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13.1 The Kidney: Structure and Function

Sudha Ekambaram, Sunil Reddy KG, BR Nammalwar

INTRODUCTION

The kidney presents in the highest degree the phenomenon of sensibility, the power of reacting to various stimuli in a direction which is appropriate for the survival of the organism; a power of adaptation which almost gives one the idea that is component parts must be endowed with intelligence. **E Starling 1909**. This chapter will focus on the anatomy, functions of the glomerulus and different part of the tubules.

ANATOMY

The kidneys are paired organs that lie on the posterior wall of the abdomen behind the peritoneum on either side of the vertebral column. They extend from T12 to L3, although the right kidney is often situated slightly lower due to the presence of liver. The kidneys grow rapidly in the first year of life, from 4.5 cm in length at birth to 6.5 cm in childhood and to 11 cm in adulthood. The weight of both kidneys at birth is about 23 g and increases to 150–200 g in adults. The renal artery and vein, nerves, and pelvis enter the kidney on the medial side, which is the hilum **(Fig. 13.1.1)**.

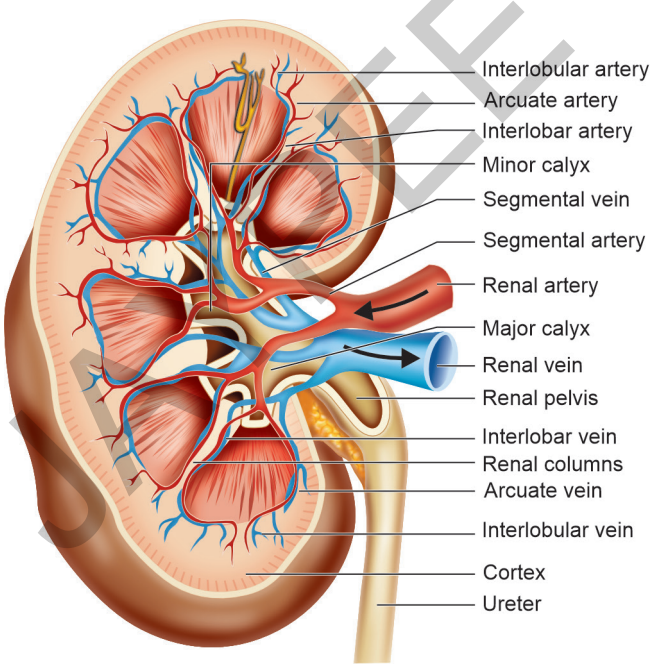

Fig. 13.1.1: Diagrammatic presentation of kidney anatomy and blood supply.

The renal tissue is divided into the outer cortex and the inner medulla, and both are composed of nephrons, blood vessels, lymphatics, and nerves. The medulla in the human kidney is divided into conical masses called renal pyramids with the intervening renal columns of Bertini, which is a medullary extension of the renal cortex in between the renal pyramids. It allows the cortex to be better anchored. The base of the pyramids originates at the corticomedullary border, and the apices are the papillae, which project into the minor calyces, wherein urine is collected from the papillae. The minor calyces are cup-like structures and join to form three or four major calyces. The major calyces in turn unite to form the pelvis, the upper expanded region of the ureter, which carries urine to the urinary bladder **(Fig. 13.1.1)**. The walls of the calyces, pelvis, and ureters contain smooth muscle that contracts to propel the urine toward the urinary bladder.

VASCULAR SYSTEM

Each renal artery branches off from the abdominal aorta just below the mesenteric artery and supplies the kidneys with blood. Renal blood flow (RBF) comprises roughly 20% of the total cardiac output. There may be one or more renal arteries supplying each kidney. The renal artery divides before entering the renal hilum into anterior and posterior divisions, which receive approximately 75% and 25% of the blood, respectively. The anterior division further divides into the upper, middle, lower, and apical segmental arteries, while the posterior division forms the posterior segmental artery. Segmental arteries subsequently divide into lobar, interlobar, arcuate, and interlobular arteries before forming the afferent arterioles, which feed into the glomerular capillaries of Bowman's capsule **(Fig. 13.1.1)**.[1]

The glomerular capillaries come together to form the efferent arterioles, which leads into a second capillary network, the peritubular capillaries, which supply blood to the nephron in the superficial cortical zone. Secondly, efferent arterioles of the nephrons that are located above the corticomedullary border (juxtamedullary nephrons) travel downward into the medulla. They further divide into straight arterioles and straight venules (vasa recta of the kidney), which surround the loop of Henle. The purpose of these vessels is to supply capillaries located in the medulla. This crucial difference plays a significant role in the medullary osmotic gradient and regulation of water excretion. Subsequently, the vessels of

both venous systems run parallel to the arterial vessels and progressively form the interlobular, arcuate, interlobar, and renal veins. Blood then leaves the kidney and enters the renal vein. Sympathetic fibers originate in the lower splanchnic nerves and travel through the lumbar ganglion to the kidney. Stimulation of the sympathetic nervous system reduces RBF by causing intrarenal vasoconstriction. It also stimulates the local renin–angiotensin–aldosterone system (RAAS) and enhances Na^+ reabsorption. The kidney also receives input from the parasympathetic nervous system by way of the renal branches of the vagus nerve, which causes vasodilatation and increased blood flow of the afferent arterioles. Due to this mechanism, sympathetic nervous stimulation will decrease urine production, while parasympathetic nervous stimulation will increase urine production.[2-4]

FUNCTIONS OF THE KIDNEY[2-4]

- Regulates the volume and composition of the body fluids
- Maintains osmotic pressure (osmolality) of the body fluids by excreting osmotically dilute or concentrated urine
- Maintains volume of the extracellular fluid by controlling Na^+ and water excretion
- Maintains concentrations of numerous ions in blood plasma (sodium, potassium, chloride, bicarbonate, phosphate, sulphate, calcium, and magnesium)
- Maintains acid–base balance by excreting H^+ ions and synthesis of ammonia
- Regulates blood pressure by modulating the intraglomerular hemodynamics, adjusting Na^+ excretion, and producing various substances (e.g., renin) that can affect blood pressure
- Eliminates waste products of metabolism, such as urea, uric acid, the end product of purine metabolism, and creatinine and also certain drugs and toxic compounds
- Produces hormones like erythropoietin, calcitriol, renin, prostaglandins, endothelins, adrenomedullin, autocrine, and paracrine molecules
- Degrades several polypeptides and hormones such as insulin, glucagon, and parathyroid hormone
- Synthesizes substances that affect RBF and Na^+ excretion, viz. arachidonic acid derivatives, prostaglandins, thromboxane A2, and kallikrein
- Gluconeogenesis

MICROSTRUCTURE AND FUNCTION

Nephrogenesis begins at gestational age of 9 weeks and is completed by approximately 36 weeks. The nephron is the smallest functional unit, and each kidney at birth will have a million nephrons. The nephron is divided into a corpuscle (made up of glomerulus and Bowman space) and the tubule. The tubule comprises multiple functional units, namely proximal tubules, loop of Henle, distal tubule, juxtaglomerular apparatus (JGA), the collecting ducts, and the ductus of Bellini **(Fig. 13.1.2)**.

