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PATHOPHYSIOLOGY OF KIDNEY DISEASES. DISORDERS OF URINE PRODUCTION AND EXCRETION. CHARACTERISTICS OF CHILDREN

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Annotation: Chronic kidney disease (CKD) is a condition in which an initial injury is superseded by a more gradual, chronic process of decreasing function that, in the most extreme cases, ultimately leads to the need for renal replacement therapy. An important consideration is that, while the initiating causes are quite varied, as CKD progresses the mechanisms involved become increasingly similar, so that eventually a set of common events contributes to inexorable loss of functional nephron mass. The mechanisms that are involved can be described as those that disrupt normal renal physiology and those by which decreasing structural integrity renders such disruption irreversible. Thus, the key to understanding progression is examining how function becomes dysregulated and how this dysfunction interacts with the process of renal scarring. This chapter will review these mechanisms.

Key words: Chronic kidney disease, Glomerular filtration rate, Diabetic nephropathy, Chronic kidney disease patient, Renal scarring

INTRODUCTION

The renal system consists of the kidney, ureters, and the urethra. The overall function of the system filters approximately 200 liters of fluid a day from renal blood flow which allows for toxins, metabolic waste products, and excess ion to be excreted while keeping essential substances in the blood. The kidney regulates plasma osmolarity by modulating the amount of water, solutes, and electrolytes in the blood. It ensures long term acid-base balance and also produces erythropoietin which stimulates the production of red blood cell. It also produces renin for blood pressure regulation and carries out the conversion of vitamin D to its active form. The renal development, the process of urine production and excretion, and the clinical significance of the renal system will be the focus of this article.

DEVELOPMENT

Three different sets of kidneys develop consecutively from the urogenital ridges, and the last set persists to become the adult kidney. The first renal tubular system is called the pronephros. Pronephros develop during the fourth week of embryonic development but quickly degenerates as mesonephros appears. Mesonephric kidney degenerates as the metanephros develops through its

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remnant is incorporated into the male reproductive system. The metanephros begins its development around the fifth week of embryonic development as ureteric buds. As the ureteric buds develop, it induces the formation nephrons.[1] The distal ends of the ureteric buds develop into the renal pelvis, calyces, and collecting ducts as the proximal aspect of the ureteric buds develop into ureters.[1][2] A structure called cloaca develops to form the rectum, anal canal, and urogenital sinus. The urogenital sinus then forms into the urinary bladder and the urethra. By the third month of fetal development, metanephric kidney is able to excrete urine into the amniotic fluid.[3]

MECHANISM

Glomerular Filtration

Glomerular filtration is the initial process in urine production. It is a passive process in which hydrostatic pressure pushes fluid and solute through a membrane with no energy requirement. The filtration membrane has three layers: fenestrated endothelium of the glomerular capillaries which allow blood components except the cells to pass through; basement membrane, which is a negatively charged physical barrier that prevents proteins from permeating; and foot processes of podocytes of the glomerular capsule that creates more selective filtration. The outward and inward force from the capillaries determines how much water and solutes crosses the filtration membrane. Hydrostatic pressure from the glomerular capillaries is the major filtration force with a pressure of 55mmHg. The other potential filtration force is the capsular space colloid osmotic pressure, but it is zero because proteins are not usually present within the capsular space. Then the capsular space hydrostatic pressure and the colloid osmotic pressure in glomerular capillaries negate the filtration force from the hydrostatic pressure in the glomerular capillaries, creating a net filtration pressure which plays a big role in the glomerular filtration rate (GFR).[4]

GFR is the volume of fluid filtered in a minute, and it depends on the net filtration pressure, the total available surface area for filtration, and filtration membrane permeability. The normal GFR is between 120 to 125ml/min. It is regulated intrinsically and extrinsically to maintain the GFR. The intrinsic control function by adjusting its own resistance to blood flow via a myogenic mechanism and a tubuloglomerular feedback mechanism. The myogenic mechanism maintains the GFR by constricting the afferent arteriole when the vascular smooth muscle stretches due to high blood pressure. It dilates the vascular smooth muscle when pressure is low within the afferent arteriole allowing more blood to flow through. Then the tubuloglomerular feedback mechanism function to maintain the GFR by sensing the amount of NaCl within the tubule. Macula densa cells sense NaCl around the ascending limb of the nephron loop.[5] When blood pressure is high, the GFR will also be high; this decreases the time needed for sodium reabsorption, and therefore sodium concentration is high in the tubule. The macula densa cell senses it and releases the vasoconstrictor chemicals which constricts the afferent arteriole and reduces blood flow. Then when the pressure is low, Na gets reabsorbed more causing its concentration in the tubule to be low, and macula densa do not release vasoconstricting molecules.[6][7]

