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REVIEW

Renal calcification in children with renal tubular acidosis: What a paediatrician should know

Mohammed Al-Beltagi, Nermin Kamal Saeed, Adel Salah Bediwy, Reem Elbeltagi, Samir Hasan, Mohamed Basiony Hamza

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Mohammed Al-Beltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31511, Alghrabia, Egypt

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Dr. Sulaiman Al Habib Medical Group, Manama, Bahrain, Manama 26671, Manama, Bahrain

Nermin Kamal Saeed, Medical Microbiology Section, Department of Pathology, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain, Manama 12, Manama, Bahrain

Nermin Kamal Saeed, Medical Microbiology Section, Department of Pathology, Irish Royal College of Surgeon, Bahrain, Busaiteen 15503, Muharraq, Bahrain

Adel Salah Bediwy, Department of Pulmonology, Faculty of Medicine, Tanta University, Tanta 31527, Alghrabia, Egypt

Adel Salah Bediwy, Department of Chest Disease, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Dr. Sulaiman Al Habib Medical Group, Manama, Manama 26671, Manama, Bahrain

Reem Elbeltagi, Department of Medicine, The Royal College of Surgeons in Ireland - Bahrain, Busiateen 15503, Muharraq, Bahrain

Samir Hasan, Department of Pediatrics, Faculty of Medicine, Tanta University Hospital, Tanta 31511, Alghrabia, Egypt

Mohamed Basiony Hamza, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31511, Alghrabia, Egypt

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, MSc, PhD, Academic Editor, Chairman, Consultant Physician-Scientist, Professor, Researcher, Department of Pediatrics, Faculty of Medicine, Tanta University, Al Bahr Street, Tanta 31527, Alghrabia, Egypt.
mbelrem@hotmail.com

Abstract

Renal tubular acidosis (RTA) can lead to renal calcification in children, which can cause various complications and impair renal function. This review provides pediatricians with a comprehensive understanding of the relationship between RTA and renal calcification, highlighting essential aspects for clinical manage-

ment. The article analyzed relevant studies to explore the prevalence, risk factors, underlying mechanisms, and clinical implications of renal calcification in children with RTA. Results show that distal RTA (type 1) is particularly associated with nephrocalcinosis, which presents a higher risk of renal calcification. However, there are limitations to the existing literature, including a small number of studies, heterogeneity in methodologies, and potential publication bias. Longitudinal data and control groups are also lacking, which limits our understanding of long-term outcomes and optimal management strategies for children with RTA and renal calcification. Pediatricians play a crucial role in the early diagnosis and management of RTA to mitigate the risk of renal calcification and associated complications. In addition, alkaline therapy remains a cornerstone in the treatment of RTA, aimed at correcting the acid-base imbalance and reducing the formation of kidney stones. Therefore, early diagnosis and appropriate therapeutic interventions are paramount in preventing and managing renal calcification to preserve renal function and improve long-term outcomes for affected children. Further research with larger sample sizes and rigorous methodologies is needed to optimize the clinical approach to renal calcification in the context of RTA in the pediatric population.

Key Words: Renal tubular acidosis; Nephrocalcinosis; Renal calcification; Hypercalciuria; Kidney stones; Metabolic acidosis; Children

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Core Tip: Children with renal tubular acidosis (RTA) may develop renal calcification, leading to complications and negatively affecting kidney function. This comprehensive review aims to provide pediatricians with a better understanding of the connection between RTA and renal calcification, emphasizing key aspects of clinical management. Relevant studies were analyzed to examine the prevalence, risk factors, underlying mechanisms, and clinical implications of renal calcification in children with RTA. Nephrocalcinosis in type 1 RTA is mainly associated with a higher risk of renal calcification. Further research with larger sample sizes and rigorous methodologies is necessary to improve our understanding of RTA-related renal calcification.

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INTRODUCTION

Renal tubular acidosis (RTA) is a group of inherited or acquired disorders. It is characterized by impaired renal tubules' ability to reabsorb bicarbonate or excrete hydrogen ions. This results in an inability to maintain acid-base balance in the body[1]. Different types of RTA are based on the specific defect in renal tubular function. Distal RTA (dRTA), also known as type 1 RTA, is the most common form of RTA. It is characterized by impaired hydrogen ion secretion in the distal renal tubules, causing reduced kidney ability to acidify urine, with acid buildup in the blood inducing metabolic acidosis. It is often associated with and can lead to the formation of calcium phosphate kidney stones[2]. Proximal RTA (type 2 RTA) is characterized by defective bicarbonate reabsorption in the proximal renal tubules, resulting in increased urinary bicarbonate loss and metabolic acidosis. Unlike type 1 RTA, type 2 RTA is associated with urinary phosphate wasting, resulting in hypophosphatemia[3]. Combined proximal and distal RTA (type 3 RTA) is a rare form of RTA that involves defects in both proximal and distal tubular acidification mechanisms with combined features of type 1 and type 2 RTA. Type 4 RTA (RTA 4), also known as RTA due to hyporeninemic hypoaldosteronism, is characterized by impaired renal acidification due to hypoaldosteronism or aldosterone resistance, resulting in reduced secretion of hydrogen ions and impaired potassium excretion[4,5].

The cause of RTA varies depending on the specific type. RTA can be inherited and caused by genetic mutations affecting the transport proteins responsible for renal tubular acidification[6]. Other causes include autoimmune diseases (such as systemic lupus erythematosus), medications (such as certain diuretics), chronic kidney disease, or urinary tract obstruction[7]. Symptoms can range from mild to severe, depending on the underlying cause and extent of acid-base imbalance. Symptoms include fatigue, weakness, poor growth or weight gain (in children), increased urinary frequency, and bone abnormalities due to metabolic acidosis[8].

RTA can cause various complications in multiple organ systems, depending on the type and severity of acid-base imbalance. The primary complication of RTA is metabolic acidosis, which occurs due to the kidneys' inability to excrete hydrogen ions or reabsorb bicarbonate effectively[1]. This can cause issues such as impaired growth and development, muscle wasting, bone demineralization (osteoporosis), and an increased risk of kidney stone formation. RTA can also disrupt electrolyte balance, leading to abnormalities like hypokalemia or hyperkalemia[9]. Hypokalemia can result in muscle weakness, fatigue, and cardiac arrhythmias, while hyperkalemia can be life-threatening and cause cardiac

abnormalities. Chronic metabolic acidosis in children with RTA can impact growth and development and lead to developmental delays. Long-standing metabolic acidosis can also affect bone health, leading to osteoporosis or rickets in children due to compensatory mechanisms like increased bone resorption to buffer the acidosis[10,11].

