.

In type 2 RTA, one must always suspect myeloma, where the filtered immunoglobulin light chains can lead to this condition by causing PCT cellular toxicity. Importantly, one must be mindful of medications such as tenofovir, cisplatin, oxaliplatin, acetazolamide and topiramate due to their carbonic anhydrase inhibitor effect (table 1). Also, while the association of SGLT2 inhibitors with type 2 RTA and Fanconi syndrome is rare, one must be mindful given the widespread use of this group of medications.

Table 1: Causes of type 2 RTA

Category	Examples
M protein disorders	- Multiple Myeloma - Light chain disease - Amyloidosis
Drugs	- Tenofovir and related anti-retroviral drugs - Carbonic anhydrase inhibitors (acetazolamide, topiramate) - Outdated tetracycline - Ifosfomide (can also cause type 1 RTA) - Platinum chemotherapy (cisplatin/oxaliplatin) - SGLT2 inhibitors

Category	Examples
Heavy metals	- Lead - Cadmium - Copper - Mercury
Familial	- Wilson disease - Lowe syndrome - Cystinosis - Tyrosinemia
Miscellaneous	- Paroxysmal nocturnal hemoglobinuria - Severe vitamin D deficiency or resistance

TYPE 1 RTA

Type 1 RTA is caused by the inability of the distal tubules to secrete H^+ . While most patients with metabolic acidosis due to any cause have low urine pH due to the renal excretion of excess H^+ as a compensatory phenomenon, in type 1 RTA, the kidney characteristically cannot lower the urinary pH to less than 5.5 due to a deficiency of H^+ in the urine.

Na^+ is reabsorbed in the tubules in exchange for a cation, such as K^+ or H^+ . As cortical collecting duct H^+ secretion is impaired in type 1 RTA, the K^+ secretion increases as compensation, leading to hypokalaemia.

While type 1 RTA may be inherited, acquired causes are more common. Up to 25% of patients with Sjogren's syndrome have this condition. Other associated conditions include systemic lupus erythematosus (SLE), hypergammaglobulinemic states, primary biliary cirrhosis, autoimmune hepatitis, hypercalciuria, obstructive uropathy, and renal transplantation (Table 2).

Table 2: Causes of Type 1 RTA

Category	Examples
Autoimmune disorders	- Sjogren's syndrome - SLE - Autoimmune hepatitis - Primary biliary cirrhosis - Rheumatoid Arthritis
Drugs	- Amphotericin - Lithium - Ibuprofen - Ifosfomide (can also cause type 2 RTA)
Hypercalciuric conditions	- Hyperparathyroidism - Vitamin D intoxication - Sarcoidosis
Miscellaneous causes	- Renal transplantation - Obstructive uropathy - Medullary sponge kidney

In both type 1 and type 2 RTAs, as indeed in any form of chronic metabolic acidosis, the skeletal system releases calcium and phosphate salts to buffer the excess H^+ ions. Over time, this can lead to osteopenia, osteoporosis, and increased urinary calcium

excretion (hypercalciuria).

Under normal conditions, urinary citrate forms a soluble complex with calcium, therefore preventing the formation of renal calcium stones, especially in conditions leading to hypercalciuria. However, citrate also serves as an important systemic buffer and, hence, in type 1 RTA, chronic acidosis stimulates increased proximal tubular reabsorption of citrate, resulting in hypocitraturia. The reduction in urinary citrate decreases calcium solubility and promotes calcium salt crystallisation.

In addition, the persistently alkaline urine characteristic of type 1 RTA markedly diminishes urinary calcium solubility. The combination of hypercalciuria, hypocitraturia, and alkaline urine increases the risk of nephrocalcinosis and nephrolithiasis, making these complications particularly common in type 1 RTA.

DIAGNOSIS OF TYPES 1 AND 2 RTA

As both type 1 and type 2 RTA present with normal anion gap metabolic acidosis and hypokalaemia, the only definitive way to distinguish between the two conditions is the urine pH (table 3). Type 1 RTA is characteristically associated with a urinary pH more than 5.5. In contrast, the urinary pH is usually lower than 5.5 in type 2 RTA, except when the patient is being treated with massive doses of alkali. Hypophosphatemia, hypouricemia, and glycosuria in the absence of diabetes mellitus point towards Fanconi syndrome.

Severe and prolonged diarrhoea can also lead to normal anion gap metabolic acidosis and hypokalaemia but can be distinguished by the urine anion and osmolar gaps as discussed below.

Normal anion gap (hyperchloremic) metabolic acidosis with hypokalaemia in diarrhoea and usefulness of urine anion and osmolar gaps to differentiate from RTA

Chronic diarrhoeal states may present with normal anion gap metabolic acidosis and hypokalaemia and hence simulate RTA. The mechanism is as follows:

- Metabolic acidosis: due to faecal loss of bicarbonate-rich pancreatic secretions
- Hypokalaemia: hypovolemia leads to activation of the renin-angiotensin-aldosterone system (RAAS) with the resultant tubular loss of K^+ under the influence of aldosterone.

The urine anion gap (UAG) calculation helps to differentiate between RTA type 1 and extra-renal causes of normal anion gap acidosis such as diarrhoeal states, being positive in the former and negative in the latter.

$$UAG \text{ (in mEq/L or mmol/L)} = \text{Urine } (Na^+ + K^+ - Cl^-)$$

The UAG is positive (between 20 and 90) in healthy individuals because the dietary, and hence urinary, Na^+ and K^+ exceed Cl^- . With metabolic acidosis from any cause including chronic diarrhoeal states, the kidney responds by excreting a heavy load

of H^+ which requires increased ammonia as a buffer. Since ammonia in the urine exists as NH_4Cl , this leads to increased urinary Cl^- with the result that the UAG becomes negative.

