Review Article

Overview of Endocrine Dysfunctions in Renal Tubular Disorders

ABSTACT: There is a rare discussion of existence of hormonal dysfunction in variants of renal tubular acidosis (RTA) and congenital renal tubular defects with established knowledge of the anatomy and pathophysiology. The research aims to understand the endocrine system by exploring the hormonal changes associated with renal tubular disorders, highlighting the ways renal tubular disorders affect multiple or focal tubular functions. This article is part of students project aim to elucidate the molecular and pathophysiological basis of various renal tubular disorders and associated endocrine disorders.

Keywords: Renal Tubular Acidosis, Proximal Convoluted Tubule, Distal Convoluted Tubule, Loop of Henle, Collecting Ducts, Endocrine hormones.

INTRODUCTION

The human body is a place where changes are imminent. These changes in our body's development occur because of a series of hormonal actions induced by the endocrine system. The endocrine system is fundamental to human existence where hormones are required to regulate various bodily processes. However, if there is a malfunction within this system, hormones will not be appropriately produced which can cause numerous endocrine disorders. The system is made up of a series of integral endocrine glands that have an influential role in different organs of the body. But it's often overlooked that the kidneys, too, are considered as an endocrine gland as well and that there's a correlation between endocrine and renal tubular disorders/diseases. It is imperative to know that the kidneys have an important role in maintaining an acid-base balance as well as the filtration of the blood. But note that kidneys secrete humoral factors; calcitriol, erythropoietin, klotho, and renin which are essentially involved in the regulation of a variety of processes ranging from bone formation to erythropoiesis. There will be key points made about the classification of renal tubular disorders as either inherited or acquired with its relevance to the anatomy, physiology, pathophysiology, clinical implication, and management aspect of it. The most common diseases affiliated with renal tubular disorders will be touched upon as well to make it easier to understand the connections between endocrine disorders and renal tubular diseases.

Anatomy

The kidneys are a pair of retroperitoneal structures that sit in between the transverse process at the level of the T12-L3 vertebrae. The right kidney is situated slightly lower than the left kidney due to the presence of the liver. Grossly, they're bean-shaped with a typical length of 10-12 cm, 5-7 cm in width, and 2-3 cm in thickness. The structures are encased in layers of fascia and fat that are arranged from superficial to deep; renal capsule, perirenal fat, renal fascia (also known as gerota's fascia or perirenal fascia), and pararenal fat. Internally, the kidneys are divided into two main areas, the outer cortex, and inner medulla. The cortex extends into the medulla and divides into sets of triangular spaces called the renal pyramids. The apexes of the pyramids are called the renal papilla with each of them associated with a minor calyx that collects urine from the pyramids. From there, several calyces merge to form a major calyx. Urine proceeds to pass through the major calyces into the renal pelvis, a flat and funnel-shaped structure that drains urine into the ureter where it will be transported to the bladder for storage.[1]

Physiology

To understand the concept of renal tubular disorders it is pertinent to know renal physiology. A nephron is the smallest functional unit of the kidney that quantifies as a million to which they're each made up of many small tubules. The tubules are closed, expanded, and folded into a double-walled cuplike structure at one end. At the beginning of the nephron is a renal corpuscular capsule or Bowman's capsule, that encloses a cluster of capillaries (microscopic blood vessels) called the glomerulus. The capsule and glomerulus together constitute a renal corpuscle that's also called a Malpighian body. Blood flows to and away from the glomerulus through small arteries (arterioles) that enter and exit it through the open end of the capsule called the vascular. As blood passes through the glomerulus and into the tubule of the nephron, it becomes filtered. A tubule can be segregated into two parts, proximal and distal. Filtered blood enters the proximal tubule where its substances are reabsorbed the most before reaching the distal tubule. Secretion occurs along the way and proceeds to add substances into the filtrate with vital compounds entering back into the circulation (i.e., glucose). Urine is the end product and is excreted from the kidney before being carried to the bladder.[2]

Pathophysiology

According to Amboss 2022, renal tubular disorders are a heterogeneous group of diseases that involve dysfunctions of transporters and channels in the renal tubular system. These dysfunctions may cause fluid loss and abnormalities in electrolyte and acid-base homeostasis. RTA results from a net decrease in tubular hydrogen secretion or bicarbonate reabsorption causing a nongap (or hyperchloremic) metabolic acidosis. There are four types of Renal Tubular Acidosis (RTA); distal renal tubular acidosis (type 1), proximal renal tubular acidosis (type 2), hyperkalemic tubular acidosis (type 4). Type 3 RTA is a combination of type 1 and 2; it's extremely rare and will not be discussed.[3] Bicarbonate (a base, the opposite of acid) is reabsorbed from the filtrate and returned to the circulation in the proximal tubule. Acid is secreted directly from the blood into the filtrate in the distal tubule and excreted in the urine. Metabolic acidosis occurs when either of these

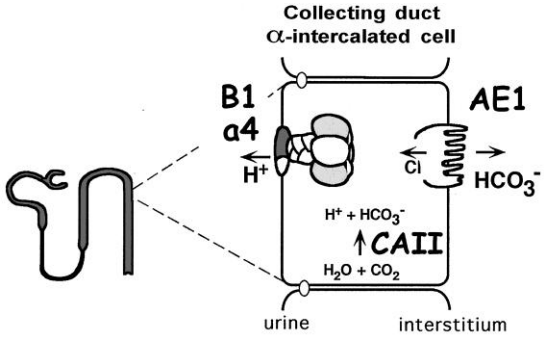
mechanisms is disrupted, resulting from either the gain of an acid or the loss of a base. The former is caused by exogenous or endogenous acid loading, resulting in metabolic acidosis with an anion gap. The latter is caused by a loss of a base from the gastrointestinal or genitourinary tract, resulting in nonunion gap or hyperchloremic metabolic acidosis.[4]