In some cases of RTA, the increased excretion of calcium in the urine can cause calcium deposits in the kidneys and nephrocalcinosis. This can lead to kidney function impairment and the development of chronic kidney disease[12]. RTA can also increase the risk of kidney stone formation due to urinary abnormalities, such as increased calcium, phosphate, and oxalate excretion. If left untreated, RTA can cause chronic kidney disease and renal damage. Children with RTA and recurrent kidney stone formation or nephrocalcinosis are at higher risk for renal complications[13]. This review provides an overview of renal calcification in children with RTA, including its pathophysiology, clinical presentation, diagnostic evaluation, and management strategies. By enhancing our understanding of this complex condition, clinicians can improve early detection, implement appropriate interventions, and optimize long-term outcomes for children affected by renal calcification associated with RTA.

METHODS

We conducted a systematic literature review to gain an evidence-based understanding of our goal. This review involved searching various electronic databases like PubMed, PubMed Central, Cochrane Library, Embase, Web of Science, CINAHL, Scopus, LISA, and NLM catalog up until July 28, 2023. We used specific keywords like Renal Tubular acidosis, Nephrocalcinosis, Renal Calcification, Hypercalciuria, Kidney Stones, Metabolic Acidosis, and Children. Our review included 111 full-text articles comprising 70 reviews, 20 research articles, 16 case reports, four consensus guidelines, one systematic review, one editorial, and one more systematic review. We only included English-language articles discussing the effects of RTA on the risk of renal calcification. Figure 1 illustrates the study's flow chart. We also checked reference lists and conducted citation searches on the included studies. We excluded articles with commercial backgrounds and reviewed those available as abstracts only.

DISCUSSION

Role of the kidneys in acid-base homeostasis

The kidneys play a crucial role in maintaining the body's acid-base balance through various mechanisms such as acid secretion and excretion, bicarbonate reabsorption and generation, ammonia regulation, and response to pH changes. One of its primary functions is to excrete excess acid by releasing hydrogen ions (H^+) into the urine. This process is essential in preventing the buildup of acid in the blood, which can result in a condition known as acidosis[14].

Bicarbonate plays a crucial role in neutralizing excess acids in the blood. The majority (85%-90%) of filtered bicarbonate is reabsorbed in the proximal tubules of the kidneys[15]. This reabsorption occurs through the secretion of protons (H^+) *via* sodium hydrogen exchangers and proton pumps (H^+-ATPase). In the lumen, hydrogen ions combine with HCO_3^- to form carbonic acid, which quickly dissociates into water and carbon dioxide. This reaction is catalyzed by the enzyme carbonic anhydrase. The generated carbon dioxide diffuses freely into the proximal tubule cell and reacts with water to form carbonic acid, catalyzed by carbonic anhydrase (CA II). The bicarbonate ions resulting from the dissociated carbonic acid exit through the basolateral membrane *via* the sodium bicarbonate exchanger[16,17].

In the kidneys' distal tubules are specialized cells known as alpha-intercalated cells that secrete hydrogen ions into the urine. At the same time, beta-intercalated cells generate new bicarbonate ions to maintain a balance between acid and base by replenishing bicarbonate in the blood. Principal cells reabsorb sodium and water while secreting K^+ to fine-tune the acid, base excretion, and urine output[18]. The bicarbonate (HCO_3^-) generated is transported to the blood in exchange for chloride (Cl^-) through the basolateral Cl^-/HCO_3^- exchanger. Additionally, the kidneys can produce ammonia (NH_3), which can combine with hydrogen ions to form ammonium (NH_4^+). Ammonium is then excreted into the urine, further contributing to acid excretion and acid-base balance[19].

The kidneys can respond to changes in blood pH by adjusting their acid-base handling mechanisms. When blood pH is too acidic, the kidneys can increase the excretion of hydrogen ions and generate more bicarbonate to restore balance. Conversely, when blood pH is too basic (alkaline), the kidneys can reduce bicarbonate reabsorption and retain more hydrogen ions, promoting acid excretion and balancing pH[16]. This intricate control of acid-base balance is essential for proper cellular function, enzyme activity, and overall physiological processes throughout the body. Any disruption in these mechanisms can lead to acid-base imbalances, such as metabolic acidosis or alkalosis, which can have significant health implications if not appropriately managed[20].

Role of the kidneys in calcium homeostasis and prevention of urolithiasis

The kidneys play a vital role in maintaining calcium homeostasis by regulating the reabsorption and excretion of calcium in response to changes in blood calcium levels and hormonal signals[21]. This fine-tuned control of calcium levels is essential for various physiological functions and for maintaining healthy bones and tissues throughout the body. Disruptions in the kidneys' ability to regulate calcium homeostasis can lead to disorders such as hypercalcemia (elevated blood calcium levels) or hypocalcemia (low blood calcium levels), which can significantly affect various organ systems and overall health. Proper kidney function is crucial for maintaining optimal calcium balance and overall calcium homeostasis in the body. Calcium homeostasis is the process of maintaining optimal calcium levels in the bloodstream

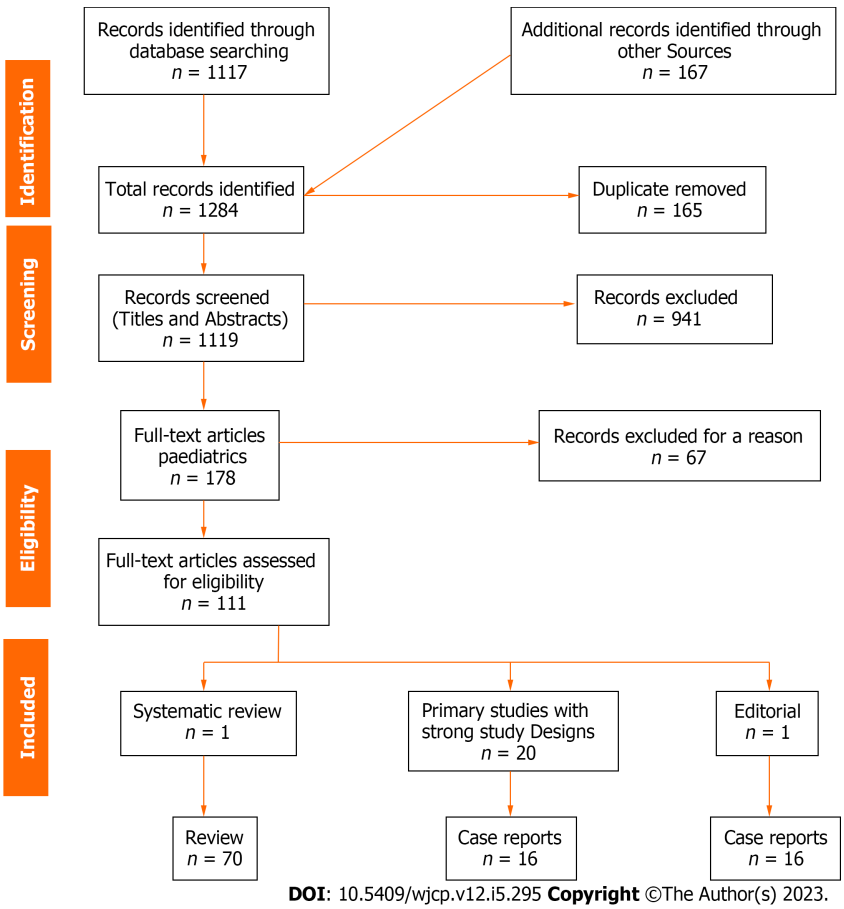

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Figure 1 Flow chart of included studies.

