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REVIEW

Understanding renal tubular acidosis

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Abstract

Renal tubular acidosis is a group of disorders characterised by metabolic acidosis, hyperchloraemia, normal anion gap, and potassium imbalance. Genetic mutations, drugs or acquired disorders disrupt the function of various transport proteins and enzymes in the renal tubules, causing diminished bicarbonate reabsorption or inability to excrete hydrogen ions, leading to proximal (type 2) and distal (type 1) renal tubular acidosis, respectively. These conditions are typically associated with hypokalaemia, which, if severe, can cause muscle paralysis and dangerous cardiac arrhythmias. A rare mixed variant (type 3), including features of both type 1 and type 2 renal tubular acidosis, has also been described. On the other hand, aldosterone deficiency or resistance leads to the hyperkalaemic form of renal tubular acidosis (type 4). If untreated, renal tubular acidosis can lead to long-term severe complications such as growth retardation, osteoporosis, rickets, osteomalacia, and renal calculi. Moreover, renal tubular acidosis might be the initial presentation of a more severe underlying pathology, such as autoimmune disease or plasma cell dyscrasias. A better understanding of the condition can help physicians diagnose and treat it early and prevent adverse outcomes.

Key words: Renal tubular acidosis; Proximal; Distal; Hyperkalaemic; Pathophysiology; Aetiology; Diagnosis

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Introduction

Renal tubular acidosis (RTA) encompasses a diverse group of congenital and acquired conditions where the kidneys are unable to exert their function of reclaiming filtered bicarbonate (HCO_3^-) or excretion of the hydrogen ions (H^+) (Palmer et al, 2021). The resulting metabolic acidosis is characterised by hyperchloraemia and a normal anion gap (Boro et al, 2021). There are four types of RTA: proximal, distal, mixed, and hyperkalaemic, with proximal, distal, and hyperkalaemic being the most common forms seen in clinical practice (Yaxley and Pirrone, 2016). However, RTA remains a poorly understood condition, especially by the less experienced clinicians, making prompt identification and diagnosis challenging. A better understanding of pathophysiology can help treating physicians suspect the conditions early and instigate appropriate workups to identify the underlying cause. The current review aims to provide an overview of renal acid-base regulation, pathophysiological processes behind the development of RTA, diagnostic workup, and treatment options.

An overview of normal renal acid-base regulation

In a normal, healthy state, the acid-base balance is tightly regulated, and the systemic arterial pH is maintained within a narrow range of 7.35–7.45. Any change in pH outside this range causes significant cellular dysfunction. The body produces over 10,000 mmol of acid per day, constituting largely volatile acids in the form of carbon dioxide (CO_2) and, to a lesser extent, non-volatile acids in the form of organic acids (lactate and β-hydroxybutyrate) and inorganic acids (sulphuric and phosphoric acid) (Shaw and Gregory, 2022). CO_2 is eliminated through the lungs, while various buffers neutralise the non-volatile acids. Bicarbonate is the most critical buffer, combating most of the daily non-volatile acid load. In the process, the HCO_3^- level falls, which the kidneys replenish through the excretion of H^+ and reabsorption and generation of HCO_3^- (Imenez Silva and Mohebbi, 2022).

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Reabsorption of the filtered bicarbonate in the proximal tubules

Almost all the HCO_3^- filtered through the glomeruli is reabsorbed by the renal tubules, and little appears in the urine. 80–85% of the filtered HCO_3^- is reclaimed in the proximal tubules, while the thick ascending limb of the loop of Henle and the collecting ducts reabsorb the remaining amount (Bhandari et al, 2024). Carbonic anhydrase (CA) and several transporters, including sodium-hydrogen exchanger paralog 3 (NHE3), hydrogen ATPase (H^+-ATPase), aquaporin 1 (AQP1) channel, sodium-bicarbonate co-transporter 1 (NBCE1), and sodium-potassium ATPase (Na^+-K^+-ATPase), are involved in the process (Imenez Silva and Mohebbi, 2022).

At the apical (tubular lumen) border, NHE3 and, to a lesser extent, H^+-ATPase enable the secretion of H^+ into the tubular lumen. H^+ combines with the filtered HCO_3^- via CA IV on the luminal membrane to form carbonic acid (H_2CO_3), which rapidly disassociates to form CO_2 and water (H_2O). CO_2 enters the tubular cell through the AQP1 channel and reacts with H_2O to form H_2CO_3 via the cytoplasmic CA II. The intracellular H_2CO_3 undergoes the same rapid dissolution to form HCO_3^- and H^+. Bicarbonate moves to the bloodstream via the basolateral NBCE1 and H^+ is secreted into the tubular lumen (Figure 1) (Bhandari et al, 2024).

Na^+-K^+-ATPase pumps in the basolateral membrane move sodium (Na^+) out of the cell in exchange for potassium (K^+), generating a Na^+ electrochemical gradient from the lumen into the cell. Na^+ moves from the tubular lumen down the concentration gradient, facilitating the tubular secretion of H^+ via the apical membrane NHE3. However, H^+ secreted in the proximal tubules does not contribute to the net H^+ excretion as all H^+ is used in the reaction with filtered HCO_3^- in the tubular lumen (Imenez Silva and Mohebbi, 2022).

