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Nephrolithiasis in Renal Tubular Acidosis: Pathophysiology, Diagnosis, and Management Strategies

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Abstract

Renal tubular acidosis (RTA) encompasses a group of disorders characterized by impaired kidney acid-base regulation, resulting in metabolic acidosis. Nephrolithiasis, the formation of kidney stones, represents a significant complication of RTA. Despite its clinical importance, the relationship between RTA and nephrolithiasis remains complex and poorly understood. This review provides a comprehensive overview of nephrolithiasis in RTA, focusing on its pathophysiology, diagnostic challenges, and management strategies. Mechanisms underlying kidney stone formation in RTA, including altered urinary pH, electrolyte abnormalities, and mineral metabolism disturbances, are explored in detail. Clinical manifestations and diagnostic considerations specific to nephrolithiasis in RTA patients are discussed, emphasizing the importance of a comprehensive metabolic evaluation and imaging procedures for accurate diagnosis. Current therapeutic approaches for treating kidney stones in RTA patients, including dietary modifications, pharmacological interventions, and surgical interventions, are reviewed. By elucidating the intricate interplay between RTA and nephrolithiasis, this review aims to enhance clinical understanding and guide optimal management strategies for patients with this challenging renal disorder.

Keywords: Renal Tubular Acidosis; Nephrolithiasis.

Abbreviations: RTA: Renal Tubular Acidosis R; dRTA - Distal renal tubular acidosis; pRTA - Proximal renal tubular acidosis; SLE - Systemic lupus erythematosus; ESWL - Extracorporeal shock wave lithotripsy; PCNL - Percutaneous nephrolithotomy; CT - Computed tomography; NH3+ - Ammonia; NH4+ - Ammonium; ACE - Angiotensin-converting enzyme; CRISPR - Clustered Regularly Interspaced Short Palindromic Repeats; BMI - Body mass index; GPX4 - Glutathione peroxidase 4; AUA - American Urological Association

Introduction

Renal tubular acidosis (RTA) encompasses a group of disorders characterized by defective renal tubular acidification, leading to systemic acid-base disturbances. This condition arises from dysregulation in the proximal tubules, distal tubules, or collecting ducts, resulting in impaired hydrogen ion secretion or bicarbonate reabsorption. The consequences of RTA extend beyond mere acid-base imbalances, often manifesting as electrolyte disturbances, bone demineralization, growth retardation, and nephrolithiasis. RTA is classified into several subtypes based on the specific defect in renal tubular function, including proximal (Type 2), distal (Type 1), and hyperkalemic (Type 4) RTA, each presenting

distinct clinical features and underlying pathophysiology [1]. Nephrolithiasis, the formation of renal calculi within the urinary tract, poses a significant complication in RTA patients. The acidic urine characteristic of RTA predisposes individuals to form calcium phosphate and uric acid stones. Furthermore, altered urinary pH and electrolyte imbalances contribute to the precipitation of stone-forming substances, exacerbating stone formation and recurrence rates. Management of nephrolithiasis in RTA patients poses unique challenges due to the underlying acid-base disturbances and electrolyte abnormalities, necessitating a comprehensive approach tailored to correct both the renal tubular defects and stone-forming tendencies [2,3].

Pathophysiology of Nephrolithiasis in RTA

Renal tubular acidosis (RTA) is a group of disorders classified based on the affected portion of the nephron into Distal RTA (Type I or dRTA), Proximal RTA (Type II or pRTA), Type III RTA, a combination of Proximal and Distal RTA, and Type IV RTA or hyperkalemic distal tubular RTA [4,5]. Under the influence of aldosterone, the distal collecting ducts produce new bicarbonate. Type I RTA occurs when α-intercalated cells of the Collecting Tubules cannot secrete H+ into the lumen. This results in the inability of new bicarbonate to be produced and released to the interstitium, with consequent metabolic acidosis and hypokalemia due to failure of the H+/K+ ATPase [4,5]. There are several causes of type I RTA. These include Amphotericin B toxicity, autoimmune diseases such as systemic lupus erythematosus (SLE) and Sjögren syndrome, analgesic nephropathy, and congenital obstruction anomalies of the urinary tract [4]. The inability of H+ excretion into the lumen leads to alkaline urine pH >5.5 [5,6]. Given the H+ ion retention seen in patients with Type I RTA, hypercalciuria develops due to elevated intestinal calcium absorption, excess release from bone, and decreased renal absorption. Citrate reabsorption is pH-dependent, and acidosis decreases excretion and hypocitraturia [7]. These three factors, alkaline urine, hypercalciuria and hypocitraturia are the main contributing factors to developing calcium phosphate nephrolithiasis in dRTA [6]. Type II RTA occurs when the Proximal Convoluted Tubule cannot reabsorb bicarbonate from the lumen, leading to elevated bicarbonate excretion in the urine and consequent metabolic acidosis. Often, Type II RTA is caused by Fanconi Syndrome, multiple myeloma, and carbonic anhydrase inhibitors [4,5]. The defect of bicarbonate reabsorption leads to elevated urinary pH >5.5 when filtered bicarbonate exceeds the threshold for reabsorption. Although patients with pRTA are present with metabolic acidosis, the functioning distal tubules allow acid to be excreted, which prevents hypercalciuria and hypocitraturia and, therefore, calcium oxalate or phosphate formation [6].