[22]. The kidneys play a crucial role in this process by reabsorbing filtered calcium, producing parathyroid hormone, metabolizing vitamin D, and excreting excess calcium. Disruptions in kidney function can lead to disorders like hypercalcemia or hypocalcemia, affecting overall health. Proper kidney function is essential for maintaining optimal calcium balance and overall calcium homeostasis in the body[23].

The kidneys play a vital role in maintaining acid-base homeostasis, which influences the solubility of minerals in the urine. Imbalances in acid-base levels can promote the formation of specific types of stones, such as uric acid stones. The kidneys are also involved in regulating calcium levels in the bloodstream. Proper calcium balance helps prevent the formation of calcium-containing stones, such as calcium oxalate stones[24]. The urinary stones, also known as uroliths, can block the urinary system and cause urolithiasis. The kidneys play a crucial role in preventing the formation of these stones. They filter waste products and excess substances from the bloodstream to form urine and regulate the amount of water reabsorbed in the renal tubules to maintain an appropriate urine concentration. Dilute urine reduces the risk of supersaturation of minerals in the urine, making it less likely for crystals to form and lead to stone formation[25].

The kidneys filter various substances from the blood, including crystal precursors like calcium, oxalate, and uric acid. Adequate fluid intake and maintaining proper urine pH are essential in preventing the accumulation of crystal precursors [26]. The kidneys produce and excrete substances like citrate, magnesium, and glycosaminoglycans that inhibit the formation and growth of crystals in the urine. These substances prevent the aggregation of crystal precursors and promote their dissolution, reducing the risk of stone formation[27]. Citrate inhibits the formation of calcium oxalate stones, a common type of kidney stone. Citrate chelates calcium ions in urine, interfering with the growth of crystals and enhancing the solubility of calcium oxalate, making it less likely for crystals to form and cause stones[28]. Proper citrate levels can be maintained through adequate fluid intake, diet, and necessary supplementation.

Efficient kidney function ensures the timely clearance of waste products and excess minerals from the urinary system. Proper acid-base balance prevents specific kidney stones like uric acid[29]. The kidneys regulate calcium levels in the bloodstream, which helps prevent the formation of calcium-containing stones like calcium oxalate stones. The kidneys play a vital role in maintaining acid-base homeostasis, which influences the solubility of minerals in the urine. Imbalances in acid-base levels can promote the formation of specific types of stones[30].

Etiology and pathogenesis of RTA

RTA refers to a group of kidney disorders that impair acid-base regulation. This results in the kidneys being unable to excrete acid or maintain the body's pH balance properly. There are various types of RTA, each with its own etiology and pathogenesis (Table 1).

Table 1 Comparison of different renal tubular acidosis types based on their etiology, pathogenesis, and key features.

Type of RTA		Type 1 RTA	Type 2 RTA	Type 3 RTA	Type 4 RTA
Prevalence		The most common type of RTA (1-2/100.000)	Less common than type 1 RTA (0.5/100.000)	Very rare	Slightly less common than type 1 RTA (1/100.000)
Location of defect		Distal nephron	Proximal nephron	Variable	Collecting duct
Etiology	**Primary**	Sporadic or hereditary (mutation of SLC4A1, H^+-K^+-ATPase, H^+-ATPase)	Sporadic or hereditary (mutation of CA-IV, NHE-3, NBC-1)	Mutation in CA-II	PHA-1, PHA-2 (Gordon's syndrome)
	Secondary	Autoimmune: Sjogren's, SLE, RA, PBC; Nephrotoxins: Amphotericn B, trimethoprim, lithium; Miscellaneous: Sarcoidosis, amyloidosis, obstructive uropathy	Autoimmune: Sjogren's; Nephrotoxins: Tetracycline, topiramate, valproate, acetazolamide; Metabolic: Wilson's disease, cystinosis, Lowe's syndrome, galactosemia, chronic hypocalcemia; Hereditary fructose intolerance, tyrosinemia; Miscellaneous: Multiple myeloma, amyloidosis	Type 1 RTA with secondary proximal tubule dysfunction, type 2 RTA with secondary distal tubule dysfunction	Aldosterone deficiency or aldosterone resistance: Hypoaldosteronism, ACEIs, ARBs; Hyporeninemic hypoaldosteronism: Diabetes, sickle cell disease; Tubulointerstitial disease (eGFR: 20-50 ml/min); Drugs: Potassium sparing diuretics, NSAIDs, trimethoprim, pentamidine, cyclosporine, tacrolimus
Pathogenesis		Impaired hydrogen ion secretion & reduced bicarbonate reabsorption in the distal tubules	Impaired bicarbonate reabsorption in the proximal tubules	Impaired distal acidification and reduced bicarbonate reabsorption	Impaired hydrogen ion secretion and decreased potassium excretion due to reduced aldosterone activity
Degree of acidosis		Severe	Mild to moderate	Mild	Mild to moderate
Key features		Acidemia, hypobicarbonatemia, inability to acidify urine properly, and loss of bicarbonate ions in urine. Hypokalemia is common	Metabolic acidosis, loss of bicarbonate ions in urine, hypobicarbonatemia, electrolyte imbalances (*e.g.*, hypokalemia, hypophosphatemia)	Metabolic acidosis, hypobicarbonatemia, variable features depending on the underlying systemic disease or medication	Metabolic acidosis, hyperkalemia, associated with hypoaldosteronism or resistance to aldosterone, potential electrolyte imbalances (*e.g.*, hyponatremia, mild hyperchloremic acidosis)
Risk of renal calcification		High	Lower than type 1 RTA	Very low (variable)	Unknown

AE1: Anion exchanger 1; CA: Carbonic anhydrase; NHE-3: Sodium-hydrogen exchanger 3; NBC-1: Sodium-bicarbonate cotransporter 1; PHA: Pseudohypoaldosteronism; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis; PBC: Primary biliary cirrhosis; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; RTA: Renal tubular acidosis.