Hydrogen ion excretion in the connecting and collecting tubules

The excretion of the daily H^+ load is primarily the function of collecting and connecting tubules. The process involves the interaction of the intercalated and the principal cells

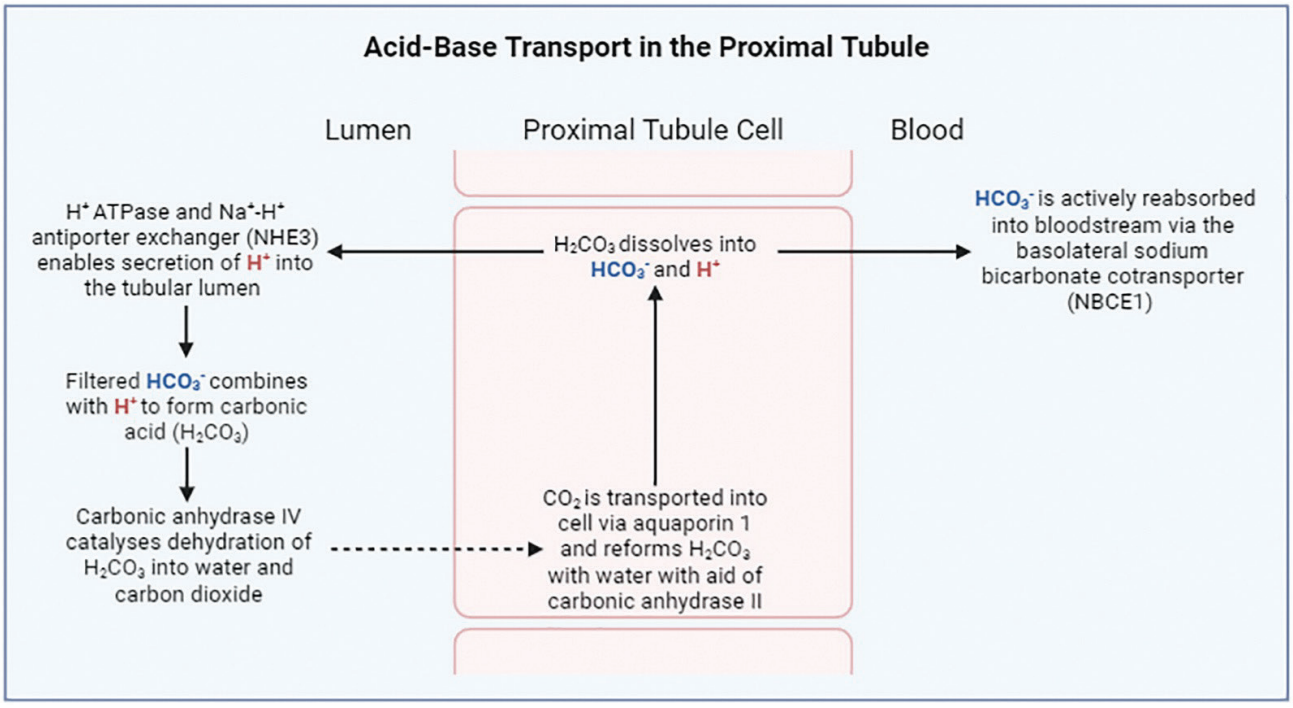

Figure 1. Bicarbonate reabsorption in proximal tubules. Prepared by author Yi Xin Li using Biorender.com. CO_2, carbon dioxide; HCO_3^-, bicarbonate; H^+, hydrogen ions; H_2CO_3, carbonic acid; H^+-ATPase, hydrogen ATPase; Na^+, sodium; NHE3, sodium-hydrogen exchanger paralog 3; NBCE1, sodium-bicarbonate co-transporter 1.

located in the distal nephrons, especially in collecting and connecting tubules (Figure 2) (Bhandari et al, 2024).

Cytoplasmic CA II in type A intercalated cells catalyses the conversion of CO_2 and H_2O into H_2CO_3 which subsequently disassociates into H^+ and HCO_3^-. H^+ is secreted through the apical membrane into the urine via the H^+-ATPase, whereas HCO_3^- is reclaimed back into the blood via the basolateral anion exchange protein 1 (AE1) (Wagner et al, 2023).

Na^+-K^+-ATPase in the basolateral membrane of principal cells moves Na^+ from the intracellular space to the bloodstream, creating an electrochemical Na^+ gradient which facilitates the movement of luminal Na^+ into the cell through epithelial sodium channels (ENaC). The negative luminal charge thus created draws K^+ from the principal cells to the tubular lumen, mainly through the renal outer medullary potassium channels (ROMK) and H^+ from the type A intercalated cells (Figure 2). Chloride (Cl^-) also moves from the lumen to the extracellular space down the electric gradient. Aldosterone opens the ENaC in principal cells and stimulates Na^+-K^+-ATPase. (Imenez Silva and Mohebbi, 2022).