Glomerular Filtration[1]

The first step in the generation of urine is glomerular filtration.[1] Systemic hydrostatic pressure passively forces fluid and solute across glomerular filtration barrier (GFB), which is semipermeable in nature. The GFB consists of:

- Fenestrated endothelium of the glomerular capillaries, which allows blood components other than cells to pass through
- Basement membrane, a negatively charged physical barrier that prevents proteins from permeating
- Foot processes of the podocytes that produce more selective filtration **(Fig. 13.1.3)**.

The amount of water and solute passing through the filtration membrane is determined by the outward and inward forces within the capillaries. Hydrostatic pressure within the glomerular capillaries is the major filtration force. The hydrostatic pressure within the capsular space and the colloid osmotic pressure in glomerular capillaries negate the filtration force of the glomerular capillaries, resulting in a net filtration pressure of 10–20 mm Hg **(Fig. 13.1.4)**.

Renal Autoregulation

Blood flow through glomerular capillaries is regulated by increasing or decreasing its own blood flow resistance through myogenic and tubuloglomerular feedback mechanisms. When the vascular smooth muscle stretches as a result of elevated blood flow, the afferent arteriole feeding the glomerular capillaries is constricted by the myogenic mechanism, limiting the amount of blood passing through the glomerular capillaries. When the blood flow inside the afferent arteriole is low, it dilates the vascular smooth muscle, enabling more blood to pass through. Tubuloglomerular feedback mechanism senses the level of Na^+ inside the tubule in order to maintain the glomerular capillary blood flow. Na^+ is detected by macula densa cells of the JGA at the ascending limb of the nephron loop. An increase in Na^+ concentration at the macula densa constricts the glomerular afferent arteriole and thus decreases glomerular capillary blood flow. A decrease in Na^+ concentration increases glomerular capillary blood flow.

The renin–angiotensin–aldosterone axis is activated in three different steps:

1. If the perfusion decreases through the JGA, the granular cells in the macula densa release the enzyme renin
2. Renin cleaves angiotensinogen to form angiotensin I
3. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE) found mainly in endothelial cells of the capillaries throughout the body, within the lungs, and the epithelial cells of the kidneys. Angiotensin II

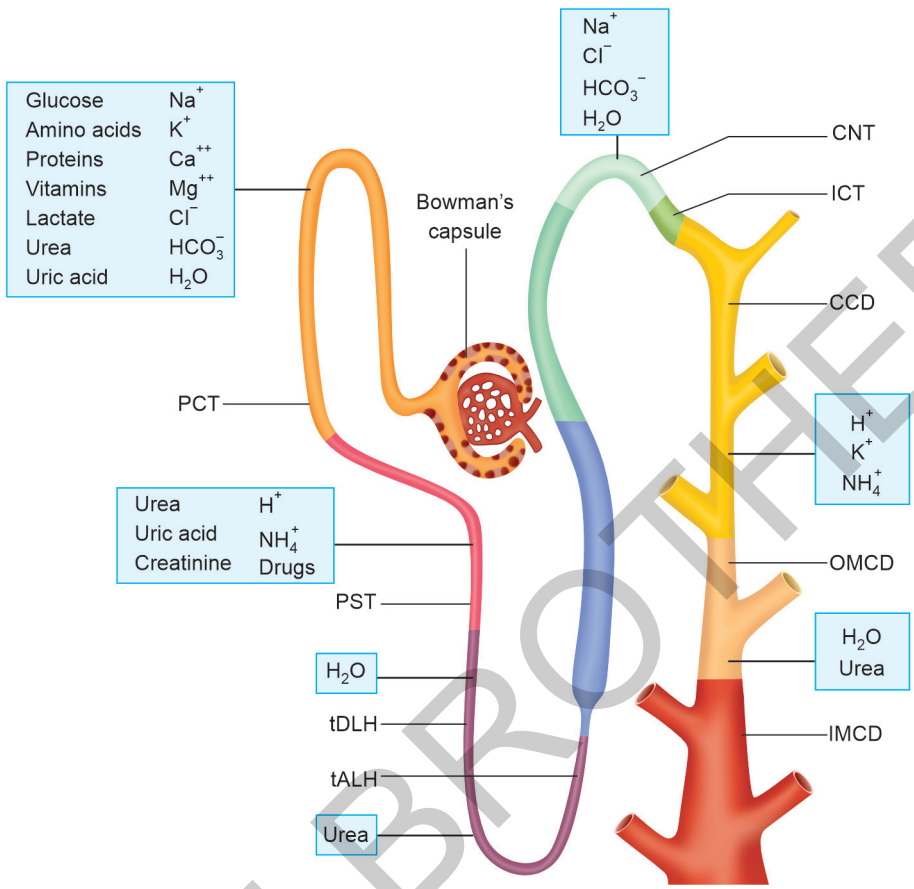

Fig. 13.1.2: Tubular segments with their reabsorption and secretion. (CCD: cortical collecting duct; CNT: connecting tubule; ICT: initial collecting tubule; IMCD: inner medullary collecting duct; OMCD: outer medullary collecting duct; PCT: proximal convoluted tubule; PST: proximal secretory tubule; tALH: thin ascending loop of Henle; tDLH: thin descending loop of Henle)

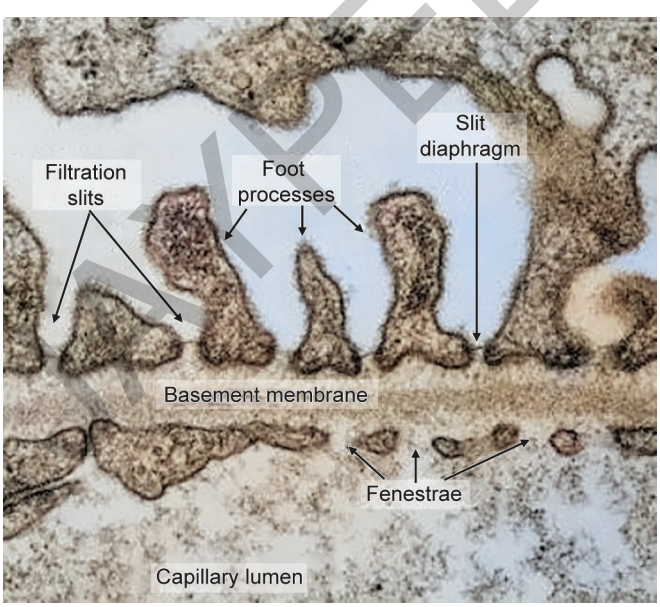

Fig. 13.1.3: Electron micrograph of the glomerular filtration barrier.