Usually, 80% of the bicarbonate ions filtered by the glomerulus are reabsorbed from the urine back into the blood in the proximal tubules of the kidneys, and the remainder are reabsorbed in the distal nephron[31]. An autosomal recessive genetic defect in the *SLC4A1* gene causes RTA type 1. This gene encodes the anion exchanger protein AE1, which transports bicarbonate ions out of the alpha-intercalated cells in the distal tubules of the kidneys[32]. The genetic defect impairs the function of the AE1 protein, which reduces the distal tubules' ability to secrete hydrogen ions into the urine and reabsorb bicarbonate ions from the urine. The defective AE1 protein reduces the transport of hydrogen ions into the urine, leading to acid buildup in the blood and acidaemia. In type 1 RTA, the defective AE1 protein also impairs the reabsorption of bicarbonate ions, resulting in a loss of bicarbonate in the urine. This leads to decreased bicarbonate concentration in the blood, which causes metabolic acidosis and various RTA symptoms[33].

Another genetic defect in the *ATP6V1B1* gene, which encodes for a subunit of the proton pump in the alpha-intercalated cells of the distal tubules, can cause type 1 RTA[34]. This type of RTA can also be associated with other systemic genetic diseases, such as Ehler-Danlos syndrome, Marfan syndrome, congenital urinary tract obstruction, or sickle cell disease[35]. It may also occur secondary to chronic kidney diseases such as chronic hypercalcemia, familial hypercalciuria, medullary sponge kidney, chronic interstitial nephritis, chronic pyelonephritis, obstructive uropathy, and renal transplant rejection. Systemic disorders can also induce type 1 RTA, such as glue sniffing and hypergammaglobulinemic states[36,37]. The inherited form of type 1 RTA is mainly diagnosed in early life or young adulthood, while the acquired secondary form can be seen at any age but commonly in adulthood. The incomplete form of type 1 RTA has an incompletely understood pathogenesis. Patients with this disorder have a constantly elevated urinary pH and hypocitraturia, as in the complete form. However, they can maintain adequate acid excretion to keep the plasma bicarbonate levels within the normal range. Meanwhile, these patients suffer from nephrolithiasis due to hypercalciuria and hypocitraturia. Therefore, an incomplete form of type 1 RTA should be considered in every calcium stone former[37].

Type 2 RTA is often caused by underlying conditions or medications affecting the function of the proximal tubules in the kidneys. However, genetic disorders like Dent disease can also lead to type 2 RTA[3]. Fanconi syndrome, which impairs reabsorption in the proximal tubules, can be inherited or acquired. It can occur due to conditions such as multiple myeloma, Wilson's disease, or certain medications (*e.g.*, ifosfamide or outdated tetracyclines)[38]. The pathogenesis of type 2 RTA involves impaired bicarbonate reabsorption in the proximal tubules, leading to a decreased net reabsorption of bicarbonate from the glomerular filtrate and contributing to metabolic acidosis. The critical pathogenic mechanism is dysfunction in the transporters or enzymes needed for bicarbonate reabsorption in the proximal tubules from the

glomerular filtrate back into the blood[39]. This dysfunction reduces bicarbonate reabsorption with bicarbonate loss in the urine instead of reabsorbing, leading to decreased blood bicarbonate levels and subsequent metabolic acidosis, which can cause various symptoms of RTA[40].

Type 3 RTA is a complex condition often caused by underlying systemic diseases or certain medications. Systemic diseases, such as autoimmune diseases (*e.g.*, systemic lupus erythematosus and Sjögren's syndrome), primary biliary cirrhosis, sickle cell disease, Marble bone disease (due to congenital carbonic anhydrase deficiency type II), and some metabolic disorders, can lead to dysfunction or renal tubular damage, impairing acid-base regulation[41,42]. Medications such as carbonic anhydrase inhibitors and some chemotherapeutic agents can cause type 3 RTA[43]. The pathogenesis of type 3 RTA is not fully understood and may vary depending on the underlying systemic disease or medication. However, the main pathogenic mechanisms include a combination of impaired distal acidification and reduced bicarbonate reabsorption. Similar to type 1 RTA, type 3 RTA may involve impaired hydrogen ion secretion in the distal tubules, resulting in reduced distal acidification of the urine. The mechanisms underlying diseases or medications that disrupt this acidification process may vary. Type 3 RTA can also involve impaired bicarbonate reabsorption, which leads to metabolic acidosis with decreased blood pH and bicarbonate levels[44,45]. The combination of impaired distal acidification and reduced bicarbonate reabsorption contributes to metabolic acidosis, with decreased blood pH and bicarbonate levels. The severity and clinical manifestations of type 3 RTA can vary depending on the underlying systemic disease or medication involved[46].

Type 4 RTA is primarily caused by conditions that affect the production or action of the hormone aldosterone. The main etiological factors include hypoaldosteronism or aldosterone resistance[47]. Aldosterone plays a crucial role in maintaining electrolyte balance and acid-base regulation. In aldosterone deficiency or dysfunction, there is impaired renal acidification, as aldosterone promotes the distal tubules of the kidneys to secrete hydrogen ions into the urine, reducing the ability to acidify the urine[48]. Hypoaldosteronism can be caused by adrenal gland disorders such as Addison's disease, congenital adrenal hyperplasia, or adrenal gland destruction, resulting in a deficiency in the production or release of aldosterone[49]. In aldosterone resistance, the kidneys fail to respond adequately to the action of aldosterone. This resistance can result from conditions like certain medications (*e.g.*, spironolactone, eplerenone), kidney diseases, or genetic disorders affecting the mineralocorticoid receptor[50]. As aldosterone also regulates potassium levels in the body by enhancing its excretion in the urine, the reduced aldosterone activity in type 4 RTA leads to impaired potassium secretion, resulting in hyperkalemia. Patients with type 4 RTA can present with muscle weakness, arrhythmia, or even cardiac arrest due to hyperkalemia[9,51].