Excretion of the daily H^+ load in the free form will require the urine pH to be lowered to below 2.5. However, urinary pH cannot fall below 4–4.5. Therefore, the excess H^+ must be buffered with other urinary compounds for excretion (Bhandari et al, 2024). Ammonia (NH_3) and phosphate (PO_4^-) are the two primary urinary buffers involved in acid excretion. PO_4^- acts as a proton acceptor, buffering urinary H^+ and excreting as titratable acid. NH_3 is principally formed in the proximal tubular cells via glutamate metabolism, generating equimolar HCO_3^- (Weiner and Verlander, 2013). NH_3 combines with the H^+ secreted by

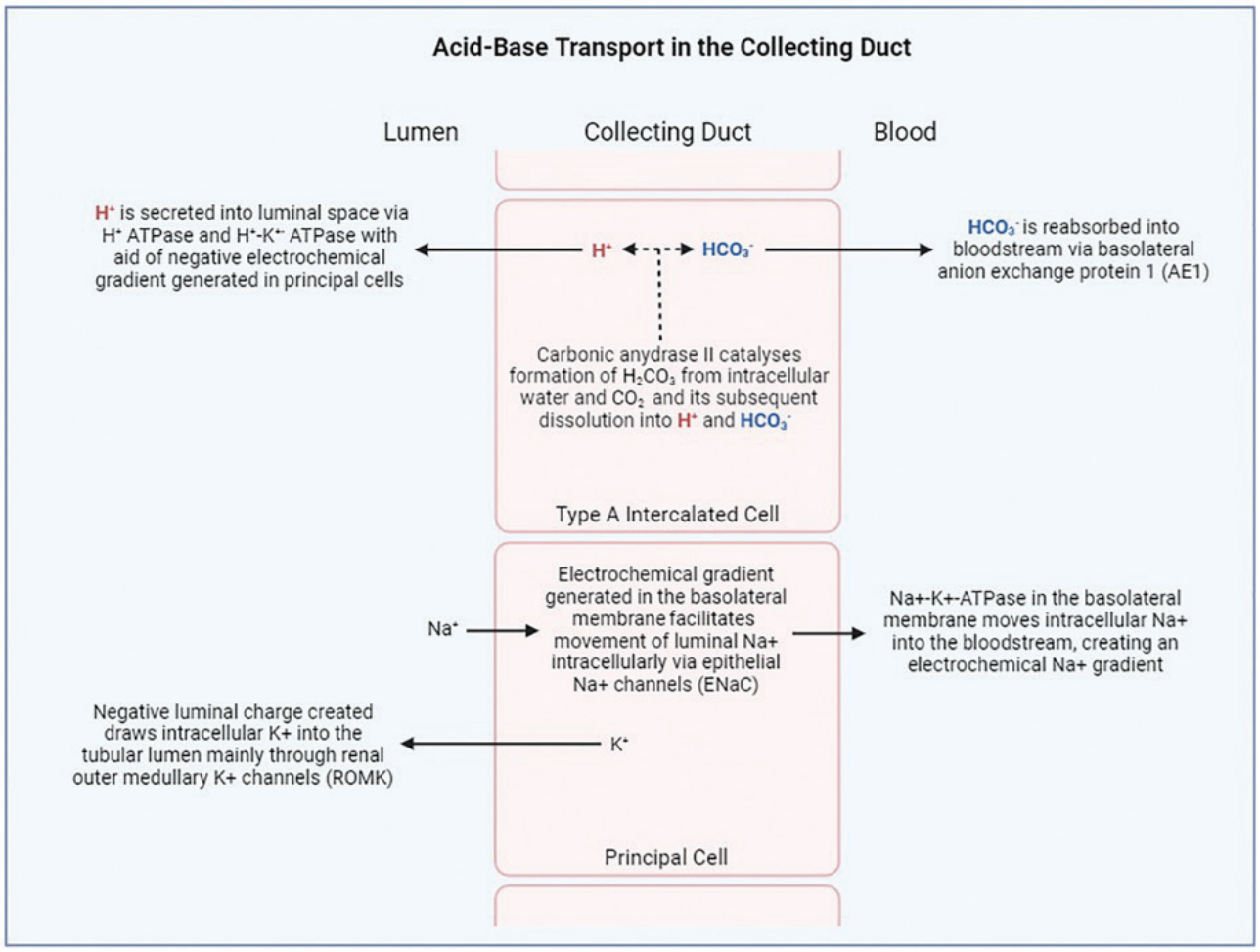

Figure 2. Hydrogen ion secretion in distal tubules. Prepared by author Yi Xin Li using Biorender.com. HCO_3^-, bicarbonate; H^+, hydrogen ions; H^+ ATPase, hydrogen ATPase; Na^+-K^+ ATPase, sodium-potassium ATPase; H^+-K^+ ATPase, hydrogen potassium ATPase; AE1, anion exchange protein 1; ENaC, epithelial sodium channels; ROMK, renal outer medullary potassium channels.

the intercalated cells to form ammonium (NH_4^+), which combines with a cation and is excreted in the urine (Bhandari et al, 2024).