Renal tubular defects are both congenital and acquired diseases of the kidney that affect the tubules to a greater extent than the glomeruli. The defects may be anatomical or physiological. Diseases that cause anatomical defects are usually hereditary and include polycystic renal disease, medullary sponge kidney, and medullary cystic disease. Diseases that cause physiologic defects in tubular transport include Fanconi Syndrome, Bartter Syndrome, Liddle Syndrome, Gitelman Syndrome, Syndrome of Mineralocorticoid Excess, and RTA 1, 2, and 4. They usually present with polyuria, electrolyte imbalance, and/or non gap metabolic acidosis. Type 1 RTA occurs when there is a problem at the end or distal part of the tubules. Type 2 RTA occurs when there is a problem at the beginning or proximal part of the tubules. Type 4 RTA is a generalized disorder that results from aldosterone deficiency or unresponsiveness of the distal tubule to aldosterone. This research will mainly focus on the physiological defects associated with congenital and acquired renal tubular disorders.

Renal tubular acidosis (RTA) is a clinical illness characterized by non-gap metabolic acidosis, hyperchloremia, and poor urine acidification due to the kidney's failure to discharge enough acid or retain enough bicarbonate ($HCO3^-$). Renal acid-base homeostasis can be separated into two processes: (1) reabsorption of filtered $HCO3^-$, which occurs largely in the proximal convoluted tubule; and (2) excretion of fixed acids via urinary buffer titration and ammonium excretion, which happens primarily in the distal nephron. The kidneys normally discharge ammonium chloride ($NH4Cl$) in reaction to acidosis. Its excretion is indirectly measured by the ammonium glycemic index (UAG). It can distinguish between acid secretion problems and bicarbonate loss/reabsorption problems: UAG = (urine Na + urine K) – urine Cl. A positive UAG indicates renal impairment of acid output in a patient with non-gap acidosis. Most individuals with non-gap metabolic acidosis, who do not have diarrhea or gastrointestinal anatomic abnormalities, will have one of the three forms of the renal tubular disorder.[4]

Type 1 RTA occurs because of defective hydrogen ion secretion therefore, urinary pH will be elevated. Hypokalemia results when potassium is excreted instead of H+ cations. Usually, Na+ is reabsorbed, and H+ is excreted to some degree, however, H+ secretion does not occur effectively in type 1 RTA, so K+ is secreted to maintain electroneutrality, eventually leading to hypokalemia. It's caused by various disorders such as sickle cell anemia, cirrhosis, drugs (mainly amphotericin B and lithium), and medullary sponge kidney. Additionally, there have been findings of three genetic mutations contributing to the development of this condition; SLC4A, ATP6V0A4, and ATP6V1B1 gene. A variation in the SCL4A gene generally occurs in an autosomal dominant pattern and less often, autosomal recessive. It prevents

the production of a functional protein, AE1, that's responsible for chlorine and bicarbonate exchange. When this occurs, the acid will not be able to be secreted as much in the urine as it should, leading to an accumulation of it in the blood and tissues that ultimately, results in metabolic acidosis. However, not everyone with this condition will develop metabolic acidosis and the reason for it is not well understood. One theory stated that the amount of dysfunctional AE1 protein varies among individuals. ATP6V0A4 and ATP6V1B1 encode for specific proteins that are part of a protein complex called vacuolar H+ ATPase (V-ATPase) that acts as a proton pump. These proteins are commonly found within the nephron and the inner ear. They help to transport protons across the cell membrane as well as regulate acid levels of the cells and surrounding areas. Mutations of these genes present in an autosomal recessive fashion and can cause metabolic acidosis and sensorineural hearing loss as a result. Untreated RTA 1 may cause children to grow slowly or for adults to develop progressive kidney and bone disease. Both children and adults may also acquire kidney stones as well.[5] Additionally, there are some endocrine conditions related to RTA 1; hyperparathyroidism and acromegaly. Hyperparathyroidism manifests as a disturbance in calcium homeostasis with RTA 1 being one of the conditions associated with it. Excessive levels of PTH further influence the proximal tubule and distal tubules to reabsorb calcium into the blood, only for its epithelium to become damaged and thus, affecting the ion channels which ultimately causes metabolic acidosis. Acromegaly is a hormonal disorder that's characterized by excessive production of growth hormone from the pituitary gland. Growth hormones influence the length and thickness of bones, maintaining blood glucose levels and regulating metabolism.[6], However, there have been findings that GH, as well as IGF-1, mediate their effects on the glomerulus and tubules of the kidney. There's enhanced glomerular filtration rate and renal plasma flow, phosphate reabsorption in the proximal tubules through upregulation of the sodium-phosphate transporters, sodium, and water sreabsorption in the distal nephron through up-regulation of ENaC, stimulation of 1α-hydroxylase with calcitriol synthesis in the proximal tubule as well as the subsequent increase in calcium absorption through (transient receptor potential vanilloid) TRPV5 and TRPV6 in the intestine and distal renal tubule, increased ammonia production in the proximal tubule and sodium-dependent mechanism in the distal tubule. People with acromegaly are shown to have hyperphosphatemia, and hypercalciuria independent of PTH.[7]