Type III RTA is a rare combination of distal and proximal defects that result from carbonic anhydrase II deficiency. Genetic causes can include mutations in chromosome 8q22 [4]. Type IV RTA results from hypoaldosteronism or resistance to aldosterone in the α-intercalated cells of the collecting duct, leading to hyperkalemia and decreased ammonia ($NH3^+$) synthesis in the proximal convoluted tube with a subsequent decrease in ammonium (NH4+) excretion, which creates an acidic urinary pH that can vary within the range of <5.5 [4,6]. Common causes of decreased aldosterone production include diabetic hypo-reninism, ACE inhibitors, angiotensin II receptor blockers, non-steroidal anti-inflammatory medication, heparin, cyclosporine, and adrenal insufficiency. Other causes that increase the risk of aldosterone resistance are drugs like trimethoprim-sulfamethoxazole and potassium-sparing diuretics [4]. Calcium stone formation is relatively rare given the etiology of Type IV RTA, and most patients may present with a degree of kidney damage resulting in low calcium concentration in the urine. Although rare, patients may be predisposed to uric acid stone formation when risk factors such as low urinary pH, type II diabetes, and obesity are present [6].

Clinical Manifestations and Diagnosis

Renal tubular acidosis (RTA) has both hereditary and acquired etiology. Congenital cases may display from mild forms, such as mild metabolic acidosis with incidental detection of kidney stones, to patients presenting rickets, delayed growth, and electrolyte alterations [9]. Likewise, it may also present as chronic kidney disease, nephrocalcinosis, or recurrent kidney stones. The latter two are the main manifestations in adults, and the probability of developing them increases with the patient's age and the delay in starting alkalinizing treatment [8-11]. Additionally, nephrolithiasis is associated with flank pain, nausea, vomiting, and hematuria, among other symptoms [10]. Regarding the diagnosis of nephrolithiasis in RTA, even though it is usually associated with distal RTA (also known as type 1 RTA) and its incomplete form, it is necessary to initially characterize the type of renal tubular acidosis that the patient presents [8,10]. Urinalysis allows us to measure pH and citrate levels in urine to identify lithogenic factors such as alkaline urine and hypocitraturia [12]. Ultrasound is the most recommended initial imaging study to identify kidney stones in children [13]. However, an X-ray with limited sensitivity in radiolucent or small-sized stones is also an alternative. Computed tomography allows us to visualize detailed images of the kidneys for renal calculi, calcifications, or associated complications [10]. Non-contrast computed tomography is more recommended in adults than children because the latter are more vulnerable to the ionizing radiation of these imaging studies [13].

Patients suspected of having kidney stones should undergo an imaging assessment to confirm the presence of a stone and to evaluate for signs of urinary blockage, such as hydronephrosis. If a stone is identified, its size and location are crucial for predicting the likelihood of natural passage and determining the appropriate course of action [14]. If not completed during the initial evaluation, a radiographic examination should be conducted, preferably with non-contrast, low-dose computed tomography (CT), to detect any remaining stones within the urinary system [15]. A

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comprehensive metabolic evaluation for kidney stones should include blood and urine tests, with at least two 24-hour urine collections [16]. Each collection should measure urine volume, pH, and the excretion levels of calcium, uric acid, citrate, oxalate, sodium, potassium, magnesium, and creatinine (for assessing collection completeness). Additionally, urinary supersaturation should be calculated. However, urine collection should be avoided if there is evidence of kidney or ureteral obstruction from existing stones or urinary tract infections [17,18].