Pathophysiology, aetiology and clinical features of renal tubular acidosis

Although all types of RTA present with normal anion gap metabolic acidosis (NAGMA), their pathophysiology and clinical presentations differ and are discussed below. Various inherited and acquired disorders can lead to the development of RTA (Table 1). The inherited abnormalities are more common in paediatric patients, while the acquired pathologies are usually the underlying causes in adults (Pereira et al, 2009).

Distal (type 1) renal tubular acidosis

In distal RTA (dRTA), the primary defect lies in the secretion of H^+ at the luminal membranes of the collecting and connecting ducts, leading to increased acid retention and NAGMA. Various mutations in the genes coding for protein channels of type A intercalated cells and certain acquired disorders, such as Sjögren's disease, have been shown to affect the transporters in the intercalated cells (Wagner et al, 2023; Cohen et al, 1992).

Mutations in genes coding for three transport proteins, the Cl^--HCO_3^- exchanger *(SLC4A1)*, the *ATP6V1B1* and *ATP6V0A4* subunits of the vacuolar-type H^+-ATPase, account for most inherited forms of dRTA (Soares et al, 2019). Mutations in other genes, including K^+-Cl^--co-transporter *(SLC12A7)*, the Cl^--HCO_3^- exchanger *(SLC26A7)*, the NH_3 channel RhCG *(SLC42A3)*, *ATP6V1C2*, and the forkhead transcription factor FOXI1, are thought to be responsible for other cases (Batlle and Arruda, 2018). Mutations of the *SLC4A1* gene are mostly inherited as autosomal dominant disorders; however, autosomal recessive mutations, accompanied by haemolytic anaemia, have also been described. Mutations in the *ATP6V0A4* and *ATP6V1B1* genes are autosomal recessive disorders usually accompanied by sensorineural hearing impairment (Table 1) (Mohebbi and Wagner, 2018).

Autoimmune diseases and drugs are the most common causes of acquired dRTA. Sjögren's syndrome is the most common autoimmune disease associated with the dRTA, with a prevalence of 6.8% to 70% reported in different publications (Ungureanu and Ismail, 2022). Hypergammaglobulinemia, other autoimmune diseases (Palmer et al, 2021), sickle cell anaemia, various renal pathologies, kidney transplant, metabolic abnormalities (Giglio et al, 2021), and several drugs (Soleimani and Rastegar, 2016) are the other causes of acquired dRTA (Table 1). Amphotericin B increases luminal membrane permeability to H^+, K^+, and magnesium (Mg^{2+}), resulting in the uptake of secreted H^+ from the urine into the extracellular fluid and urinary wasting of K^+ and Mg^{2+} (Wazny and Brophy, 2000).

H^+-ATPase is the primary portal of H^+ secretion in distal tubules, and its reduced expression or malfunction considerably diminishes kidneys' ability to excrete acid load (Smulders et al, 1996). Disorders of the AE1 protein impair the ability of intercalated cells to move the intracellularly generated HCO_3^- to the extracellular fluid compartment, leading to high intracellular pH impeding H^+ generation and secretion (Soleimani and Rastegar, 2016). The serum HCO_3^- level falls and can be as low as 10 mmol/L in untreated cases. The urine pH typically remains above 5.5 despite a systemic acidotic state (Table 2). However, a few cases with urine pH slightly below 5.5 have also been reported, and dRTA can still be considered a possibility if no other cause for NAGMA can be identified (Pereira et al, 2009).

Renal K^+ wasting and hypokalaemia are common in dRTA (Table 2). Na^+ movement across the apical membrane of the distal nephron segments is coupled with the reabsorption of Cl^- and secretion of K^+ and H^+ to maintain electroneutrality (Smulders et al, 1996). The increased K^+ secretion in dRTA counterbalances diminished H^+ secretion from the type A intercalated cells, leading to hypokalaemia. The other possible underlying mechanisms are increased distal Na^+ delivery due to acidosis-driven reduction in proximal tubular Na^+ reabsorption. This stimulates enhanced distal tubular Na^+ reabsorption and K^+ secretion. Aldosterone stimulation also contributes to increased urinary K^+ wasting (Trepiccione et al, 2021). At times, the K^+ wasting can be severe, causing serious sequelae such as muscle paralysis (Vasquez-Rios et al, 2019).

Nephrocalcinosis, nephrolithiasis, and skeletal abnormalities are frequently observed in dRTA (Table 2). Chronic metabolic acidosis leads to increased osteoclastic and reduced osteoblastic activity with a net effect of increased bone resorption, calcium (Ca^{+}) efflux and hypercalciuria (Bushinsky and Krieger, 2022).