ATP6V1B1	recessive dRTA w/ deafness
ATP6V0A4	recessive dRTA
SLC4A1	dominant dRTA
CA2	osteopetrosis w/ RTA

Figure 1. Genetic variants in RTA 1 either give rise to an isolated condition of distal renal tubular

acidosis (RTA/RTA 1) or alongside with deafness or osteopetrosis. Source: https://jasn.asnjournals.org/content/13/8/2178

Type 2 RTA occurs because of decreased bicarbonate reabsorption in the proximal tubule. Initially, the urinary pH will be elevated because of bicarbonate loss. Reabsorption of bicarbonate is essential to maintaining its serum levels because, without it, metabolic acidosis occurs. But with continuous loss of it, the serum bicarbonate and, eventually, the urine bicarbonate concentrations decrease. As the filtered load of bicarbonate drops, all urine bicarbonate can be reabsorbed by the distal tubule causing the urinary pH to fall.[4] The most common cause for this condition in adults is multiple myeloma but there are drug-related causes such as the use of streptozocin or acetazolamide and additionally, there's an association with a genetic condition like Wilson's disease.[9] Wilson's disease occurs in both types 1 and 2 RTA. It's an autosomal recessive disorder characterized by excess copper stored in body tissues, specifically the liver, brain, kidneys, bones, and cornea.[10] Copper is required for the copper-dependent enzyme, lysyl oxidase, which partakes in cross-linkage formation in elastin and collagen. Deficiency of it, because of decreased ceruloplasmin, leads to loss of activity of this enzyme as well as loss of exposure of it to copper chelating agents resulting in bone demineralization and deposition of copper in the joints. Copper accumulation begins at birth, but the symptoms of this disorder then generally appear between the 20th and 40th years of life. Endocrine symptoms of Wilson's disease may include growth and adolescent disorders, hypoparathyroidism, metabolic bone disease, and hypothyroidism. However, there seems to be a lack of medical literature on the prevalence and extent of these endocrine symptoms in Wilson's disease. Also, distal RTA and Proximal RTA have been reported in patients with Wilson's disease as well. The clinical manifestations of RTA in Wilson's disease include many aspects that may include urolithiasis, hypercalciuria, renal calcification, low bone mass, and periodic hypokalemic paralysis. Diabetes is rarely described in patients with Wilson's disease. Excessive hepatic fat deposition and nuclear glycogen deposition have been hypothesized to contribute to hepatic insulin resistance in these individuals.[11] Bone abnormalities such as osteopenia, osteoporosis, and arthropathy are common clinical findings. With resorption occurring, blood calcium levels become elevated leading to increased urinary calcium levels, leading to hypercalciuria, renal stones develop.[12] Penicillamine, zinc, and trientine are therapies traditionally used to treat Wilson's disease. Fanconi syndrome is considered to have a major association with the development of RTA 2. The proximal tubule is the site where there's high reabsorption of ultrafiltrate and it's driven by the basolateral Na/K-ATPase. Impairment of the Na+/K+-ATPase is what leads to Fanconi syndrome and ultimately, there's a loss of the function of the apical Na+/H- exchanger as well Na+/HCO2+ co-transporter. Signs and symptoms show hypokalemia with increased urinary potassium wasting due to the activation of the rennin-angiotensin-aldosterone system (RAAS) in response to the hypovolemia induced by increased excretion of bicarbonate (the body always tries to retain electroneutrality). Additionally, it has been found that there is impairment of the conversion of 25(OH)-cholecalciferol to the

active 1, 25(OH) 2-cholecalciferol which can lead to patients with RTA 2 having osteomalacia.[13] Untreated RTA 2 may cause children to grow slowly and develop rickets and overall, bone disease in adults.[14] Alteration of calcium handling within the renal tubule occurs in metabolic acidosis. Ionized calcium is filtered by the glomerulus and is reabsorbed by both passive paracellular and active transcellular pathways. This mechanism is demonstrated predominantly in the proximal tubule and thick ascending limb of the loop of the handle. Paracellular transportation requires both a driving force and tight junction permeability. In the proximal tubule, the driving force for calcium reabsorption comes from sodium movement that's mediated by the sodium hydrogen exchanger 4 (NHE3) which allows calcium to move alongside water through the tight junctions. In the thick ascending limb, there's a similar mechanism through the formation of a positive luminal region expressed through the activity of the Na^+, K^+, $2CI^-$ co-transporter (NKCC2) alongside (renal outer medullary potassium channel) ROMK for the calcium to influx paracellularly. Permeability is induced by calcium-sensing receptor (CaSr) signaling in the presence of hypocalcemia, so it enhances calcium reabsorption. But Claudin-14 prevents calcium reabsorption in the thick ascending limb with its expression increased in metabolic acidosis through activation of the calcium-sensing receptor which signals the presence of increased calcium levels. This leads to increased urinary calcium excretion which increases NHE3 activity which should, as expected, reduce urinary calcium secretion, thus, further contributing to the dissociation with sodium reabsorption and calcium reabsorption leading to increased urinary excretion.[15]