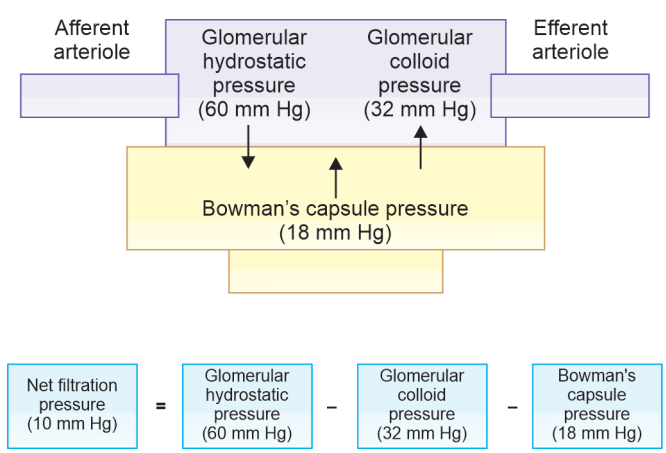

Fig. 13.1.4: Pressures regulating effective glomerular filtration.

acts on angiotensin receptors and releases aldosterone from the zona glomerulosa in the adrenal cortex, which constricts efferent arterioles and maintains glomerular filtration rate (GFR) **(Fig. 13.1.5)**.

Tubular Reabsorption[2-4]

Proximal Convoluted Tubule

The proximal convoluted tubule (PCT) is the first segment in the tubule with two distinctive regions, PCT1 and PCT2. PCT cells are characterized by the greatest capacity for absorption. The PCT reabsorbs almost all of the glucose, amino acids, 65% of Na^+, and most of the water. The basolateral Na^+/K^+-ATPase pumps 3 Na^+ out of the cell and 2 K^+ into the cell and activates the "secondary active" transport of a number of other solutes **(Fig. 13.1.6)**. Na^+ is reabsorbed through both a secondary active transport and a passive paracellular diffusion by an electrochemical gradient along with vitamins, amino acids, and glucose. Water is reabsorbed through osmosis. Additionally, passive diffusion is used to reabsorb lipid-soluble solutes. By means of passive paracellular diffusion, fueled by a chemical gradient, urea is also reabsorbed in the PCT.

Loop of Henle

This segment has a hairpin configuration with a thin descending limb and both a thin and a thick ascending limb (TAL). The thin descending limb is highly permeable to water, with reabsorption occurring passively via aquaporin 1 (AQP1) channels. Very low amounts of urea, Na^+, and other ions are reabsorbed into the tubule. This increases tubular fluid osmolarity to ~1,200 mOsm/L.

Water reabsorption is driven by the hyperosmotic environment due to active reabsorption of Na^+ in TAL. The TAL is impermeable to water but permeable to Na^+ and Cl^-. As the liquid returns through the thin ascending limb, the Na^+ and Cl^- diffuse paracellularly out of the tubule into the surrounding tissue. This is due to the difference in osmolarity between the tubule and the interstitium, where the Na^+ and Cl^- concentrations are lower. However, the primary site of Na^+ reabsorption in the limb of Henle is the TAL. Na^+/K^+/ATPase, located on the basolateral membrane, creates a negatively charged intracellular environment, thereby generating an electrochemical gradient. Na^+ ions then move into the cell (from the tubular lumen) down the electrical and chemical gradients through the Na/K/Cl cotransporter (NKCC) on the apical membrane **(Fig. 13.1.7)**. This transporter moves one Na^+ ion, one K^+ ion, and two Cl^- ions across the apical membrane. K^+ ions are transported back into the tubule by renal outer medullary potassium (ROMK) channels on the apical membrane. Cl^- ions are transported into the tissue fluid via chloride channel-Kb (ClC-Kb). The loop of Henle contributes to the absorption of approximately 25% of filtered Na^+. This leads to a drop in the osmolarity of fluid from 1,200 to 100 mOsm/L, and a hypotonic solution arrives at the distal tubule. In addition to the above concentrating mechanisms, there is significant paracellular reabsorption of Mg^{+2}, Ca^{+2}, Na^+, and K^+ and synthesis of uromodulin.

Juxtaglomerular Apparatus

The JGA **(Fig. 13.1.8)** is a specialized structure formed by the ascending limb of Henle, the glomerular afferent and efferent arterioles, and the extraglomerular mesangial cells. It is located near the vascular pole of the glomerulus, and its main function is to regulate blood pressure and the filtration rate of the glomerulus.

The macula densa is a collection of specialized epithelial cells in the distal convoluted tubule (DCT) that detect Na^+ concentration of the fluid in the tubule. In response to elevated

Fig. 13.1.5: Renin–angiotensin–aldosterone system. (ACE: angiotensin-converting enzyme; AT: angiotensin)

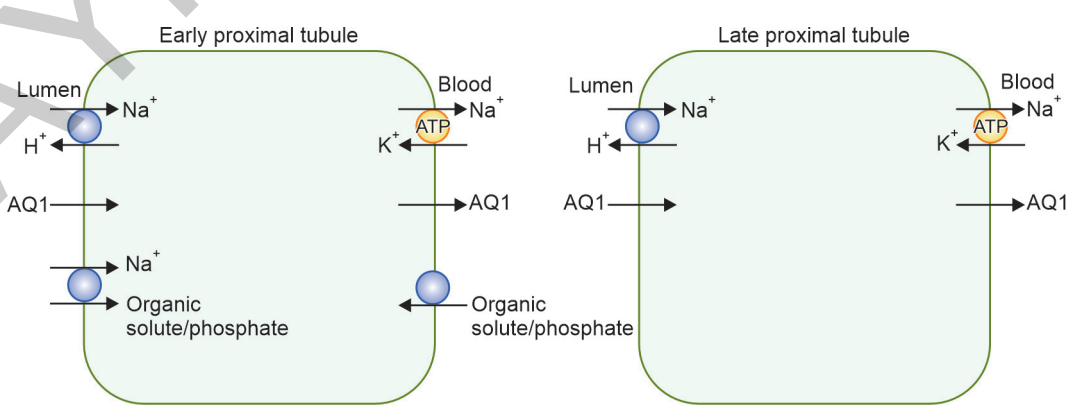

Fig. 13.1.6: Segments of the proximal tubule with their transcellular transporters. (AQ: aquaporin; ATP: adenosine triphosphate)

Na^+, the macula densa cells trigger the contraction of the afferent arteriole, reducing the flow of blood to the glomerulus and the GFR. The juxtaglomerular cells, derived from smooth muscle cells, of the afferent arteriole secrete renin when blood pressure in the arteriole falls. Renin increases blood pressure by RAAS. Lacis cells are flat and elongated and found outside the glomerulus near the macula densa.