Table 1. Causes of renal tubular acidosis

Type of RTA	Congenital/Genetic disorders	Acquired		
		Medications	Metabolic	Others
Distal (Type 1)	Wilson's disease, Sickle cell anaemia, Ehlers-Danlos syndrome, Marfan's syndrome, Genetic mutations *(SLC4A1, ATP6V1B1, ATP6V0A4, SLC12A7, SLC26A7, SLC42A3, ATP6V1C2)*	Amphotericin B, NSAIDs, Lithium carbonate, Ifosfamide, Intravenous zoledronate	Hypercalciuria, Hyperparathyroidism, Vitamin D intoxication, Idiopathic hypercalciuria	Sjogren's syndrome, SLE, RA, Kidney transplant, Chronic obstructive uropathy, Medullary sponge kidney
Proximal (Type 2)	Lowe syndrome, Dent's disease, Wilson's disease, Cystinosis, Hereditary fructose intolerance, Galactosemia, Glycogen storage disease (type I), Mitochondrial disorders, Tyrosinemia, NBCE1 mutation	Carbonic anhydrase inhibitors (acetazolamide topiramate), Aminoglycosides, Tenofovir, Adefovir, Cidofovir, Valproate, Cisplatin, Ifosfamide, Heavy metals (lead, cadmium, mercury, copper)	Hypocalcemia, Vitamin D deficiency, Vitamin D resístanse	Monoclonal gammopathy, Multiple myeloma, Light chain disease, Amyloidosis, Renal transplant, Paroxysmal nocturnal haemoglobinuria, Tubulo-interstitial nephritis
Mixed (Type 3)	Carbonic anhydrase II deficiency			
Hyperkalaemic (Type 4)	Sickle cell anaemia, Congenital isolated hypoaldosteronism, Pseudohypoaldostero-nism type 1 and type 2 (Gordon's syndrome)	Potassium-sparing diuretics (spironolactone, eplerenone, amiloride), Beta blockers, NSAIDs, Calcineurin inhibitors (cyclosporine, tacrolimus), Heparin, Trimethoprim, Pentamidine	Primary adrenal insufficiency	Hyporeninemic hypoaldosteronism, Diabetic nephropathy, Hypertensive nephropathy, Multiple myeloma, Monoclonal gammopathy, Renal transplant rejection, Chronic urinary tract obstruction
Voltage-dependent renal tubular acidosis		Lithium, Amiloride		Severe hypovolemia, Sickle cell disease, Lupus nephritis, Urinary tract obstruction

NSAIDs, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; RTA, renal tubular acidosis.

Table 2. Salient features of proximal and distal renal tubular acidosis

Proximal renal tubular acidosis	Distal renal tubular acidosis
Impaired proximal tubular HCO_3^- absorption	Impaired distal tubular H^+ secretion
Normal anion gap metabolic acidosis	Normal anion gap metabolic acidosis
Serum HCO_3^- usually 14–20 mmol/L	Serum HCO_3^- may be < 10 mmol/L
Urine pH typically below 5.5	The urine pH typically remains above 5.5
Hypokalaemia is common	Renal K^+ wasting and hypokalaemia
Usually associated with Fanconi syndrome	Hypocitraturia
■ Hypophosphataemia ■ Rickets and osteomalacia ■ Aminoaciduria ■ Glucosuria	Nephrocalcinosis Nephrolithiasis Skeletal abnormalities

HCO_3^-, bicarbonate; H^+, hydrogen ions; K^+, potassium.

Acidosis enhances citrate reabsorption in proximal tubules, causing hypocitraturia (Coradin et al, 2024). Urinary citrate is a potent inhibitor of Ca^+ stone formation, and hypocitraturia predisposes to renal Ca^+ deposition and renal calculi (calcium phosphate [$CaPO_4$] and Ca^+ oxalate) (Table 2). Moreover, persistently high urine pH favours $CaPO_4$ precipitation, nephrocalcinosis, and renal stone formation (Magni et al, 2021).

An incomplete variant of dRTA, characterised by a low normal serum HCO_3^- but a urinary pH above 5.5, hypocitraturia, hypercalciuria, and renal calcification, has also been described and should be suspected in patients with nephrocalcinosis and renal calculi (Trepiccione et al, 2021).

Proximal (type 2) renal tubular acidosis

In proximal (pRTA) or type 2 RTA, various genetic mutations, acquired disorders, or drugs can disrupt the function of specialised transporters, pumps, and enzymes involved in HCO_3^- reabsorption in the proximal tubules (Table 1). The resultant HCO_3^- wasting leads to NAGMA and low serum HCO_3^- levels (Soleimani and Rastegar, 2016). However, the serum HCO_3^- level does not drop as low as in dRTA and usually ranges between 14–20 mmol/L (Table 2). With time, the distal nephron segments adapt to increase their capacity to reabsorb the increased HCO_3^- load, preventing serum HCO_3^- from falling to a very low level (Kashoor and Batlle, 2019). As the distal tubular function is intact, the urine pH can fall below 5.5, distinguishing it from the dRTA (Manz et al, 1984).

Hypokalaemia is a frequent feature of proximal RTA (Table 2). Increased distal Na^+ and HCO_3^- delivery stimulates K^+ secretion from the principal cells in the distal tubules, leading to K^+ wasting (Palmer et al, 2021).

Isolated proximal tubular HCO_3^- reabsorption abnormality is uncommon, and most patients present with features of a generalised proximal tubular defect called Fanconi syndrome (Table 2). This syndrome is characterised by urinary wasting of compounds primarily reabsorbed in the proximal tubules, leading to wasting of PO_4^-, glucose, amino acids, and HCO_3^- (Xu et al, 2024). Hypophosphataemia, coupled with acidosis-induced bone resorption and low active vitamin D levels, leads to rickets, osteomalacia, and associated skeletal abnormalities (Manz et al, 1984).