Types of Kidney Stones Associated with RTA

Various forms of distal renal tubular acidosis (dRTA) are predisposed to kidney stone formation. Specifically, type 1 distal RTA and type 3 mixed and incomplete distal RTA are characterized by compromised alpha-intercalated cells within the distal tubule, resulting in diminished bicarbonate generation and impaired excretion of hydrogen ions, consequently leading to persistently alkaline urine with a pH > 5.5 [19]. This alkaline milieu, coupled with the retention of hydrogen ions, triggers excessive stimulation of intestinal calcium absorption and calcium release from bone while renal calcium reabsorption diminishes, culminating in hypercalciuria. Furthermore, the heightened reabsorption of citrate in this context leads to hypocitraturia, further fostering the formation of calcium stones, particularly calcium phosphate stones, due to the urine's alkaline nature [20]. Moreover, beyond the commonly associated types of kidney stones in RTA, other rare scenarios exist, such as Fanconi syndrome linked with Dent's disease, which contributes to the spectrum of nephrolithiasis complicating RTA. These less prevalent associations underscore the diverse etiologies and complexities involved in nephrolithiasis among RTA patients, necessitating comprehensive diagnostic and management approaches tailored to individual cases [21].

Management Strategies

Managing nephrolithiasis in renal tubular acidosis (RTA) necessitates a multifaceted approach encompassing dietary modifications, pharmacological interventions, and surgical procedures. Dietary modifications prevent stone formation by addressing the underlying metabolic abnormalities associated with RTA. Patients are advised to adopt a low-sodium, low-protein diet to mitigate the risk of hypercalciuria and calcium stone formation. Additionally, increasing fluid intake, particularly water, helps to maintain dilute urine and prevent the concentration of stone-forming substances. Moreover, dietary measures aimed at alkalinizing the urine, such as consuming citrate-rich foods or supplements, can counteract the acidic urinary pH characteristic of RTA and inhibit the formation of calcium phosphate stones [22].

Pharmacological interventions targeting specific mechanisms implicated in nephrolithiasis pathogenesis are integral to RTA management. Alkali supplementation with oral bicarbonate or citrate preparations corrects systemic acidosis and normalizes urinary pH, reducing the propensity for stone formation. Thiazide diuretics may mitigate hypercalciuria by enhancing renal calcium reabsorption, while potassium citrate supplements help counteract hypocitraturia and promote urinary citrate excretion, inhibiting calcium stone formation [23]. Medications targeting underlying metabolic abnormalities, such as vitamin D analogs or bisphosphonates, may address bone demineralization secondary to RTA-associated hypercalciuria. Surgical interventions and minimally invasive procedures may be warranted in refractory or recurrent nephrolithiasis cases in RTA patients. Extracorporeal shock wave lithotripsy (ESWL), ureteroscopy with laser lithotripsy, or percutaneous nephrolithotomy (PCNL) are employed to fragment and remove larger calculi. In select cases, surgical correction of anatomical abnormalities contributing to stone formation, such as ureteropelvic junction obstruction or ureteral strictures, may be necessary to prevent recurrence [24]. Close collaboration between nephrologists, urologists, and dietitians is imperative to devise individualized management plans tailored to the specific subtype of RTA and associated comorbidities.

Prevention and Long-term Management

There is more than one condition that can lead to RTA, and strategies about how to prevent it are still under study. In certain instances, like in inherited cases, it cannot even be prevented [25]. However, one of the most important recommendations when treating and following up on patients with RTA is to have a multidisciplinary team in place to manage its multiple clinical manifestations [26]. Diet and lifestyle can also play a role during the long-term management of RTA. Maintaining an optimal metabolic state is crucial during the long-term management of patients with the disease [30]. Preventing the formation of kidney stones is an essential target when managing patients with RTA. One of the recommendations is the ingestion of sodium bicarbonate or sodium citrate solution, as this has shown a positive impact on preventing kidney stones [27,29]. Another strategy is to increase the ingestion of high-alkali foods, like vegetables and fruits, decrease the ingestion of low-acid producers' foods like animal protein derived, and avoid diets high in sodium. Modifications in ingesting citrus juices, fruits, and calcium have also been recommended [28,29]. Exercise and hydration can also play a role in the formation of kidney stones in patients with Renal Tubular Acidosis [29,31]. Appropriate hydration to compensate for excessive sweating after moderate exercise or working at high temperatures can help reduce the crystallization of calcium oxalate and uric acid in the urine [31,32]. Probiotics, caffeine consumption, and avoiding supplementation with vitamins C and D are preventive strategies that are still under study, and additional explanation is required [32]. Even though there is still no specific recipe for preventing the formation of kidney stones in patients with RTA, multiple efforts are being made to establish and discover new strategies that will improve the quality of life in patients with the disease.