Distal Tubules

The distal tubule starts shortly after the macula densa **(Fig. 13.1.9)** and comprises the DCT and the connecting tubule (CNT). The DCT is the shortest segment of the nephron, of about 5 mm in length, and consists of two distinct subsegments, DCT1 and DCT2. The role of the DCT is the absorption of Na^+, Cl^-, Mg^{+2}, and Ca^{+2} ions. The DCT1 and DCT2 together reabsorb roughly 5–10% of the filtered Na^+ load. Both are impermeable to water. The movement of these ions is dependent on the Na^+/K^+-ATPase transporter on the basolateral membrane of the cells. This excretes Na^+ ions into the extracellular fluid and brings K^+ ions into the cell. This process occurs via primary active transport, as ATP is directly needed to set up the gradient. The Na^+ concentration gradient generated allows Na^+ to enter the cell from the lumen of the DCT, along with Cl^- ions, which occurs through the sodium-chloride cotransporter (NCC). The Cl^- ions then exit the cell through a Cl^- ion uniporter on the basolateral membrane into the extracellular fluid, preventing accumulation within the cell. In addition to NCC, the DCT2 segment expresses the amiloride-sensitive epithelial Na^+ channel (ENaC) on the apical side.

Approximately 10% of filtered K^+ reaches the distal tubule and downstream. The luminal K^+ concentration progressively increases, indicating that a large amount of K^+ secretion occurs along the distal tubule. The K^+ secretion is mediated by the ROMK channel. In addition, the basolateral K^+ efflux into peritubular interstitium in the DCT is by K^+ transporters, ClC-Kb (voltage-gated Cl^- channel) and KCC4 (potassium chloride cotransporter).

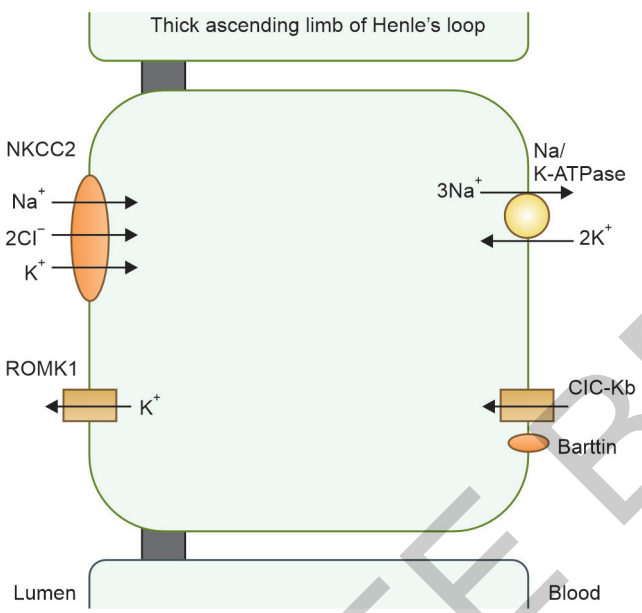

Fig. 13.1.7: Thick ascending limb of loop of Henle with their transcellular transporters. (ClC-Kb: chloride channel-Kb; NKCC2: Na/K/Cl cotransporter; ROMK: renal outer medullary potassium)

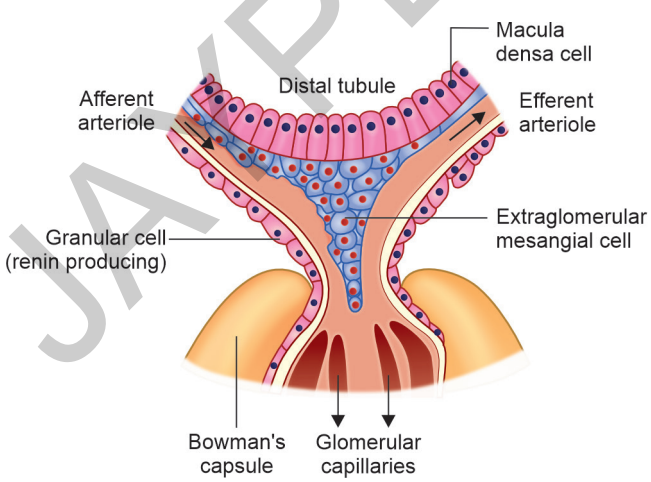

Fig. 13.1.8: Diagrammatic presentation of the juxtaglomerular apparatus.

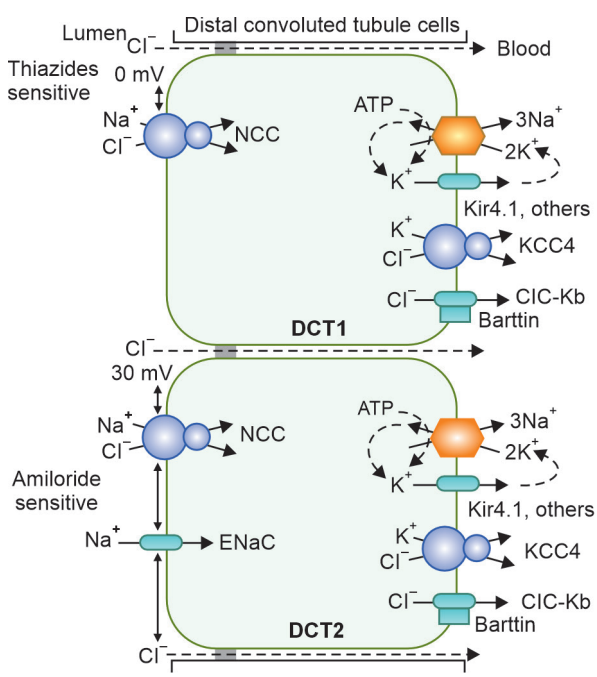

Fig. 13.1.9: Distal convoluted tubules 1 and 2 with their transporters. (ATP: adenosine triphosphate; ClC-Kb: chloride channel-Kb; DCT: distal convoluted tubule; ENaC: epithelial Na^+ channel; KCC4: potassium chloride cotransporter; NCC: sodium-chloride cotransporter)

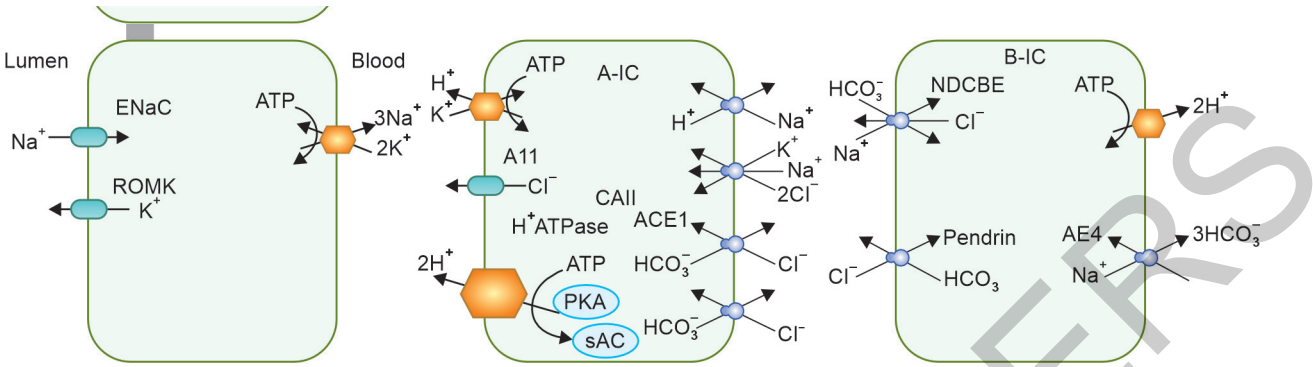

Fig. 13.1.10: Cortical collecting ducts and their transporters. (AE: anion exchanger; ATP: adenosine triphosphate; ENaC: epithelial Na^+ channel; IC: intercalated cells; NDCBE: sodium-driven Cl^-/HCO_3^- exchanger; PKA: protein kinase A; ROMK: renal outer medullary potassium; sAC: soluble adenylyl cyclase)