Autosomal recessive mutations of the NBCE1 gene *(SLC4A4)* are linked with isolated inherited pRTA, short stature and ocular abnormalities. An X-linked disease, Lowe syndrome or oculocerebrorenal syndrome (OCRL), due to mutations in the *OCRL* gene, characterised by eye anomalies and mental retardation, also has features of Fanconi syndrome and pRTA. Mutations of *CLCN5* and *OCRL* genes are linked with Dent's disease, an X-linked autosomal recessive disorder causing generalised proximal tubular disorder, proteinuria, hypercalciuria with nephrocalcinosis and nephrolithiasis, and progressive renal impairment. Cystinosis, tyrosinemia, hereditary fructose intolerance, galactosemia, Wilson disease, and glycogen storage disease (type I) are other inherited disorders presenting with genetic Fanconi syndrome (Table 1) (Haque et al, 2012).

Monoclonal gammopathies, including multiple myeloma, light chain disease, and amyloidosis, are the most common acquired aetiologies in adults (Kashoor and Batlle, 2019). They mainly present with generalised proximal tubulopathy. Table 1 summarises the other reported causes of acquired pRTA and Fanconi syndrome (Haque et al, 2012; Kashoor and Batlle, 2019).

Mixed (type 3) renal tubular acidosis

Mixed or type 3 RTA is rare and seldom seen in clinical practice. It has both dRTA and pRTA features characterised by severe metabolic acidosis and hypokalaemia. Mutation of a gene on chromosome 8 at q22 causing CA II deficiency is the underlying pathology, presenting with osteopetrosis, growth retardation, cerebral calcification, and moderate-to-severe mental retardation (Haque et al, 2012).

Hyperkalemic renal tubular acidosis

Hyperkalemic or type 4 RTA results from aldosterone deficiency or resistance. Aldosterone is a mineralocorticoid steroid hormone which increases the expression of ENaC and Na^+-K^+-ATPase in the principal cells located in the late distal convoluted tubule, the connecting tubules, and the collecting duct system through specific cytoplasmic mineralocorticoid receptors (Wagner, 2014). The net effect is Na^+ reabsorption as well as H^+ and K^+ secretion (Batlle and Arruda, 2018).

Aldosterone deficiency or resistance produces hyperkalaemia, which inhibits the proximal tubular NH_3 generation, which, together with reduced H^+ secretion, produces NAGMA (Batlle and Arruda, 2018). Serum HCO_3^- usually remains above 15 mmol/L, and urine pH can be decreased below 5.5 (Karet, 2009).

However, it is important to differentiate type 4 RTA from the hyperkalemic variant of dRTA called voltage-dependent RTA (VD-RTA), where reduced distal Na^+ delivery impairs H^+ and K^+ secretion. In this scenario, urine pH usually remains above 5.5 (Batlle and Arruda, 2018).

The most common cause of type 4 RTA in adults is hyporeninemic hypoaldosteronism (Table 1), which is observed in patients with mild to moderate chronic kidney disease (CKD), primarily due to diabetic nephropathy (Batlle and Arruda, 2018). Diabetes may lead to reduced renin release due to injury to the juxtaglomerular apparatus, defects in the stimulation factors or suppressed plasma renin activity, autonomic dysfunction, or a primary increase in renal salt retention with volume expansion (Sousa et al, 2016).

Nonsteroidal anti-inflammatory drugs use can result in reduced aldosterone synthesis by inhibiting prostaglandin production in the macula densa, which reduces renin release (Kim and Joo, 2007). Calcineurin inhibitors (cyclosporine, tacrolimus) diminish the secretion and responsiveness to aldosterone, causing hyperkalaemia and acidosis. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) diminish the release of aldosterone. Heparin and low-molecular-weight heparin directly affect adrenal cells, leading to low serum aldosterone levels. K^+-sparing diuretics (spironolactone, eplerenone) block the action of aldosterone or close the Na^+ channels (amiloride). Trimethoprim and pentamidine also cause hyperkalaemia by closing Na^+ channels in collecting ducts (Galbiati, 2020).

Voltage-dependent renal tubular acidosis

Severe hypovolemia, sickle cell disease, lupus nephritis, urinary tract obstruction, and certain drugs, such as lithium and amiloride, reduce distal tubular Na absorption, causing hyperkalaemia and NAGMA (Table 1) (Kurtzman, 2000).

Diagnostic workup

Renal tubular acidosis should be suspected in patients with unexplained NAGMA and K^+ abnormalities (hypokalaemia or hyperkalaemia). Other common causes of NAGMA, such as diarrhoea and large-volume intravenous sodium chloride infusion, should be excluded before working up for RTA. Although RTA can be a feature of CKD and may be associated

with other renal pathologies, the glomerular filtration rate (GFR) is typically normal or mildly reduced in isolated true RTA (Yaxley and Pirrone, 2016).