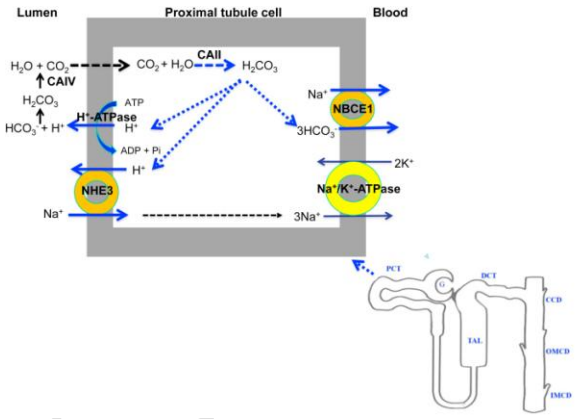


Figure 2. RTA 2 affects NHE3, CA IV & PCT causing impairment of bicarbonate reabsorption.
Source: [http://Pathophysiology of Renal Tubular Acidosis: Core Curriculum 2016]

Type 4 RTA is caused by a reduction of distal tubular electronegativity. This is usually due to aldosterone deficiency or resistance but its physiological decrease in sodium reabsorption can be seen in hypothyroidism and hyperthyroidism. Aldosterone predominantly acts upon the collecting duct to stimulate Na+ reabsorption and K+ secretion in the principal cells. It also stimulates H+ secretion in the intercalated cells. A lack of aldosterone action causes a decrease in distal sodium reabsorption leading to decreased tubular electronegativity, decreased drive for H+ and K+ secretion, acidosis, and hyperkalemia. [4] One of the causes for RTA 4 is Addison's disease. Develop due to damage to the adrenal glands (primary adrenal insufficiency) or abnormalities of the pituitary gland or hypothalamus causing a lack of production of stimulating hormones which eventually leads to decreased synthesis of cortisol and

aldosterone (secondary and tertiary adrenal insufficiency). When it occurs, patients begin to experience dehydration, excessive thirst, fatigue, and muscle weakness. The hallmark for RTA 4 is hypoaldosteronism with mild non-gap metabolic acidosis. Without aldosterone, fewer sodium channels (ENaC) will be available for sodium reabsorption and there will be reduced potassium secretion. It should be noted that hyperkalemia in and of itself decreases ammonium excretion. There's decreased production of ammonia in both the proximal convoluted tubule and thick ascending limb which diminishes the kidney's ability to excrete acid thus, worsening metabolic acidosis. This is due to the suppression of renal ammonia genesis that causes potassium to shift into the cells which allow for hydrogen ions to be excreted into the urine, acidifying the urine and causing intracellular alkalosis in the tubules and turn, reducing ammonia production.[17] Relative hypoaldosteronism from hyporeninemic states can be seen in patients with diabetic nephropathy, hypertensive nephropathy, tubulointerstitial diseases, and AIDS.[4] Almost all patients with RTA 4 have varying degrees of hyperkalemia that are asymptomatic. Most cases of RTA 4 are sporadic, but some are familial. Pseudo hypoaldosteronism (PHA) type 1 and 2 is linked to RTA 4. PHA type 1 is inherited in either an autosomal dominant or recessive manner and is characterized by hypotension with hyperkalemia and acidosis. The dominant form of PHA type 1 leads to mutations in the mineralocorticoid receptor allowing for resistance against aldosterone resulting in hyponatremia and hyperkalemia. The recessive form of PHA type 1 causes mutations in the ENaC of the collecting duct. It manifests during infancy as severe salt wasting, hypotension, hyperkalemia, and acidosis. There have also been some complications of recurrent respiratory infections, chronic cough, and increased respiratory secretions in a few patients with this condition. PHA type 2 leads to hypertension with hyperkalemia and acidosis. It's also known as Gordon Syndrome and familial hyperkalemic hypertension. There have been two genes identified in this condition, WNK1 and WNK4 genes. Mutation of WNK4 and WNK1 genes both lead to sodium and potassium retention due to suppression of the Na+, CI- co-transporter (NCCT), and ROMK.[18] If untreated, patients may develop muscle weakness as a result of elevated potassium levels in the blood as well as arrhythmias and even cardiac arrest. [14] Hypothyroidism is considered to be associated with RTA 4. Kidney development and function are under the influence of thyroid hormones. In the absence of these hormones, the number of renal transport proteins is reduced in expression and function. An experiment was conducted among rats where they were injected with methamexadole to induce hypothyroidism. It was found that Na+-Pi co-transporters have decreased in function followed by Na+/Ca2+ exchanger, Na+-K+-ATPase, and aquaporins.[19] In the case of hyperthyroidism, polyuria is one of the clinical manifestations due to a downregulation of aquaporins 1 and 2 followed by high blood pressure, cardiac output, and renal blood flow. Hyponatremia is another common finding due to decreased Na+-H+ exchanger and Na+-Pi co-transporter activity. Additionally, hyperthyroidism also displays decreased sodium reabsorption in both the distal and proximal tubules with corrections made

from treatment.[20] Diabetes mellitus, also known as diabetes, is a condition in which your body does not produce enough insulin or does not utilize it properly. Type 1 and Type 2 are the most common types of Diabetes Mellitus. Children are more likely to develop type 1 diabetes than adults. Juvenile diabetes mellitus, or insulin-dependent diabetes mellitus, is another name for the condition. Type 2 diabetes, which is more frequent, usually affects adults over the age of 40 and is referred to as adult-onset diabetes mellitus. It is also known as non-insulin-dependent diabetes mellitus. In Type 2 the pancreas produces insulin, but your body doesn't utilize it correctly. About 30% of patients with Type 1 (juvenile-onset) diabetes and 10% to 40% of those with Type 2 (adult-onset) diabetes eventually will suffer from kidney failure.[21] Type IV Renal Tubular Acidosis (Type 4 RTA) is an under-diagnosed condition that is more common in those with diabetes who have substantial renal impairment. Considered to be highly frequent, with a rate of 3.8% of hospital admissions in some studies, and is becoming more prevalent among the elderly, exacerbated by polypharmacy.[22] Diabetes is a leading cause of renal failure, which in turn causes the death of 10-20% of diabetics. Type 2 diabetes is frequently observed in patients with various hormonal diseases including acromegaly, Cushing syndrome, pheochromocytoma, hyperthyroidism, and glucagonoma.