Connecting tubule (CNT) lies between the DCT and the initial portion of the collecting duct system (CDS) and functionally simulates both segments. The CNT (1) is impermeable to water even with antidiuretic hormone (ADH); (2) participates in active Ca^{2+} reabsorption, in response to PTH and calcitriol; (3) partially reabsorbs Na^+ by a thiazide-sensitive NaCl cotransporter (NCC); (4) reabsorbs Na^+ in exchange for K^+ secretion in principal cells; and (5) aldosterone stimulates uptake of Na^+ by the luminal ENaC and K^+ secretion by the luminal K^+ channels that are accumulated in the cell by the apical K^+ transporter $Na^+ - K^+$-ATPase.

Collecting Duct[4]

The CNT from different nephrons merge together to form the cortical collecting duct (CCD). The collecting duct system fine-tunes salt and water reabsorption and plays a major role in acid–base balance. The two main cell types of the CCD are principal cells and intercalated (IC) cells **(Fig. 13.1.10)**. The principal cells are responsible for Na^+ reabsorption via the amiloride-sensitive sodium channel ENaC. Principal cells also secrete K^+ via the ROMK potassium channel. The ability of the CCD to absorb water is controlled by antidiuretic hormone (ADH). In the presence of ADH, AQP2-containing vesicles fuse with the apical membrane, allowing water to enter the cell. Water exits from the basolateral aspect via AQP3 and AQP4 channels. The action of ADH on the CCD allows the production of concentrated urine and protects against dehydration.

In contrast to principal cells, IC cells express high levels of carbonic anhydrase (CA) and are involved in acid–base regulation. There are two types of IC cells, type A and B. Type A cells use cytoplasmic CA to produce H^+ and HCO_3^- ions. H^+ is secreted into the lumen by an apical H^+ ATPase pump and HCO_3^- is pumped out of the basolateral surface via an HCO_3^-/Cl^- exchanger. Type B intercalated cells have an inverse orientation of pumps and channels as compared to type A cells. In type B IC cells, the HCO_3^-/Cl^- exchanger (Pendrin) is located in the apical membrane and the H^+ ATPase pump is located in the basolateral membrane domain. Through the action of cytoplasmic CA, type B IC cells secrete HCO_3^- and reabsorb H^+. Experimentally induced metabolic acidosis results in conversion of type B IC cells to type A IC leading to H^+ secretion and returning pH to normal range.

The CCD continues into the outer medulla as the outer medullary collecting duct (OMCD). This tubular segment is lined by principal cells that are involved in Na^+ reabsorption and by type A IC cells. Type B IC cells are rarely found in the OMCD. Several OMCD contribute tributaries to the inner medullary collecting ducts (IMCD) that have correspondingly larger luminal diameters. The terminal portions of the IMCD (ducts of Bellini) are lined by taller columnar cells that open into the papillae. The IMCD epithelium expresses urea transporters that play an important role in maintaining the high medullary interstitial concentration of urea. It is this hypertonic interstitium that facilitates urine concentration by the countercurrent multiplication mechanism of the LOH and DT.

CONCLUSION

The kidney has two major functions (1) simple process of filtration, all the components of the blood except cells, and (2) tubules intelligently manipulates filtration, absorption, secretion, components of the blood to maintain internal milieu.

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13.2 Diagnostic Evaluation of Kidney and Urinary Tract

Menka Yadav, RN Srivastava

INTRODUCTION

There are only a few specific manifestations of kidney diseases in infants and children. Other clinical features are subtle or vague and may not lead to a suspicion of an underlying kidney disorder. Kidney diseases should be considered in children with failure to thrive, unexplained fever, obscure anemia, rickets, and dyselectrolytemia with acid–base abnormalities. A family history of kidney disease should always be obtained. A meticulous urinalysis is the crucial diagnostic investigation, and expert ultrasonography is required in most cases. Computed tomography (CT) and magnetic resonance imaging (MRI) and radionuclide studies must be used judiciously.

CLINICAL FEATURES

Common presenting features suggestive of an underlying kidney disease include gross hematuria, edema, hypertension, dysuria, flank pain, polyuria, urinary incontinence, and decrease in urine output.

Hematuria

Urine color may vary from frank red to shades of brown, described as cola- or tea-colored. A small amount of blood (1 mL in 1 L of urine) is sufficient to change the urine color. Concentrated urine looks like mustard oil and is often mistakenly reported as hematuria. Myoglobinuria, porphyria, or alkaptonuria may cause brown discoloration of urine, while administration of rifampicin and pyridium and ingestion of sugar beet or red dyes impart a reddish orange color. Hematuria should be confirmed by microscopy and differentiated from hemoglobinuria and methemoglobinuria. The dipstick test identifies heme and thus is not specific for red blood cells (RBCs). The supernatant in a centrifuged urine with hematuria is clear but is pink in hemoglobinuria and myoglobinuria. Urine microscopy is confirmatory, and the presence of dysmorphic red cells suggests the glomerular origin. Important causes of hematuria and the steps of evaluation are listed in the chapter "Asymptomatic Hematuria."

Edema

Facial edema is an important feature of kidney disease and is often ignored unless acute and associated with other abnormalities such as gross hematuria or oliguria. Nephrotic syndrome characteristically manifests with gradually increasing periorbital edema, which is often mistakenly attributed to an allergic or eye problem. In acute glomerulonephritis (GN), edema is turgid and persistent, whereas in nephrotic syndrome, the swelling is soft and pits on pressure. Nephrotic syndrome is easily differentiated from other causes of edema such as severe malnutrition, congestive cardiac failure, and cirrhosis of the liver.

Oliguria

A decrease in urine volume denotes kidney dysfunction. Oliguria is defined as a urine output <400 mL/day/1.73 m^2 or <0.5 mL/kg/h (<1 mL/kg/h in newborns). Anuria may result from severe dehydration and hypovolemia, complete obstruction of the urinary tract, or profound kidney parenchymal injury.

Polyuria

Urine volumes >2 L/m^2/day reflect impaired urinary concentration. Polydipsia is often associated. Conditions causing excessive solute excretion (osmotic diuresis, e.g., diabetes mellitus) or reduced proximal tubular reabsorption (Fanconi syndrome and isolated hypercalciuria) lead to mild polyuria. Impaired distal concentration due to vasopressin deficiency (central diabetes insipidus) or a lack of tubular response to vasopressin (nephrogenic diabetes insipidus) will lead to profound water losses. Distal tubular dysfunction may be inherited or result from obstructive uropathy, chronic hypokalemia, or interstitial nephritis. Polyuria and polydipsia are important features of nephronophthisis, a familial nephropathy that manifests during infancy.