Renal calcification in RTA

Calcification of the kidneys occurs when calcium deposits accumulate in the kidneys, leading to various issues such as kidney stones, nephrocalcinosis, and chronic kidney disease[52]. Nephrocalcinosis happens when calcium salts accumulate in the renal tubules and interstitium of the kidneys. Kidney stones, on the other hand, form due to the presence of solid masses or calculi made of hard calcium deposits in the renal pelvis, calyces, or ureters[53]. Nephrocalcinosis can occur at three levels. Molecular or chemical levels are usually observed in patients with evident hypercalcemia and can be treated by correction of hypercalcemia. Microscopic nephrocalcinosis occurs when the mineral deposits of renal tissue can be seen by light microscopy, and it is often a precursor to the macroscopic type. The macroscopic type can be identified by different imaging methods[54]. Renal calcification can be a complication of RTA, and its severity is influenced by the level of acidosis, hypercalciuria, and other risk factors such as dehydration and a high protein diet, which increase the risk of nephrocalcinosis in RTA. Nephrocalcinosis occurs more frequently in type 1 RTA, less frequently in type 4 RTA and 2 RTA, and rarely in type 3 RTA[4]. About 20% of patients with nephrocalcinosis have either inherited or acquired type 1 RTA. Therefore, when a patient presents with kidney stones and nephrocalcinosis, it is essential to consider a diagnosis of type 1 RTA, as the prevalence of either complete or incomplete type 1 RTA in nephrolithiasis is about 7% and 14%, respectively[55].

Renal calcification in RTA can arise from various factors, including low urinary citrate, high urinary calcium, and metabolic acidosis. Chronic metabolic acidosis stimulates bone resorption, releasing calcium into the bloodstream and potentially depositing it in the kidneys[56]. The severity of metabolic acidosis directly affects the prevalence of renal calcification. Type 1 RTA (classical RTA) exhibits an H^+ excretion defect in the distal nephron, leading to urinary alkalinization and calcium phosphate precipitation, eventually forming stones[57]. Additionally, patients with RTA have kidneys that cannot synthesize enough citrate, which helps prevent calcium deposition in the kidneys. Citrate is filtered into the urine but is partly reabsorbed in the proximal tubule, where its absorption depends on pH and systemic and intracellular factors[58]. Acidosis increases citrate reabsorption and its intracellular metabolism, resulting in low urinary citrate levels that increase the risk of renal calcification. Low citrate levels, combined with increased bone resorption, elevate urinary calcium levels, further increasing the risk of renal calcification. Other factors such as hyperparathyroidism, increased dietary calcium intake, and certain medications can also contribute to serum calcium levels, potentially increasing the risk of renal calcification[59].

Factors that increase the risk of renal calcification

It has been previously mentioned that the type and severity of RTA can increase the risk and magnitude of acidosis. Other conditions that a child with RTA may experience can also increase the risk of renal calcification. One of the most common risk factors for renal calcification is hypercalciuria. Hypercalciuria may be primary, such as idiopathic hypercalciuria, or secondary due to hyperparathyroidism, hypervitaminosis D, bone resorption caused by immobilization, or long-term use of medications like furosemide, corticosteroids, or adrenocorticotropic hormone[54,60,61].

Hyperoxaluria is another critical factor that can induce urinary crystallization. Most oxalates come from an endogenous source, as nutrition only provides about 10% of urinary oxalates. Primary hyperoxaluria type 1 is a rare, autosomal recessive disease of the glyoxylate metabolism due to weak or absent activity of hepatic-specific peroxisomal alanine-glyoxylate aminotransferase[62]. Primary hyperoxaluria type II is even rarer and is caused by defects in D-glycerate dehydrogenase and hydroxy pyruvate reductase[63]. Primary hyperoxaluria type III is due to a recently discovered mutation in the *HOGA1* gene on chromosome 10, which encodes for a mitochondrial 4-hydroxy-2-oxoglutarate aldolase[64]. Secondary enteric hyperoxaluria occurs due to increased intestinal oxalate absorption caused by intestinal surgery, necrotizing enterocolitis, inflammatory bowel disease, celiac disease, cystic fibrosis, abetalipoproteinemia, and ethylene glycol intoxication[65]. Hypocitraturia is another risk factor in the pathogenesis of nephrocalcinosis, commonly seen in the complete type of RTA, especially with severe metabolic acidosis. However, it can also be observed in patients with malabsorption syndromes, hypokalaemia, and persistent mild or latent metabolic acidosis. Hypocitraturia is common in certain parts of the world, such as Turkey. Preterm infants are also more likely to have hypocitraturia[66,67]. Certain medications may also increase the risk of nephrolithiasis. Poorly soluble drugs can act as a nidus for stone formation. Other medications have lithogenic effects, such as vitamin D supplementation and loop diuretics, while some drugs, such as carbonic anhydrase inhibitors, can induce hypercalciuria[68,69].

Clinical presentation and diagnosis of renal calcification in RTA

The diagnosis and clinical manifestations of renal calcification in RTA depend on the specific type of RTA. Renal calcifications can appear as kidney stones or nephrolithiasis, which is caused by the buildup of calcium and other minerals in the renal tubules. To diagnose renal calcification in RTA, doctors use a combination of clinical evaluation, laboratory tests, and imaging studies. Kidney stones can cause symptoms such as nausea, vomiting, severe flank pain, haematuria, polyuria, polydipsia, and recurrent urinary tract infections[24]. Other symptoms of RTA vary depending on the type. For instance, acidotic breathing, salt cravings, and electrolyte imbalances such as hypokalaemia can lead to weakness, muscle cramps, and cardiac arrhythmias[70]. In the long term, metabolic acidosis associated with RTA can hinder a child's growth and development, causing failure to thrive, poor mineralization of bones, resistant rickets, and bone pain in some instances. Therefore, physicians need to measure infants and young children's length/height and weight and calculate their body mass index every 3 mo and every 6 mo for older children until they reach their final height. Chronic and progressive nephrocalcinosis may lead to chronic renal failure and its typical manifestations[71]. Other systemic symptoms depend on the underlying cause of RTA. For example, autosomal recessive forms of type 1 RTA are associated with hearing loss. In addition, Fanconi syndrome, a potential cause of type 2 RTA, may cause symptoms such as hypokalaemia, bicarbonate wasting, polyuria, low-molecular-weight proteinuria, glycosuria, generalized aminoaciduria, and phosphaturia, leading to hypophosphatemia[72,73].

Various laboratory tests can help determine the electrolyte levels, kidney function, and acid-base balance of a person with RTA and nephrocalcinosis. Urine tests help measure the pH and citrate levels of urine, which can provide information about the presence of kidney stones, crystals, and other abnormalities[74]. A safe and simple acid load test is performed to confirm the diagnosis of RTA and determine its type. This test assesses the ability of the kidneys to excrete and remove a predetermined acid load. The patient is given a known amount of ammonium chloride, which acidifies the blood for 3 d. Then, the patient's urine pH is monitored over time to test the kidneys' ability to excrete acid in the urine. In persons with normal kidney function, the urine pH will decrease to less than 5.3 after administering ammonium chloride. However, in patients with RTA, the urine pH may not decrease due to the kidneys' inability to excrete acid properly[75]. The test helps differentiate between different types of RTA. For instance, in type 2 RTA, the urine pH will decrease after administering ammonium chloride, but the fractional bicarbonate excretion will be elevated. In type 1 RTA, the urine pH will not decrease, and the fractional bicarbonate excretion will be normal or reduced[76]. The results of the acid load test in different types of RTA are summarized in Table 2. In some cases, genetic testing may be done to identify underlying genetic causes of RTA. Prenatal genetic testing can also be performed in high-risk families with a known case of hereditary RTA[77]. Table 3 compares clinical and laboratory data between type 1 and type 2 RTA. Table 4 shows some of the genetic disorders that may cause different types of RTA.