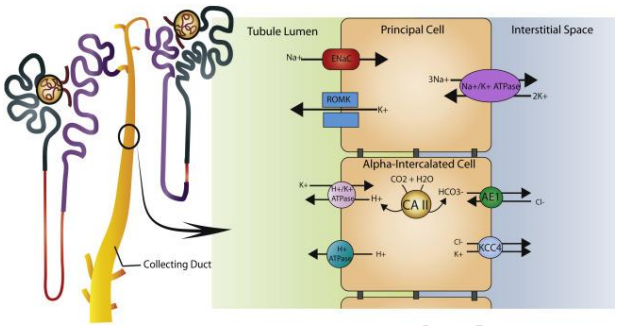


Figure 3. RTA 4 primarily affects ROMK and ENaC leading to sodium wasting and potassium retention. Source: https://www.ackdjournal.org/article/S1548-5595(18)30100-9/fulltext#relatedArticles

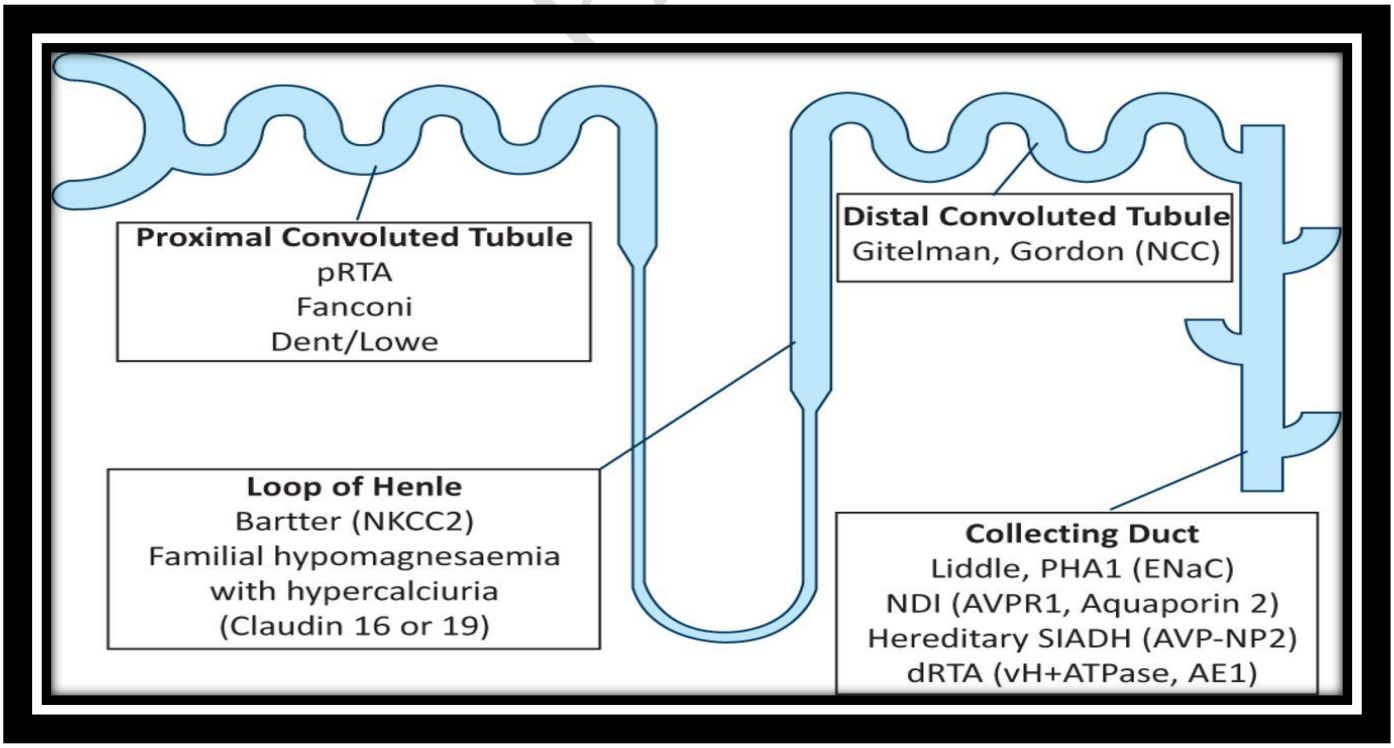
Congenital renal tubular disorders extend from the proximal convoluted tubule to the collecting ducts with abnormalities causing different cascades of endocrine abnormalities. Signs and symptoms may overlap among the following conditions with a few factors that aid to distinguish among the conditions. According to MedlinePlus, it is noted that Fanconi syndrome is a disorder of the kidney in which certain substances normally absorbed into the bloodstream by the kidneys are released into the urine instead.[24] This disorder is either caused by a faulty gene, due to damage to the kidneys over some time, or it’s idiopathic. Fanconi syndrome is an acquired or inherited defect of the proximal tubules that lead to malabsorption of various substances that are usually absorbed. These substances include amino acids, bicarbonate, glucose, phosphate, calcium, proteins, and uric acid with increased excretion of magnesium, sodium, and potassium. Also, it is noted that 70% of phosphate in the filtrate is reabsorbed at the proximal tubule, so this condition leads to phosphate wasting and

hypophosphatemia.[25] With the loss of calcium and phosphate, rickets may develop in children and osteomalacia in adults.