Abdominal Pain

Flank pain is often present in acute pyelonephritis and nephrolithiasis. Young children may not be able to localize the pain. Ultrasonography is a useful tool for the evaluation of the anatomy of kidneys and urinary tract.

Abnormalities of Micturition

Constant bedwetting, weak urinary stream, dribbling, and crying during micturition are abnormal and require evaluation. Distal obstruction, most commonly from posterior urethral valve, should be excluded in male infants. Persistent dribbling

suggests abnormal ureteric insertion distal to bladder neck. Spinal dysraphism should be excluded in patients with neurogenic bladder.

Enuresis and Daytime Symptoms

Involuntary voiding occurring only at night and being the only complaint (monosymptomatic nocturnal enuresis) is quite common in young children and does not require detailed investigation. Voiding problems during daytime, such as urgency, frequency, or holding maneuvers, suggest an underlying bladder dysfunction. Detailed history and examination, including neurological evaluation (anal tone, sensory loss over the perineum), are carried out. Constipation is frequently present (bladder bowel dysfunction) and should be treated appropriately. Recurrent urinary tract infections (UTIs) are commonly associated with voiding dysfunction and constipation. Voiding diary informs on type of bladder (overactive vs. underactive) and functional bladder capacity. Urine flowmetry and the study of bladder function may be required.

Abnormalities on Urinalysis

Microscopic hematuria [>3 RBC/high power field (HPF)] is occasionally detected in an asymptomatic child on routine urinalysis. It may be associated with mild-to-moderate proteinuria. The presence of these abnormalities should be confirmed on repeated, careful urine examination. Persistent microscopic hematuria or microscopic hematuria associated with proteinuria suggests an underlying glomerular, or occasionally tubulointerstitial abnormality.

Isolated microscopic hematuria is most commonly due to idiopathic hypercalciuria (defined as random urine calcium: creatinine ratio of >0.2 mg/mg in ≥2-year-olds or 24-hour urine calcium >4 mg/kg body weight).

Transient, mild proteinuria may be observed during fever, following exercise, and during infections. Persistent proteinuria is most commonly due to kidney disease and should always be investigated to find the cause. Orthostatic proteinuria, defined as elevated protein excretion in upright position but normal in recumbent position, is not uncommon (2–20%) and can be excluded using split 24 hours proteinuria assessment.

Other Features

The presence of dysuria, flank pain, and cloudy urine suggests UTIs. Tenderness in the Kidney angle and fever indicate pyelonephritis. Features suggestive of chronic kidney disease (CKD) include hypertension, growth retardation, normocytic normochromic anemia, and rachitic deformities. The presence of palpable kidney may suggest hydronephrosis, multicystic dysplastic kidney, polycystic kidney disease (kidneys being bilaterally enlarged), or Wilms' tumor.

LABORATORY EVALUATION

Urinalysis

A detailed examination of urine is crucial in the evaluation of kidney disease. The first morning specimen is more concentrated and preferred since formed elements lyse quickly in dilute urine. Urine is examined promptly or stored at 4°C. A clean catch midstream specimen can be obtained in older children, but in neonates and infants, transurethral catheterization or suprapubic bladder puncture is preferred, especially to confirm UTI.

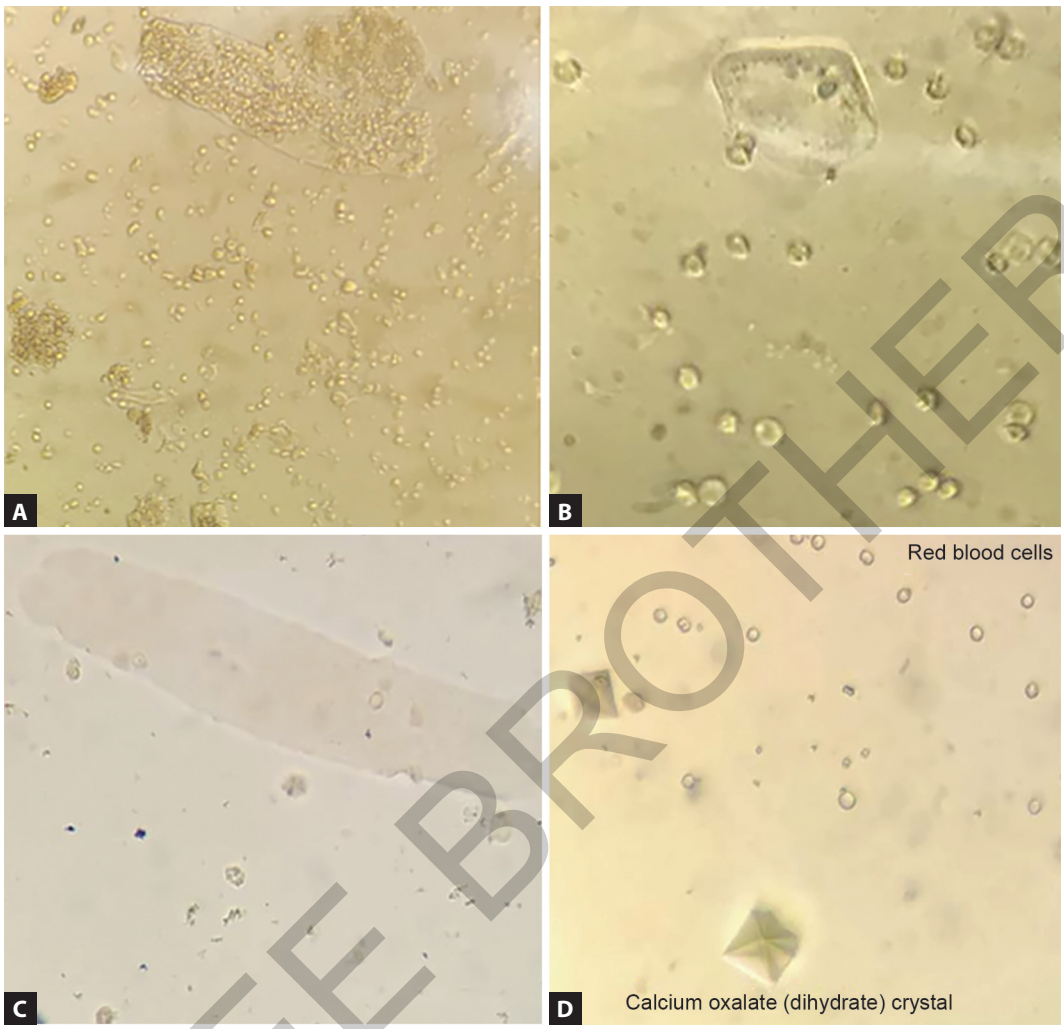
Examination of urine specific gravity or osmolality aids the evaluation for polyuria, while the measurement of urine pH assists in determining tubular acidification abnormalities. Determination of urine electrolytes and fractional excretion is necessary for the diagnosis of various tubulopathies (e.g., Fanconi syndrome and Bartter syndrome). While dipstick can detect glucose, other reducing sugars require biochemical tests, e.g., Benedict's test for detection.