In type 1 RTA, as the distal nephron is unable to secrete H^+ effectively, there is an absence of increase in ammonium production and excretion despite the presence of metabolic acidosis. Consequently, urinary NH_4Cl excretion remains low, the urinary Cl^- does not rise, and the UAG remains inappropriately positive. A positive UAG in the setting of hyperchloremic metabolic acidosis and hypokalaemia therefore supports the diagnosis of type 1 RTA.

The urine osmolar gap (UOG) is another method of indirectly assessing renal NH_4^+ excretion in response to acidosis. It is calculated as the difference between the urine's measured osmolality and calculated osmolality, using the following formula:

$$UOG = \text{measured osmolality} - ([2 \times (Na + K)] + \text{urea} + \text{glucose (if present)})$$

A high urine osmolar gap indicates the presence of unmeasured solutes, which we can assume to be ammonium in the absence of exogenous administration of osmotically active substances such as mannitol or alcohols. This suggests that renal acid excretion is intact. In contrast, a low urine osmolar gap indicates low ammonium excretion, suggesting type 1 RTA.

The UOG is preferable to the UAG in patients with chronic kidney disease (CKD) and in patients with urinary excretion of unmeasured anions, such as in diabetic ketoacidosis.

Table 3: Differentiating features between types 1 and 2 RTA

Type	Type 1 RTA (distal RTA)	Type 2 RTA (proximal RTA)
Pathophysiology	Inability to secrete H^+	Inability to reabsorb HCO_3^-
Urine pH	pH >5.5 (low H^+ in urine)	pH <5.5 (compensatory increase in distal tubular H^+ secretion)
Renal calculi	Nephrolithiasis and nephrocalcinosis	No renal stones
Associated metabolic disturbances	No Fanconi syndrome	May have Fanconi syndrome: glycosuria, phosphaturia, uric aciduria and aminoaciduria.
Treatment	Alkali and K^+ replacement	Alkali and K^+ replacement (bigger doses of alkali often required)

TYPE 4 RTA (HYPERKALEMIC DISTAL TUBULAR ACIDOSIS)

Patients with type 4 RTA present with normal anion gap metabolic acidosis and hyperkalaemia. Type 4 RTA is the commonest amongst the RTAs.

Under normal circumstances, H^+ and K^+ are secreted by the collecting duct (CD) due to the intraluminal negativity generated secondary to aldosterone-induced reabsorption of Na^+ . With hypoaldosteronism or tubular unresponsiveness to aldosterone, less H^+ and K^+ are secreted into the tubules.

Hyperkalaemia additionally causes decreased tubular secretion of H^+ by decreasing renal ammonia generation; ammonia is one of the chief buffers for H^+ in the urine and is derived from breakdown of glutamine by phosphate-dependent glutaminase (PDG) in the PCT cells. Hyperkalaemia decreases PDG activity and therefore decreases ammonia production.

The aetiology of type 4 RTA can be divided into three groups based on the pathophysiology:

- Aldosterone deficiency:

- Hyporeninemic hypoaldosteronism is quite common in diabetes mellitus
- Other causes of hypoaldosteronism include NSAIDs, calcineurin inhibitors (cyclosporine and tacrolimus), ACEI or ARB groups of drugs, heparin or low-molecular-heparin.

- Tubular unresponsiveness or resistance to aldosterone:

- Potassium-sparing diuretics by either antagonising the action of aldosterone by competing for the aldosterone receptor (spironolactone and eplerenone) or closing the epithelial sodium channels in the luminal membrane (amiloride and triamterene).
- Antibiotics — Trimethoprim and pentamidine can cause type 4 RTA by closing the epithelial sodium channels in the collecting tubule with the resultant inability to excrete K^+ and H^+ .

- Voltage-dependent renal tubular acidosis (RTA):

- Markedly reduced distal Na^+ delivery as a result of reduced Na^+ intake and/or increased Na^+ reabsorption in the proximal tubules. This may occur in severe and prolonged hypovolaemia, sickle cell disease, and urinary tract obstruction.

MANAGEMENT

Types 1 and 2 RTA

Treatment of both types 1 and 2 RTA consists of potassium replacement and alkali therapy. One should be careful when administering sodium bicarbonate because the resultant Na^+ loss in urine may increase K^+ secretion and thus exacerbate hypokalaemia. In this setting, it is advisable to replace K^+ before the acidosis is corrected. As an alternative, potassium citrate is

often useful in these patients.

As explained above, type 1 RTA patients have low urinary citrate, which makes them more predisposed to recurrent urinary stones. Potassium citrate can be especially useful in this patient group.

Also, type 2 RTA often needs much bigger doses of alkali because of the tendency of the kidneys to excrete more HCO_3^- as the serum HCO_3^- concentration increases.

Type 4 RTA

In patients who are not hypertensive or volume overloaded, administration of a synthetic mineralocorticoid such as fludrocortisone may be effective. Fludrocortisone enhances Na^+ reabsorption in the distal nephron and, by promoting H^+ and K^+ secretion, corrects the acidosis and hyperkalaemia.

In patients with hypertension or known heart failure, fludrocortisone may be undesirable due to its fluid-retaining property. In such situations, a thiazide or loop diuretic may be beneficial. These agents, by increasing distal delivery of Na^+ , enhance Na^+ reabsorption through epithelial sodium channels, generating a favourable luminal electrical gradient that promotes the secretion of both H^+ and K^+ ions, thus correcting the acidosis and hyperkalaemia.

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