Figure 4. Display of a variety of conditions in different locations of the tubule. Source: https://doi.org/10.7861/clinmedicine.12-5-476

However, serum levels of 1, 25-(OH) 2D don't seem to increase as expected from the resultant secondary hyperparathyroidism that occurs in response to low blood calcium levels. It's thought that in addition to impaired reabsorption of the mentioned substances, there's also, dysfunction of the hydroxylation of 25-OH-D into its active form through the usage of an enzyme, 1α-hydroxylase, that's normally produced by the proximal convoluted tubules. Overall, calcium, phosphate, and dysfunctional vitamin D production all play a major role in the development of rickets and osteomalacia with persistent phosphaturia maintaining those conditions. Clinical complications associated with Fanconi syndrome include polyuria, polydipsia, dehydration, and hypokalemia with a failure to thrive in growth serving to be an evident feature among children with Fanconi syndrome. There have also been some cases in that hepatic damage and cirrhosis can also occur because of Fanconi syndrome.[26]

The next renal tubular disorder is Bartter syndrome. It is an inherited disorder caused by defective salt reabsorption with mutations that inactivates the loop diuretic sensitive NKCC2 in the thick ascending limb of the loop of Henle, resulting in salt wasting, hypokalemia, and metabolic alkalosis. In some cases, Bartter syndrome becomes apparent before birth. The disorder can cause polyhydramnios which is an increased volume of fluid surrounding the fetus (amniotic fluid) that elevates the risk for premature birth. Beginning in infancy,



affected individuals often fail to grow and gain weight at the expected rate (failure to thrive). They lose excess amounts of salt in their urine which leads to dehydration, constipation, and polyuria. In addition, a large amount of calcium is lost through the urine (hypercalciuria), which can cause weakening of the bones (osteopenia) and deposition in the kidneys leading to hardening of the kidney tissue (nephrocalcinosis). Chloride is usually reabsorbed across the luminal membrane of the thick ascending loop using NKCC2 which is driven by the low intracellular concentration of Na^+ and Cl^- that is generated by the Na^+, K^- ATPase. The ROMK aids the NKCC2 by secreting potassium from the cell into the lumen that drives the paracellular transport of Ca^{2+} and Mg^{2+} from the lumen into the blood. When there is a defect in the NKCC2, chloride, and sodium will be unable to be reabsorbed and potassium will not be secreted causing an accumulation of chloride and sodium in the urine with potassium building up in the cells. There will be excess excretion and overall loss of salt and water from the body resulting in decreased blood volume. RAAS will be over-activated and will ultimately lead to secondary hyperaldosteronism with increased sodium reabsorption in the distal convoluted tubule as well as potassium wasting. Additionally, with elevated renin involved, there will also be hyperplasia of the juxtaglomerular apparatus. There are genetic variants of Bartter syndrome that can give rise to a spectrum of clinical implications, but most patients demonstrate the failure to thrive in growth during the first year of life followed by muscle twitches and spasms. Nausea, vomiting, lethargy, personality changes, and tetany can also be detected because of hypomagnesemia found in 50% of affected patients.[27]

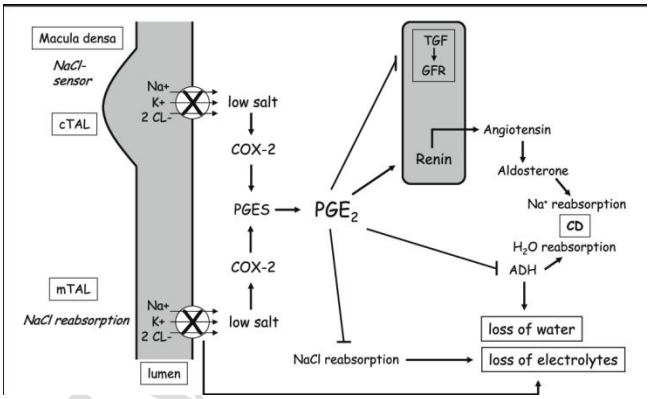


Figure 5. Barter syndrome is characterized by the inactivation of NKCC2 leading to sodium wasting, loss of water, and overall, loss of electrolytes as potassium secretion increases due to overstimulation of RAAS. Source: https://www.semanticscholar.org/paper/Bartter-and-Gitelman-like-syndromes%3A-salt-losing-or-Seyberth-Schlingmann/d11775f12495270e5ce49b5231fa8c8bc682e9f7

Gitelman syndrome, also known as familial hypokalemia-hypomagnesemia, is another renal disorder this is caused by mutations of the thiazide diuretic-sensitive NCC co-transporter in the distal convoluted tubule. It is also a rare, autosomal recessive, genetic disorder in which there is a specific defect in kidney function. This defect impairs the kidney's ability to reabsorb salt and causes changes in various electrolyte concentrations as well as contraction of extracellular fluid volume (thus causing symptoms of dehydration). The electrolyte abnormalities of Gitelman syndrome are like that of patients taking thiazide diuretics. The electrolytes affected are primarily mineral