Proteinuria

Urine protein can be estimated with heat precipitation or sulfosalicylic acid as turbidity that is graded from trace, 1+ to 4+. Dipstick testing is more convenient and is graded similarly (trace: 15 mg/dL; 1+: 30 mg/dL; 2+: 100 mg/dL; 3+: 300 mg/dL; 4+: 2 g/dL). Prolonged immersion of the reagent strip and alkaline urine may cause a false-positive dipstick result. Composite sticks are available for examining pH, glucose, protein, RBCs, leukocyte esterase, and nitrite. The latter two tests help in the diagnosis of UTI. Normal children excrete <100 mg/m^2/day of protein in urine, which is chiefly tubular Tamm–Horsfall protein. Since collection of 24-hour urine specimens is often difficult, the ratio of protein to creatinine (mg/mg) in a random sample can be used. Normal values are <0.5 in infants and <0.2 in older children; values >2 suggest nephrotic range proteinuria. Urine protein-to-osmolality ratio, proposed as a useful alternative in children with poor muscle mass, is not commonly used in clinical practice.

Microscopic Examination

Fresh, centrifuged specimen should be examined. RBCs and leukocytes can be counted under microscope (count/HPF) in centrifuged sample and more accurately in a counting chamber (count/mm^3), which avoids the loss of red cells during centrifugation.[1] More than 5 neutrophils per HPF (leukocyturia) with bacteriuria suggest UTI. Microscopic hematuria is defined as the presence of >3 RBCs per HPF in a centrifuged specimen **(Figs. 13.2.1A to D)**. Phase contrast microscopy is helpful to examine red cell morphology, casts, and crystals. Dysmorphic RBCs showing fragmented, crenated appearance indicate glomerular source of red cells, whereas



Figs. 13.2.1A to D: Urine microscopy shows the presence of (A) Dysmorphic red blood cells and a red blood cell cast in a patient with systemic lupus nephritis; (B) Epithelial cells and red blood cells in a patient with immunoglobulin A (IgA) nephropathy; (C) Waxy hyaline cast (normal finding); and (D) Calcium oxalate dihydrate crystal with red blood cells in a patient with hypercalciuria.

normal-looking cells are derived from pelvicalyceal or distal parts. Red cell casts indicate glomerular inflammation. White blood cell casts formed of clumped neutrophils suggest acute pyelonephritis. Hyaline casts (from Tamm–Horsfall protein in tubules) and epithelial cell casts can be identified. Fatty casts and oval fat bodies are commonly found in nephrotic syndrome. Crystals of various compositions (calcium oxalate, phosphate, uric acid, cystine, etc.) can be observed. While calcium oxalate, urate, and phosphate crystals can be seen in normal conditions, the presence of cystine and cholesterol crystals is pathological.

Timed Urine Collection

Because of difficulties in accurately collecting all specimens of urine, 12-hour or 24-hour collections are undertaken when definitely needed, e.g., for quantitative measurement of calcium, phosphate, creatinine, magnesium, or oxalate for the diagnosis of metabolic abnormalities underlying urolithiasis (refer to Chapter 13.13) or in evaluation of tubular dysfunction (refer to Chapter 13.11). Timed protein excretion is helpful in the assessment of response to therapy in secondary causes of nephrotic range proteinuria (>40 mg/m^2/h). The first morning void is discarded, followed by the collection of every voided sample till the first void of the subsequent day. The adequacy of collection can be confirmed using creatinine excretion of 10–15 mg/kg/day in girls and 15–20 mg/kg/day in boys.

Blood Tests

The normal level of blood urea ranges between 20 and 40 mg/dL. Factors that reduce kidney perfusion can cause a reversible increase in blood urea levels. The levels are

also increased during excessive tissue breakdown, trauma, gastrointestinal bleeding, and the use of corticosteroids and tetracycline. Urea levels are low in the presence of hepatic failure and on a low protein diet. Normal blood urea level does not necessarily indicate normal kidney function since the glomerular filtration rate (GFR) must decline to about <75% of normal for the levels to increase.

The level of serum creatinine varies inversely with the GFR, of which it is a better indicator than blood urea. Serum creatinine is not readily affected by prekidney factors. However, these levels are related to the muscle mass and may overestimate GFR in the presence of malnutrition. Hyperbilirubinemia (bilirubin level >5 mg/dL) interferes with the measurement of creatinine. GFR may be estimated in children as follows:

$$\text{Glomerular filtration rate} = \frac{k \times \text{height (in cm)}}{\text{Serum creatinine (mg/dL)}}$$

where $k = 0.413$. Recently, serum cystatin C levels have been suggested to be a better marker of GFR. It is a protein secreted by all nucleated cells and is freely filtered, not secreted by tubules, and totally reabsorbed.[2]

Serum albumin is reduced in patients with nephrotic syndrome proteinuria, occasionally below 1.5 g/dL. In children with nephrotic syndrome, hypercholesterolemia is typically present.

The levels of complement factor 3 (C3) in blood are reduced in postinfectious GN, membranoproliferative glomerulonephritis (MPGN), and lupus nephritis. Estimation of C3 and C4 levels is helpful in GN and other complement-mediated disorders, e.g., atypical hemolytic uremic syndrome. In systemic lupus erythematosus (SLE), C3 levels reflect disease activity. The normal range varies as per laboratory reference.

Antinuclear antibodies (ANAs) are antibodies directed against chromatin-associated or ribonucleoprotein particles. They are not specific and may be increased in many autoimmune diseases such as SLE, juvenile rheumatoid arthritis, polyarteritis nodosa (PAN), and autoimmune hepatitis. ANA titers >1:100 form the entry criteria for SLE as per ACR-EULAR (American College of Rheumatology–European League Against Rheumatism) criteria. Antibodies to double-stranded DNA (anti-dsDNA) is specific to SLE, while increased titer of antineutrophil cytoplasmic antibody (ANCA) is seen in a group of small vessel vasculitis, including microscopic polyangiitis, granulomatosis with polyangiitis, and renal-limited vasculitis.

Tests of Tubular Function

Testing for specific tubular function is indicated by clinical features. For example, children with polyuria may require water deprivation test and vasopressin administration, and bicarbonate or ammonium chloride loading tests are performed in those with impaired urinary acidification. These tests are discussed in Chapter 13.11.

Estimation of Kidney Reserve

Once the decline in GFR is noted, significant decline in kidney function has already occurred. Similarly, after recovery from acute kidney injury, a certain level of kidney function is already lost despite an apparently normal serum creatinine. This lost kidney reserve is the ability of kidneys to increase basal GFR following stress, e.g., protein load. Kidney reserve can be measured using creatinine clearance following amino acid or protein load.