Before proceeding to laboratory testing of RTA, a comprehensive history and physical examination should be conducted. Notably, the clinician should be on active alert for any underlying systemic conditions that could result in RTA, such as features of autoimmune, conditions, chronic inflammatory diseases and malignancies. Particular attention should be directed toward a comprehensive family history and drug history to survey the patient's long-term medications and any illnesses that potentially run in the family (Mohebbi and Wagner, 2018).

Urine pH measurement in the diagnosis of renal tubular acidosis

Although urinary pH is not a diagnostic test for RTA, it can assist in differentiating between different types. A urine pH above 5.5 in acidosis usually suggests dRTA or aldosterone resistance. However, a few cases of dRTA with urine pH less than 5.5 have also been reported (Kim et al, 2004). Moreover, urine pH might be above 5.5 in NAGMA, associated with chronic diarrhoea and toluene poisoning, erroneously suggesting dRTA (Yaxley and Pirrone, 2016).

A urine pH under 5.5 signifies intact distal H^+ excretion, pointing towards possible pRTA or aldosterone deficiency. However, the urine pH can be above 5.5 if a patient with proximal RTA is treated with alkali and the urine HCO_3^- load increases above the tubular reabsorptive capacity. It must also be remembered that urine pH is also affected by diet, medication, hydration status, and bacterial contamination. These factors should be considered while interpreting the results (Yaxley and Pirrone, 2016).

Diagnosis of proximal (type 2) renal tubular acidosis

Confirmation of urinary HCO_3^- wastage is required to diagnose pRTA. In metabolic acidosis, with normal proximal renal tubular function, the kidneys attempt to conserve HCO_3^- maximally, and little, if any, HCO_3^- is lost in the urine. Consequently, the fractional excretion of HCO_3^- ($FEHCO_3$) is typically less than 5% in such cases. Excess HCO_3^- is lost in the urine in pRTA, and the $FEHCO_3$ is higher than this threshold (Haque et al, 2012).

The HCO_3^- loading test is the gold standard for diagnosing patients with equivocal readings. In acidosis, with a low plasma HCO_3^- concentration and an intact proximal tubule function, urine HCO_3^- levels generally do not increase significantly with the infusion of sodium bicarbonate ($NaHCO_3$), as most of the additional filtered HCO_3^- is efficiently reabsorbed by the proximal tubules. In patients with pRTA, the urine HCO_3^- rises rapidly following the $NaHCO_3$ infusion, and $FEHCO_3$ usually increases above 15–20%. Urine pH also rapidly rises to 7 or above (Yaxley and Pirrone, 2016; Bhandari et al, 2024). HCO_3^- infusion can exacerbate hypokalaemia, and the serum K^+ can drop to a dangerously low level. Therefore, care must be exercised while performing the test (Haque et al, 2012).

Diagnosis of distal (type 1) renal tubular acidosis

Indirect measures of distal tubular urine acidification abilities are used to diagnose dRTA. Urine NH_4^+ is reduced in dRTA and increases in extrarenal causes of hypokalaemic NAGMA, such as in chronic diarrhoea. Urine pH might be above 5.5 in both scenarios. However, direct measurement of urinary NH_4^+ is not widely available, and indirect estimation of urine NH_4^+ using urinary osmolal gap or urinary anion gap measurements can be used instead. The urinary anion gap is typically positive in dRTA and negative in extrarenal NAGMA. The urine osmolal gap is usually less than 150 mosm/kg in dRTA and above 200 mosm/kg in extrarenal NAGMA. However, these tests remain controversial and should only be seen as screening rather than diagnostic tests (Uribarri and Oh, 2021). Therefore, there remains a gap in the diagnostic evaluation of dRTA, and further research is needed to develop a more reliable, simple investigation.

A short ammonium chloride (NH_4Cl) loading test remains the gold standard for confirming the diagnosis of dRTA. Administration of oral NH_4Cl acidifies the urine in normally functioning distal tubules, and the urine pH falls below 5.3. In patients with dRTA, urinary pH does not decrease as expected (Yaxley and Pirrone, 2016). However, NH_4Cl causes unpleasant gastrointestinal side effects in most patients, and the test is not often used.

Simultaneous furosemide and fludrocortisone tests are an alternative. Administration of furosemide (40–80 mg) and fludrocortisone (1 mg) increases the distal Na^+ delivery, stimulating the distal H^+ secretion. In normal individuals, the urine pH falls below 5.3. However, the pH remains above 5.5 in patients with dRTA (Mohebbi and Wagner, 2018; Bhandari et al, 2024).

Diagnosis of hyperkalemic type 4 renal tubular acidosis

Hyperkalaemia in a patient with NAGMA and normal or near-normal kidney function usually points towards type 4 RTA or VD-RTA (Yaxley and Pirrone, 2016). Serum aldosterone measurements can further differentiate the possible underlying mechanisms. Serum aldosterone and renin levels are low in hyporeninemic hypoaldosteronism, the commonest cause of hyperkalemic RTA. Low aldosterone level with high renin level signifies reduced aldosterone production by the adrenal glands. High aldosterone levels are seen in aldosterone resistance and VD-RTA (Batlle and Arruda, 2018; Bhandari et al, 2024).