ions, specifically potassium, calcium, magnesium, sodium, and chloride. Genetic causes of hypertension can result from mutations of NCC (Gordon syndrome) or of ENaC (Liddle syndrome). They are a 'mirror image' of Gitelman syndrome and pseudo hypoaldosteronism type 1 respectively.[29] Gitelman syndrome is a salt-wasting nephropathy and as a result, there's sodium and chloride wasting and subsequent water loss that leads to hypovolemia. Changes in blood volume will trigger RAAS to release renin from the juxtaglomerular apparatus which will eventually lead to the production of angiotensin II that will stimulate the adrenal glands to produce aldosterone. Symptoms may range from asymptomatic to severe and can occur anytime from later childhood to adulthood in contrast Bartter syndrome that has symptoms appear during infancy to early childhood.[30] Its symptoms present in a similar manner to Bartter Syndrome regarding volume depletion leading to fatigue, nausea, vomiting, muscle weakness, and abdominal pain. However, these symptoms seem to be more common in individuals with Gitelman Syndrome than Bartter Syndrome. Patients experiencing tetany in the hands, feet, arms, legs, and/or face with facial paresthesia is also a common finding in Gitelman Syndrome. Lab values will also show hypomagnesemia with a urinalysis revealing low urinary calcium levels.[31]

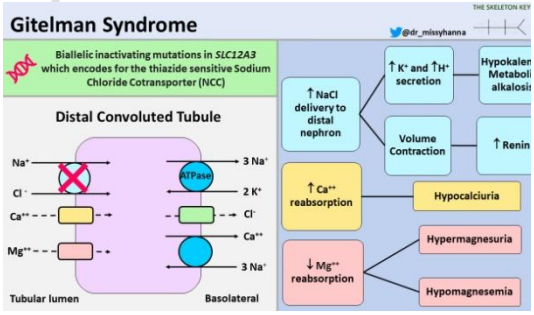


Figure 6. Gitelman Syndrome is caused by dysfunction of the NCC channel which impairs sodium reabsorption, overactivated RAAS, and ultimately, causes excessive potassium secretion leading to hypokalemia. Hypercalciuria, hypermagnesuria and hypomagnesemia arise as well. Source: https://www.grepmed.com/images/13188/pathophysiology-nephrology-gitelman-syndrome-diagnosis

Liddle syndrome is a childhood autosomal dominant condition that causes overactivity of ENaC due to mutations to the SCNN1A, SCNN1B, SCNN1G genes that encode the subunits for ENaC. The amiloride-sensitive ENaC is regulated by aldosterone which increases the number of open ENaCs, the activity of the Na^+–K^+–ATPase, and the number of ROMK channels. The net effect is to increase Na^+ reabsorption and K^+ secretion/excretion. A defect in ENaC results in excess reabsorption of sodium in the collecting duct. Elevated sodium levels in the blood lead to hypertension with the favor of potassium secretion causing metabolic alkalosis. The combination of elevated blood pressure and lowered plasma potassium levels suppresses RAAS, ultimately causing hyporeninemia.[33] Often, it's known as pseudo hyperaldosteronism because it mimics the symptoms associated with hyperaldosteronism, but the distinguishing factor is that aldosterone and renin levels are low. A set of symptoms displayed by this condition is not distinct to differentiate Liddle syndrome from other conditions. Other than readings of elevated blood pressure, this condition often presents to be difficult to diagnose. However, regarding elevated blood pressure, it can be the most notable finding among patients who, majority-wise, develop early-onset hypertension in adolescence. Secondary hypertension resistance to antihypertensives

in children and teenagers can also serve as a sign for testing to be done for Liddle Syndrome. In addition to hypertension, there is hypokalemia and metabolic alkalosis as well. Another distinguishing point is that patients with Liddle syndrome tend to respond well to amiloride whereas spironolactone is ineffective. Spironolactone is considered one of the mainstay drugs for Bartter and Gitelman Syndrome rather than Liddle Syndrome.[34]

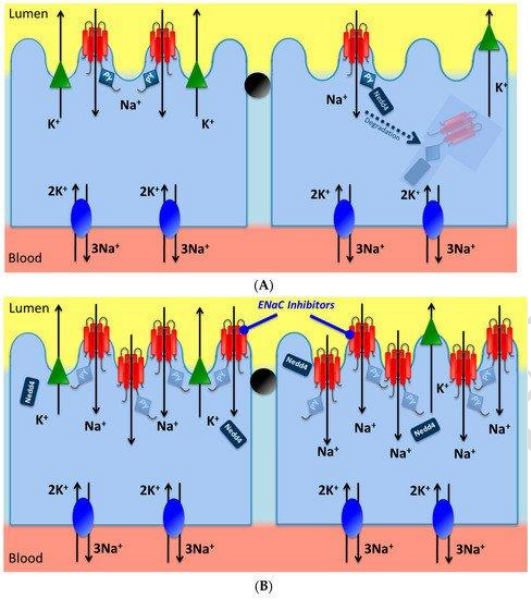


Figure 7. (A)ENaC is expressed on the luminal side of the distal nephron epithelium and allows the passage of Na^+ ions from the lumen toward the cytoplasm. Proline-rich sequence (indicated as PY) regulates channel internalization and degradation. ENaC function is combined ROMK (green triangles) and Na^+/K^+ ATPase (blue ovals) and it is crucial for electrolyte homeostasis, consisting of sodium renal reabsorption and potassium excretion; (B) Mutations of the *SCNN1B* and *SCNN1G* genes causes the loss or disruption of the proline-rich sequence. These mutations are gain-of-function and determine an increased membrane density of ENaC and a consequent increase in renal Na^+ reabsorption.
Source: https://www.mdpi.com/1422-0067/19/3/812/htm