IMAGING STUDIES

Performance of diagnostic imaging in children requires expertise, experience, and patience. Appropriate sedation should be used whenever required. Care is taken to minimize exposure to both radiation and radiocontrast. The guiding principle of *A*s *L*ow *A*s *R*easonably *A*chievable (ALARA) must be followed. Common imaging techniques used are listed below.

Plain X-ray of the Abdomen

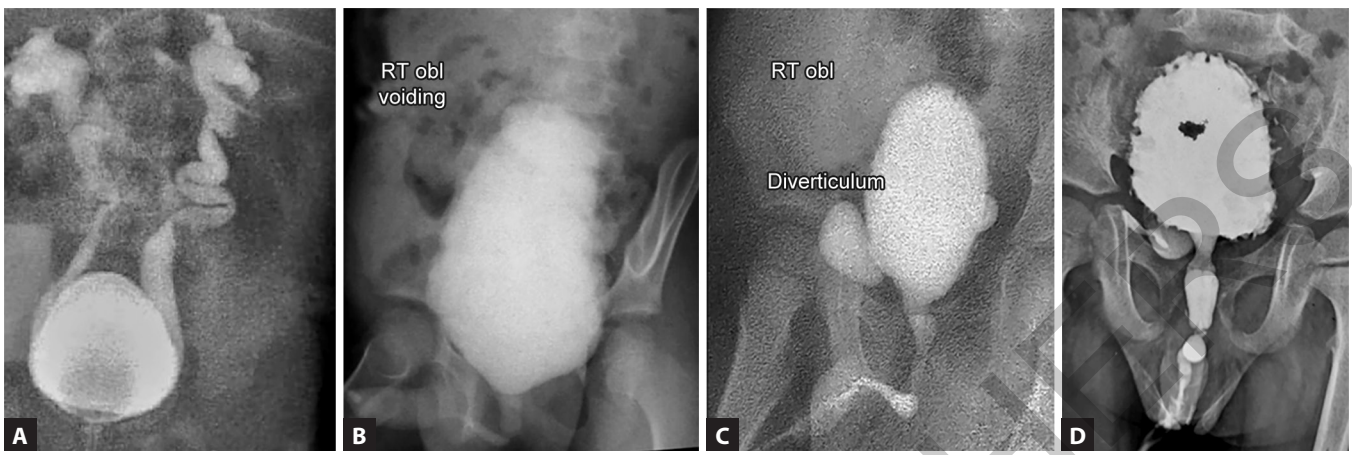
A plain radiograph has limited utility, chiefly in detecting small radiopaque kidney calculi and ureteric calculi without proximal ureteral dilatation. Radiographs also assist in the evaluation of the spine in children with neurogenic bladder, assessment for changes of kidney osteodystrophy, and screening for metastatic bone disease.

Intravenous Pyelography

The use of intravenous pyelography (IVP) or excretory urography has declined due to the advent of ultrasonography and radionuclide studies. It is currently indicated for detailed evaluation of structural anomalies, e.g., duplex kidneys and horseshoe kidneys, and for ureteric calculi. IVP requires bowel preparation and administration of an ionic contrast (urograffin, 3–4 mL/kg) with films taken at 1–5 minutes, 10–15 minutes, and a late pelvic film for the bladder. Hydration is necessary to avoid contrast nephropathy. The test is avoided in neonates since urinary concentration of the contrast is inadequate.

Micturating Cystourethrogram

Micturating cystourethrography (MCU), or voiding cystourethrography, is useful for the diagnosis and grading of vesicoureteric reflux (VUR) **(Figs. 13.2.2A to D)** and the detection of bladder and urethral abnormalities. Following urinary catheterization, radiocontrast agent is introduced



Figs. 13.2.2A to D: Micturating cystourethrogram showing (A) Bilateral grade 5 vesicoureteric reflux in a patient with primary vesicoureteric reflux; (B) Elongated bladder in a patient with neurogenic bladder; (C) Bladder diverticuli in a boy following ablation for posterior urethral valves (right oblique view); and (D) Dilated posterior urethra with trabeculated urinary bladder. (RT obl: right oblique view)

into the bladder; films are taken while the child is voiding. Voiding films provide information on the presence of dilated posterior urethra, bladder neck hypertrophy, and bladder trabeculations. Strict aseptic precautions are required. Oral amoxicillin or parenteral gentamicin (administered 30–60 minutes prior to the procedure and 6 hours afterward) may be administered prophylactically.

Ultrasonography

Ultrasound gives excellent information on anatomical aspects **(Fig. 13.2.3)**. It is especially suited for children.

Since it is painless, requires no sedation or radiocontrast administration, and can be repeated safely. Ultrasound is useful in guiding procedures such as kidney biopsy or fine needle aspiration. The major limitation of ultrasonography is that it is operator-dependent; interpretation in children requires considerable experience.

The kidney cortical echotexture is compared with the liver, spleen, and kidney medulla; nonspecific changes may occur with kidney parenchymal disease. Objective documentation of pelvicalyceal dilation using anteroposterior diameter helps in serial follow-up. Measurement of kidney size helps assess its growth. Doppler evaluation is useful for the assessment of blood flow. Large rectal diameter on ultrasound provides clue to underlying constipation in a child with voiding dysfunction.

Antenatal Ultrasonography

Evaluation in antenatal period allows detection of common abnormalities such as unilateral or bilateral hydronephrosis and multicystic dysplastic kidney. Particular attention is directed toward the amount of amniotic fluid, anteroposterior diameter of the kidney pelvis and pelviectasis, kidney echotexture, and the appearance of the ureters and urinary bladder. Distended bladder with bilateral hydronephrosis suggests distal obstruction as seen with posterior urethral valves, while unilateral hydronephrosis with normal ureters and bladder suggests pelviureteric junction obstruction.

Computed Tomography

Noncontrast helical CT scanning is useful in identifying very small calculi, which might not be detected on ultrasonography. CT provides excellent anatomical details, which is especially useful in evaluating abdominal masses (e.g., tumor or abscess). The disadvantages include radiation exposure, the need for sedation, and contrast administration.

Magnetic Resonance Imaging

Magnetic resonance imaging is used for the detection of spinal abnormalities such as tethered cord. MRI provides superior resolution and avoids radiation. Magnetic resonance urography is an alternative to IVP and provides clear information of kidney function and excretion. However, the procedure requires sedation.

Radionuclide Imaging

The term radionuclide refers to the radioactive substances that are the molecules containing radioactive atoms. When those atoms decay, they emit energy in the form of gamma rays or alpha or beta particles that are detected by the nuclear medicine camera. Radionuclide methods are increasingly replacing conventional radiocontrast studies such as IVP and angiography, since they are noninvasive, highly sensitive, and involve lower radiation exposures.[3] They are used to assess differential kidney function and kidney perfusion and to identify cortical scars, intrakidney masses, and upper tract dilatation. Radionuclide scans also provide valuable information on kidney allograft perfusion and function.

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