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Emerging Research and Future Directions

Studies have shown that low urine output and dehydration are common risk factors of nephrolithiasis, with a less common condition associated with calcium nephrolithiasis being Renal Tubular Acidosis (RTA), precisely Type 1 RTA. In type 1 RTA, there is a defect in the alpha intercalated cells in the distal tubules of the kidney, leading to decreased secretion of hydrogen ions and decreased reabsorption of bicarbonate, resulting in non-anion gap metabolic acidosis. In compensation, there is increased reabsorption of citrate, as this gets converted to bicarbonate in the body, driving the pH up; however, urinary citrate is a protective factor in stone formation, especially calcium stones, as it binds to calcium being excreted, inhibiting the supersaturation that leads to stone formation [33]. RTA's type 2 and 4 can also develop nephrolithiasis through different mechanisms, as the inability to reabsorb bicarbonate and an acidic urinary pH can lead to uric acid nephrolithiasis. With the increasing prevalence of nephrolithiasis in the community, new advances are being worked on to understand how to improve the treatment and prevention of the disease in the first place. Lifestyle and habit modifications are essential in nephrolithiasis prevention, as studies have shown that maintaining a reference body mass index, avoiding cigarette smoke, limiting sodium and oxalate-rich foods, decreasing vitamin C supplement consumption, and limiting animal protein decreases the risk of stone formation [34]. Other studies have found that yellow tea has reduced nephrolithiasis formation in animal models, although more studies need to be done to support it [35]. One recent study found that by utilizing CRISPR, they can selectively increase the translation of a gene (GPX4) that has been proven to be a protective factor in the formation of calcium oxalate stone formation, by countering ferroptosis, a gene known to increase calcium oxalate stone formation [36]. Nephrolithiasis has some complex challenges, as it can be a multifactorial disorder, and identifying the proper etiology for preventing recurrent nephrolithiasis can be difficult. With current data and lifestyle modifications education, patients have a 50% chance of having a recurrent nephrolithiasis event within the next 10 years after the first episode. Current imaging diagnostics for nephrolithiasis have some limitations in accuracy, cost, and exposure; developing non-invasive, accurate, and cost-effective diagnostic tools could help diagnose early stones and monitor progression. Future research opportunities on the psychological impact of kidney stones on patients' lives can be done, as well as how much patient education prevents the recurrence of nephrolithiasis.

Conclusion

Renal tubular acidosis (RTA) represents a complex spectrum of disorders characterized by defective renal tubular acidification. This leads to systemic acid-base disturbances and predisposes individuals to nephrolithiasis. The pathophysiology of nephrolithiasis in RTA involves many factors, including disturbances in urinary pH regulation, electrolyte abnormalities, and altered mineral metabolism. Management of nephrolithiasis in RTA patients requires a comprehensive approach to address the underlying metabolic abnormalities and stone-forming tendencies. Dietary modifications are pivotal in preventing stone formation by addressing metabolic abnormalities associated with RTA, while pharmacological interventions target specific mechanisms implicated in nephrolithiasis pathogenesis. Surgical interventions and minimally invasive procedures may be necessary in refractory cases to alleviate the stone burden and prevent recurrence. Moreover, nephrolithiasis prevention and long-term management in RTA entail a multidisciplinary approach involving lifestyle modifications, pharmacotherapy, and close monitoring. Emerging research aims to improve our understanding of nephrolithiasis pathogenesis and develop novel therapeutic strategies, including genetic manipulation and lifestyle modifications. Additionally, advancements in diagnostic tools and patient education initiatives promise to enhance early detection and preventive interventions. Future research endeavors should focus on elucidating the complex etiology of nephrolithiasis, assessing its psychological impact on patients, and identifying effective strategies for recurrence prevention. Overall, a comprehensive understanding of nephrolithiasis's pathophysiology, diagnosis, and management strategies in RTA is essential for optimizing patient care and improving outcomes in this challenging clinical scenario.

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