Syndrome of Apparent Mineralocorticoid Excess (SAME) is an autosomal recessive condition caused by impairment of a gene that encodes for the enzyme, 11**β**-hydroxysteroid dehydrogenase type 2. Located on the collecting tubule, mineralocorticoid receptors serve to be stimulated by aldosterone to increase sodium reabsorption and potassium secretion. However, mineralocorticoid receptors are nonselective for aldosterone and have an equal affinity towards cortisol. Cortisol can produce aldosterone-like effects which are where 11**β**-hydroxysteroid dehydrogenase type 2 (11**β**-HSD2) will undergo its role to inactivate cortisol. It will become cortisone to protect the mineralocorticoid receptors from constant activation by circulating cortisol. Defects in the enzyme lead to apparent cortisol excess resulting in pseudo hypoaldosteronism with symptoms of early-onset hypertension (especially in childhood), failure to thrive, low birth weight, polyuria with lab values showcasing hypokalemia, metabolic alkalosis, hypernatremia and low levels of renin and aldosterone. Further note that SAME can also be an acquired condition due to ingestion of licorice. This is because its active component, glycyrrhizin acid, has been shown to inhibit the activity of 11**β**-HSD2 thus, leading to cortisol-driven mineralocorticoid hypertension. The resulting implications are like those who have inherited the condition but do not present with poor growth development.[36]

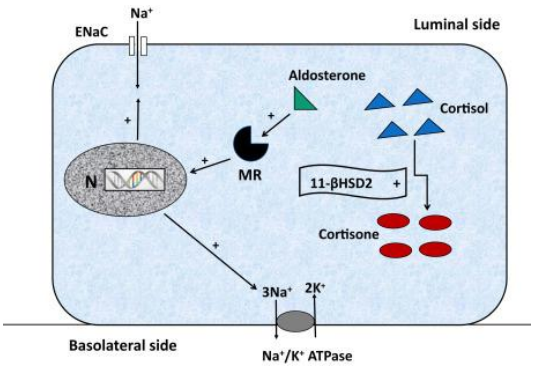


Figure 8. Normally, aldosterone exerts its effect on the principal cells in the distal tubule and cortical collecting duct by binding to a cytoplasmic mineralocorticoid receptor (the receptor is translocated to the nucleus). The effects include increased activity, number of ENaCs, and activity of the basolateral Na-K ATPase channels. Cortisol is converted to cortisone via an enzyme, 11β-hydroxysteroid dehydrogenase 2 (11-βHSD2), thereby preventing action on the mineralocorticoid receptor (MR) Source: https://www.kireports.org/article/S2468-0249(20)31540-0/fulltext

Management

Tubular disorders can be divided into different syndromes based on their symptoms. The administration of a base (typically bicarbonate or citrate) to neutralize excess blood acid or replenish bicarbonate loss in the urine is used to treat renal tubular disorders. Thiazide diuretics (such as hydrochlorothiazide) may be required if given bases are ineffective.[38] Potassium-sparing diuretics are used if it's an inherited physiologic renal tubular defect.[3] Treatment of the underlying disease, such as lupus, may ameliorate the acidosis if the disorder is associated with another sickness. The medication-induced renal tubular disorder may necessitate the discontinuation of the offending medicine. To avoid the problems of extended renal tubular disorder, adherence to therapy is crucial, regardless of the treatment regimen. The renal stone formation, for example, if left untreated, can lead to chronic kidney failure and the need for dialysis.[38]

Conclusion

Renal tubular disorders are a wide range of anomalies that involve dysfunction of channels and transporters in the renal tubular system. These disorders are classified as either congenital or acquired with either anatomical or physiological defects. Congenital and physiological defects highlight Bartter syndrome, Liddle syndrome, Gitelman syndrome, and Syndrome of Mineralocorticoid Excess that pertain to metabolic acidosis and hyperkalemia. Congenital and anatomical defects include polycystic renal disease, medullary sponge kidney, and medullary cystic disease. Fanconi syndrome is both an acquired and congenital condition with renal tubular acidosis type 2 as the resulting manifestation. Other acquired conditions include renal acidosis type 1 and 4 with endocrinal conditions being one of the causes of their development. RTA 1 can arise from a hormonal condition known as acromegaly, both RTA 1 and 2 can arise from diabetes mellitus as well as RTA 4, Wilson's disease is often linked with RTA 2, and hyperthyroidism and hypothyroidism can be seen in RTA 4. Due to their heterogeneity, diagnoses of acquired renal tubular disorders are a challenging feat since investigations are solely based on clinical features and laboratory findings but hereditary conditions are often confirmed through genetic testing. It's important that once there's a confirmation of an anomaly of the kidneys, management should be undertaken as soon as possible to ensure maximum and desirable results as well as lessen the risk for complications later on.

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Abbreviations

RTA = Renal Tubular Acidosis

UAG = Ammonium Glycemic Index

V-ATPase = Vacuolar-type ATPase

PTH = Parathyroid Hormone

TRPV = Transient Receptor Potential Vanilloid

ENaC = Epithelial Sodium Channel

RAAS = Renin-Angiotensin-Aldosterone System

NHE3 = Sodium-Hydrogen Antiporter 3

NKCC2 = Sodium-Potassium-Chloride Co-transporter

NCC = Sodium-Chloride Co-transporter

NCCT = Sodium-Chloride Symporter

ROMK = Renal Outer Medullary Potassium Channel

PHA = Pseudohypoaldosteronism

CaSr = Calcium-sensing receptor

AE1 = Anion exchanger 1