In addition, laboratory investigations are necessary for serial follow-up of already diagnosed patients. For example, in patients with hereditary type 1 RTA, fasting venous blood gas analysis, blood urea, serum creatinine, potassium, sodium, chloride, phosphate, calcium, alkaline phosphatase, and albumin are needed every 3-4 mo in infants and young children and every 6 mo for older children and adults[7]. Annual urinalysis, urine creatinine, sodium, potassium, calcium, and citrate are also required. The analysis frequency may be increased in individual cases. Annual audiometry is necessary for cases with type 1 RTA due to the high risk of hearing impairment[78].

When diagnosing renal calcification in patients with RTA, imaging studies can help detect kidney stones or calcifications within the kidneys. The type of imaging used depends on availability, patient characteristics, and the suspected extent of calcification (Table 5). X-rays commonly detect kidney stones, which appear as dense, white shadows in the kidneys and urinary tract. Ultrasound is a non-invasive technique that is useful in creating images of the kidneys and surrounding structures to detect kidney stones. Ultrasound can be done annually to evaluate nephrocalcinosis, urolithiasis, and cysts in asymptomatic individuals[79]. Computed tomography (CT) scans provide detailed cross-sectional images of the kidneys, allowing for a more precise evaluation of renal calcifications and any associated complications. Non-contrast CT is to be done first; then, contrast study may sometimes be helpful to clarify complex or confusing cases. However, contrast can obscure calcific densities. Therefore, contrast scans are usually indicated during the follow-up evaluation of patients with kidney stones[80]. Magnetic resonance imaging (MRI) is used in cases where CT scans are contraindicated or not preferred, such as in patients with allergies to contrast agents used in CT scans. MRI can also provide detailed images of the kidneys, but it may not be as readily available as other imaging modalities[81]. Imaging studies, especially ultrasound and CT scans, are crucial for diagnosing and managing renal calcification in patients with

Table 2 Acid load test in different types of renal tubular acidosis

Type of RTA	Urine pH	Fractional bicarbonate excretion
Type 1 RTA	Does not decrease	Normal or decreased
Type 2 RTA	Decreases	Increased
Type 3 RTA	Variable	Variable
Type 4 RTA	Does not decrease	Decreased

RTA: Renal tubular acidosis.

Table 3 Comparison of clinical and laboratory data between type 1 and type 2 renal tubular acidosis

Feature		Type 1 RTA	Type 2 RTA
Prevalence		More common than type 2 RTA	Less common than type 1 RTA
Cause		Usually isolated, inherited, autosomal recessive forms are associated with hearing loss	Usually secondary to a systemic disease, most often metabolic disease, *e.g.*, Fanconi syndrome
Clinical features	Nephrocalcinosis	Often present	Occasionally present
	Polyuria (increased urine output)	Common	Common
	Polydipsia (increased thirst)	Common	Common
	Dehydration	Less common	Less common
	Bone abnormalities	Usually, severe	Variable
	Failure to thrive (children)	Occasional	Uncommon
	Rickets/osteomalacia (children)	Occasional	Uncommon
	Metabolic acidosis	Severe acidosis; is easily corrected with bicarbonate supplementation	Usually milder but difficult to correct; requires high doses of bicarbonate supplementation
Laboratory Finding	Serum HCO_3^- (bicarbonate)	Decreased	Decreased
	Serum potassium	Low	Normal/low
	Urine pH	> 5.5	< 5.5
	Fractional excretion of bicarbonate	< 5%	> 15%
	Urine-blood PCO_2	< 20 mmHg	> 20 mmHg
	Phosphaturia and hypophosphatemia	Absent	Present (variable)
	Tubular defects – low-molecular-weight proteinuria, aminoaciduria, glycosuria	Absent	Present (variable)
	Hypercalciuria	Often present	Occasionally present

RTA: Renal tubular acidosis.

RTA. They allow clinicians to visualize the extent and nature of the calcifications, determine appropriate treatment strategies, and monitor treatment response over time[82]. However, it is essential to remember that the choice of imaging modality should be based on the specific clinical scenario, and imaging findings should be integrated with other clinical information to arrive at a comprehensive diagnosis and treatment plan. Early diagnosis and treatment of renal calcification in RTA can help prevent serious complications[1].

Management of nephrocalcinosis

Managing nephrocalcinosis in RTA involves identifying the root cause and addressing the complications associated with the condition. The treatment method utilized depends on the type of RTA and the severity of nephrocalcinosis. The primary objectives of management are to correct the acidosis, reduce urinary calcium excretion, and prevent further calcification. For type 1 RTA, the primary management goal is to decrease urinary calcium excretion. Oral alkaline therapy, such as oral sodium bicarbonate or citrate, is utilized to correct metabolic acidosis. The average dosage is 1.9 mEq/kg/d and is adjusted based on the blood and urine pH. Young patients typically require higher doses due to their high growth rate[83]. Patients with type 1 RTA caused by vacuolar H^+-ATPase variants may require higher doses of alkali

Table 4 Genetic causes of different types of renal tubular acidosis

Gene involved	Inheritance	Location of gene	RTA type caused	Affected protein	Main clinical feature
SLC4A1 gene	AD AR	17q21-q22	Type 1 RTA	AE1	Type 1 RTA, hereditary spherocytosis
CA2 gene	AR	8q21.2	Type 1 RTA, type 3 RTA	CA II	Osteopetrosis, brain calcification, RTA
ATP6V1B1	AR	2q13	Type 1 RTA	H^+-ATPase	Sensorineural deafness
ATP6V0A4		7q33-q34			
SLC4A2 gene	AR	7q36.1	Type 2 RTA	AE2	PBC
SLC4A4 gene	AR	4q13.3	Type 2 RTA	(NBC)	Ocular abnormalities
SLC2A2 gene	AR	3q26.2	Type 2 RTA	GLUT2	Fanconi-Bickel syndrome, NIDDM
CLCN5 gene	X-linked recessive	Xp11.23	Type 2 RTA	H^+/Cl^- exchanger	Dent disease type 1, HHR
OCRL1 gene	X-linked recessive	Xq26.1.	Type 2 RTA	OCRL enzyme	Dent disease, type 2, LOCRS
NR3C2 (*MR*) gene	AD	4p	Type 4 RTA	MLR NRC	PHA1, hyperkalemia, salt wasting & hypotension
SCNN1A, *SCNN1B*, and *SCNN1G* genes	AR	SCNN1A (12p3). SCNN1B, & SCNN1G located in (16p12-p13)	Type 4 RTA	ENaC	Liddle syndrome, sodium loss from the kidneys and other organs, including the sweat glands, salivary glands, and colon