Summary of treatment of renal tubular acidosis

Correction of metabolic acidosis and electrolyte imbalance are the cornerstones of managing pRTA and dRTA. While treatment of the underlying cause, such as autoimmune disease or multiple myeloma, and stopping the offending drugs are essential for managing secondary RTAs, correction of acidosis and hypokalaemia is still required in many cases (Yaxley and Pirrone, 2016).

Alkali therapy can prevent or, in many cases, reverse the complications associated with pRTA and dRTA, such as growth retardation, osteomalacia, rickets, and renal stones. A starting HCO_3^- dose of 0.5–1.0 mmol/kg/day is usually recommended for adult patients with dRTA (Giglio et al, 2021). However, the dose needs to be individualised. Paediatric patients and patients with pRTA often require much higher initial doses (5–15 mmol/kg/day). Low-dose thiazide diuretics can help as adjunct treatment and reduce the HCO_3^- dose requirement in more severe cases. Thiazide diuretics can enhance renal HCO_3^- retention by producing volume contraction (Haque et al, 2012). Therapy aims to bring the serum HCO_3^- levels within normal limits (22–24 mmol/L). Regular monitoring and titration of the HCO_3^- dose are needed. Sodium bicarbonate or sodium citrate are the usual agents of choice; however, excess Na^+ load might worsen $CaPO_4$ stone formation, and potassium bicarbonate ($KHCO_3$) or potassium citrate might be better options (Mohebbi and Wagner, 2018).

An open-label extension study showed promising results after a phase II/III trial using a prolonged-release formulation of K^+ citrate and $KHCO_3$, ADV7103. Plasma HCO_3^- and K^+ levels were within the normal limits in 69–86% and 83–93% of patients, respectively—75% of patients adhered to the treatment. An average improvement of quality of life of 89% was reported at 24 months of study (Bertholet-Thomas et al, 2021). More recently, prolonged-release alkali supplementation has also been reported in paediatric patients (Tan et al, 2024). However, these treatments are not yet available for commercial use. Further trials are needed to develop simpler treatment regimens to help reduce the therapy burden on the patients and improve outcomes.

In dRTA, alkali therapy and correction of acidosis alone can reduce urinary K^+ wasting, correcting hypokalaemia. However, K^+ supplements must be given to all patients with severe hypokalaemia before initiating alkali therapy to prevent further worsening of K^+ levels. In contrast, alkali treatment can exacerbate hypokalaemia in pRTA by increasing distal K^+ secretion. Concomitant use of thiazide diuretics can potentially worsen hypokalaemia as well. Therefore, careful monitoring and correction of hypokalaemia is almost always required. In some cases, K^+-sparing diuretics (amiloride, spironolactone, eplerenone) can help as additional measures. Patients with Fanconi syndrome lose PO_4^- in urine and have reduced activation of vitamin D, causing musculoskeletal complications, and supplementation is usually required (Haque et al, 2012).

In type 4 RTA, mineralocorticoid (fludrocortisone) and glucocorticoid treatment is indicated in patients with primary adrenal insufficiency. Although fludrocortisone can also be effective in hyporeninemic hypoaldosteronism, it causes extracellular fluid volume expansion, especially in patients with renal impairment, making its use rather difficult.

Furosemide, alone or combined with fludrocortisone, can effectively control hyperkalaemia and acidosis in such situations (Sebastian et al, 1984).

Conclusion

Renal tubular acidosis is a group of inherited or acquired disorders of renal tubules affecting the kidney's ability to regulate normal acid-base and potassium balance. The condition is characterised by NAGMA and is associated with either hypokalaemia or hyperkalaemia, depending on the underlying pathophysiological process. If left unrecognised and untreated, it can lead to various complications, such as growth retardation, failure to thrive, osteoporosis, rickets, osteomyelitis, renal calculi, and progressive renal failure. K^+ abnormalities can present with severe muscle paralysis and cardiac arrhythmias. Early identification and treatment can prevent or improve most of the adverse effects.

Key points

- Hyperchloremic NAGMA and serum potassium abnormalities characterise RTA.
- Different types of RTA involve diverse pathophysiological processes, including impaired HCO_3^- absorption, reduced hydrogen ion secretion, and aldosterone deficiency or resistance.
- Several genetic abnormalities, drugs, and acquired disorders are known to cause RTA.
- Untreated or unrecognised RTA can lead to serious musculoskeletal, renal, and cardiac complications.
- Timely diagnosis and correction of acidosis and potassium abnormalities is imperative for better outcomes.

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Availability of data and materials

All the data of this study are included in this article.

Author contributions

SSYW, HT, WQJH, SA and YXL were involved in writing the first draft, literature search and literature review. YXL was also responsible for drawing the figures. AE was involved in design of the review, literature search and review, critically reviewing and revising the manuscript. MMJ was responsible for the conception and design of the review, critically reviewing and revising the first draft, writing the final draft of the manuscript, literature search and review, and responding to the reviewers' comments. All authors contributed to important editorial changes of important content in the manuscript. All authors read and

approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of interest

The authors declare no conflict of interest.

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