AD: Autosomal dominant; AE1: Anion exchanger 1 protein; AE2: Anion exchanger 2 protein; AR: Autosomal recessive; CA II: Carbonic anhydrase II; ENaC: Epithelial sodium channels located on the luminal membrane of the collecting tubule; GLUT2: Glucose transporter 2; HHR: Hereditary hypophosphatemic rickets; OCRL: Lowe oculocerebrorenal syndrome; MLR NRC: The mineralocorticoid receptor (or MR, MLR, MCR), also known as the aldosterone receptor or nuclear receptor subfamily 3, MR: Mineralocorticoid receptor, group C; NBC: Sodium bicarbonate cotransporter, which regulates bicarbonate secretion, absorption, and intracellular pH. NIDDM: Noninsulin-dependent diabetes mellitus, PBC: Primary biliary cirrhosis; PHA1: Primary pseudohypoaldosteronism type 1; RTA: Renal tubular acidosis.

Table 5 Comparison of different imaging modalities in nephrocalcinosis due to RTA

Modality	Advantages	Limitations
X-ray	Readily available; Cost-effective; Quick initial assessment; Suitable for detecting large, dense stones	Limited sensitivity for smaller or radiolucent stones; No detailed anatomical information
Ultrasound	Can be used to assess kidney size, shape, and echogenicity; Non-invasive; Real-time imaging; Widely available; Initial assessment of kidney stones and medullary cyst	Reduced sensitivity for smaller or deeply located calcifications; Limited anatomical details
CT	Excellent spatial resolution; Detailed cross-sectional images; Highly sensitive for detecting kidney stones and calcifications; Assesses impact on kidney function and urinary tract	Involves exposure to ionizing radiation; Contrast agents may be contraindicated in some patients; Not suitable for all patients due to contrast use
MRI	No ionizing radiation; Detailed images of the extent of calcification and surrounding soft tissue damage; Multiplanar imaging capability; Can provide information on tissue characteristics and perfusion	It may not be as readily available as other modalities; Limited sensitivity for detecting small or faint calcifications

CT: Computed tomography; MRI: Magnetic resonance imaging.

than those with heterozygous *SLC4A1* gene mutations[84]. A sustained-release granular form of potassium citrate and bicarbonate can be used in a 1:2 ratio to maintain normal serum bicarbonate levels[85]. This action improves urinary citrate, reduces the rate of nephrolithiasis, and ensures adequate growth in children[2]. Potassium citrate and additional potassium chloride are supplied as needed to correct hypokalemia. Thiazide diuretics, particularly hydrochlorothiazide, have been used to treat renal hypercalciuria and reduce the risk of nephrolithiasis[86]. The calcium/creatinine ratio can detect hypercalciuria and hypocitraturia, which may indicate inadequate correction of acidosis. In some cases, surgery may be necessary to remove kidney stones. Screening for sensorineural hearing loss during childhood is essential, and any issues should be monitored and treated accordingly[87].

When managing type 2 RTA, the primary goals are treating the root cause, correcting acidosis, promoting growth, and preventing bone deformities. These goals are typically achieved through oral bicarbonate supplements to compensate for urinary bicarbonate losses, with high doses of alkalies (10-15 mEq/kg/d)[88]. Depending on the severity, additional

measures may be necessary to address potassium and electrolyte imbalances. Potassium is administered at a dose of 1-5 mEq/kg/d, phosphate at a dose of 20-40 mg/kg/d, sodium at a dose of 3-5 mEq/kg/d, and magnesium at a dose of 25-50 mg/kg/d. Children with type 2 RTA usually require higher doses of bicarbonate therapy than those with type 1 RTA to maintain bicarbonate levels around the kidney threshold. In some cases, a potassium-sparing diuretic may be prescribed[3]. Vitamin D is vital in promoting calcium absorption and bone health. In type 1 RTA, the kidneys struggle to activate vitamin D, so active vitamin D supplementation in the form of calcitriol 20-40 ng/kg/day, combined with regular monitoring of urinary calcium levels and annual renal ultrasounds, is necessary to prevent nephrocalcinosis and osteoporosis[89]. Vitamin D supplementation may be unnecessary for type 2 RTA, as vitamin D activation is unaffected. However, vitamin D deficiency can induce type 2 RTA[90]. Nutritional intake should be monitored by specialized nutritionists, as children with RTA often have compromised nutritional status due to poor nutrient intake, polyuria, polydipsia, and increased sodium and nutrient loss. It is recommended to consume calorie-dense foods rich in potassium and phosphorus, along with sufficient fluids. Patients with RTA should consume less acidic foods, such as animal meat, and more alkaline-based foods, such as vegetables and fruits[1].

The treatment for type 3 RTA involves using alkaline therapy and addressing any specific underlying causes. In type 4 RTA, management requires controlling the underlying reason for the mineralocorticoid disorder. This may involve treating conditions like hyperaldosteronism or evaluating medication use[91]. Daily intake of 0.1 mg of fludrocortisone can effectively manage hyperaldosteronism-associated hyperkalemia. However, this is not generally recommended due to the high risk of hypertension, edema, and heart failure. Patients with hyperkalemia can effectively manage their condition by limiting their dietary potassium intake to 40 to 60 mEq daily and using diuretics such as loop or thiazide when necessary[92].

Nephrocalcinosis management in RTA should be tailored to each patient's specific condition, medical history, and the underlying cause of RTA. Since it is a progressive condition, it is crucial to start strategies to prevent, diagnose, and treat RTA-associated nephrocalcinosis early[93]. These early strategies and interventions can help control nephrocalcinosis and prevent it from producing severe complications. Encouraging adequate fluid intake can help dilute the urine, prevent the concentration and crystallization of calcium and other minerals in the urine, and reduce the risk of calcium deposition in the kidneys[24]. It is crucial to keep urinary calcium levels below < 0.1 mmol (< 4 mg)/kg and oxalate < 0.5 mmol (< 45 mg)/1.73 m^2 within 24 h of urine collection. Additionally, it is vital to keep urinary citrate levels above 1.9 mmol (365 mg)/1.73 m^2 in males and 1.6 mmol (310 mg)/1.73 m^2 in females within 24 h of urine collection[94].

Dietary adjustments should be made based on the type of RTA to prevent and treat nephrocalcinosis. Limiting calcium and oxalate intake is recommended to reduce the formation of kidney stones[95]. A low-sodium diet can also help decrease urinary calcium excretion, but sodium salts like sodium bicarbonate and citrate may increase calcium excretion and worsen stone disease[96]. Therefore, potassium bicarbonate or potassium citrate may be better alternatives, especially for patients with active calcium stone disease. In type 1 RTA, minimizing urinary potassium loss and correcting hypokalemia can alleviate or even reverse nephrocalcinosis, lowering the rate of calcium kidney stones and potentially correcting osteoporosis[97]. Reducing acidic and oxalate-rich foods like spinach, rhubarb, and beets can also be beneficial, but it is essential to consult a healthcare professional to avoid nutrient deficiencies[98]. Regular exercise and maintaining a healthy weight are also crucial in improving kidney function and reducing the risk of kidney stones. Lastly, avoiding passive smoking is essential in preventing nephrocalcinosis in children with RTA, as smoking can harm the kidneys[99].

Reviewing the medication chart, specifically for type 1 RTA, is important. Medications that can worsen nephrocalcinosis, such as carbonic anhydrase inhibitors, should be assessed and adjusted if needed[100]. Conversely, certain medications may help manage nephrocalcinosis depending on its severity and cause. For instance, thiazide diuretics can minimize calcium excretion in the urine, which could benefit specific cases of nephrocalcinosis[101]. Potassium-sparing diuretics, like amiloride, may help maintain blood potassium levels, especially when taking thiazide diuretics[102]. Pain management may be necessary for those experiencing kidney stone-related pain. Non-steroidal anti-inflammatory drugs or opioids are standard options for pain relief[103].

Regular monitoring of kidney function, electrolyte levels, and urinary calcium excretion is crucial for detecting any complications early, evaluating the effectiveness of the treatment, and identifying any progression of nephrocalcinosis [104]. Nephrocalcinosis can increase the likelihood of developing kidney stones, so preventive measures like dietary adjustments, increased fluid intake, and medication (such as potassium citrate) may be advised[66]. Genetic counselling can help provide information about inheritance patterns, assess the risk to family members, and guide family planning decisions for hereditary forms of RTA[105].

Prognosis of renal calcification in patients with RTA

The outlook for renal calcification in patients with RTA can differ depending on factors such as the type of RTA, underlying cause, extent of calcification, and treatment effectiveness. The type of RTA can impact the prognosis and management of renal calcification. For instance, type 1 RTA is usually linked with nephrocalcinosis and kidney stones[1]. Early detection of renal calcification and proper RTA management are crucial for a better prognosis. Treating the underlying acid-base imbalance, alkaline therapy, and controlling calcium excretion can help slow down the progression of nephrocalcinosis and prevent further kidney damage[106]. Nephrocalcinosis increases the risk of kidney stone formation, leading to recurrent kidney stone episodes and potential complications if not managed effectively. Preventive measures such as dietary adjustments, fluid intake, and medication can help reduce the risk of stone formation[107]. The extent of nephrocalcinosis and its impact on kidney function are vital in determining the prognosis. Extensive nephrocalcinosis can sometimes lead to chronic kidney disease and its associated complications. Identifying and treating the underlying cause of RTA and nephrocalcinosis are crucial[108]. For example, in type 1 RTA, potassium citrate or bicarbonate supplementation can help correct the acidosis and prevent stone formation. In type 2 RTA (proximal RTA), treatment may involve addressing the underlying cause, such as a genetic disorder or specific medications. Other medical

conditions or comorbidities can also impact the prognosis of nephrocalcinosis in RTA patients[109]. Managing these conditions alongside RTA and nephrocalcinosis is essential for overall health and outcomes. Regular monitoring and follow-up with healthcare providers are necessary for patients with RTA and renal calcification. Periodic evaluation of kidney function, imaging studies (*e.g.*, ultrasound and CT scans), and urine analysis can help assess the progression of the condition and guide treatment adjustments if needed[110]. The prognosis can vary significantly among individuals due to individual variability. It is important to recognize that early and comprehensive medical management is essential to optimize outcomes. Regular follow-up with healthcare providers, adherence to treatment plans, and lifestyle modifications can help improve the long-term prognosis for patients with nephrocalcinosis and RTA[111].

Limitations of the study

Several potential limitations could impact the reliability and generalizability of the study findings. There might be a limited number of studies and data available on renal calcification in children with RTA due to the relative rarity of this condition. This can reduce the included studies' sample size and statistical power, making it challenging to draw robust conclusions. In addition, the studies included in the review have differences in methodologies, patient populations, and definitions of renal calcification. This heterogeneity can make it challenging to compare and synthesize the results. We should also consider that RTA is not a single condition but rather a group of disorders with different underlying causes and manifestations. We should consider the variability in RTA types, their treatment approaches, and their potential impact on renal calcification. There is also a lack of longitudinal data and control groups in some studies, which limits our ability to fully understand the progression and impact of renal calcification on children with RTA. Furthermore, many studies included in the review may have been conducted in specific populations, which can limit the generalizability of the findings to other populations. Another significant limitation of the study is that we included studies published in English, which could result in the omission of important studies and potentially bias the results.

CONCLUSION

Our comprehensive review of the current literature underscores the significance of renal calcification as a critical concern for children with RTA. Our analysis reveals that renal calcification is a prevalent issue among children with RTA, with varying degrees of risk associated with different RTA types. Notably, type 1 RTA is frequently linked to nephrocalcinosis, emphasizing the importance of early detection and tailored management strategies for affected patients. While we acknowledge the limitations within the reviewed studies, such as the small number of available studies, methodological heterogeneity, and potential publication bias, they collectively emphasize the critical role of timely diagnosis and appropriate RTA management in reducing the risk of renal calcification and its associated complications. In particular, alkaline therapy remains a cornerstone treatment, effectively addressing the acid-base imbalance and minimizing the formation of kidney stones. To advance our understanding and guide clinical practice further, it is evident that future research efforts should focus on larger sample sizes, longitudinal data, and more rigorous methodologies. These endeavors will undoubtedly contribute to a more nuanced comprehension of the intricate relationship between RTA and renal calcification. By doing so, we can better inform treatment and prevention strategies, ultimately enhancing the long-term outcomes and quality of life for children affected by this condition.

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Country/Territory of origin: Egypt

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536; Nermin Kamal Saeed 0000-0001-7875-8207; Adel Salah Bediwy 0000-0002-0281-0010; Reem Elbeltagi 0000-0001-9969-5970; Samir Hasan 0000-0002-0759-7394.

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