The extrinsic control maintains the GFR and also maintains the systemic blood pressure via the sympathetic nervous system and the renin-angiotensin-aldosterone mechanism. When the volume of fluid in the extracellular decreases excessively, norepinephrine and epinephrine get released and causes vasoconstriction leading to a decrease in blood flow to the kidney and the level of GFR. Also, the renin-angiotensin-aldosterone axis gets activated by three means when the blood pressure drops. The first is the activation of the beta-1 adrenergic receptor, which causes the release

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of renin from the granular cells of the kidney. The second mechanism is the macula densa cells which senses low NaCl concentration during decreased blood flow to the kidney and trigger the granular cells to release renin. The third mechanism is the stretch receptor around the granular cells senses decreased tension during decreased blood flow to the kidney and also trigger the release of renin, therefore, regulating the glomerular filtration.[6]

Tubular Reabsorption

The four different tubular segments have each unique absorptive properties. The first is the proximal convoluted tubule (PCT). The PCT cells have the most absorptive capability. In the normal circumstance, the PCT reabsorbs all the glucose and amino acids as well as 65% of Na and water. The PCT reabsorb sodium ions by primary active transport via a basolateral Na-K pump. It reabsorbs glucose, amino acids, and vitamins through secondary active transport with Na and an electrochemical gradient drives passive paracellular diffusion. The PCT reabsorbs water by osmosis that is driven by solute reabsorption. It also reabsorbs lipid-soluble solutes via passive diffusion driven by the concentration gradient created by reabsorption of water. Reabsorption of urea occurs in the PCT as well by passive paracellular diffusion driven by a chemical gradient.[8]

From the PCT, the non-reabsorbed filtrates move on to the nephron loop. The nephron loop functionally divides into a descending and an ascending limb. The descending limb functions to reabsorb water via osmosis. This process is possible due to the abundance of aquaporins. Solutes do not get reabsorbed in this region. However, in the ascending limb, Na moves passively down its concentration gradient in the thin segment of the ascending limb, and also sodium, potassium, and chlorides get reabsorbed together through a symporter in the thick segment of the ascending limb. The presence of Na-K ATPase in the basolateral membrane keeps this symporter functional by creating an ionic gradient. There is also the reabsorption of the calcium and magnesium ions in the ascending limb via passive paracellular diffusion driven by the electrochemical gradient. No water reabsorption in the ascending limb.[9]

The next tubular segment for reabsorption is the distal convoluted tubule (DCT). There is a primary active sodium transport at the basolateral membrane and secondary active transport at the apical membrane through Na-Cl symporter and channels. This process is aldosterone regulated at the distal portion. There is also calcium reabsorption via passive uptake controlled by the parathyroid hormone. Aldosterone targets the cells of the distal portion of the DCT causing synthesis and retention of apical Na and K channel as well as the synthesis of Na-K ATPase.[8]

Right after the DCT, there is a collecting tubule where the final stage of reabsorption occurs. The reabsorptions that occur here include primary active sodium transport at basolateral membrane; secondary active transport at apical membrane via Na-Cl symporter and channels with aldosterone regulation; passive calcium uptake via PTH-modulated channels in the apical membrane; and primary and secondary active transport in the basolateral membrane.[10]

Clinical Significance

The renal system pathologies have a wide range of clinical presentations. Emphysematous urinary tract infections, chronic kidney disease, nephrolithiasis, and urinary incontinence in men and women are topics of discussion below.

Emphysematous UTI is a form of UTI, where infections of the lower or upper urinary tract present with gas formation. Escherichia coli and Klebsiella pneumoniae commonly cause emphysematous UTI although Proteus, Enterococcus, Pseudomonas, Clostridium, and Candida spp can be part of the causative organism.[18] The common risk factors seen in patients with

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emphysematous urinary tract infections are diabetes and urinary tract obstruction.[19] Emphysematous UTI usually manifests as cystitis, pyelitis, and pyelonephritis with common presentations such as fever, chills, flank or abdominal pain, nausea, and vomiting. Laboratory testing can reveal elevated serum creatinine, pyuria, leukocytosis, and hyperglycemia. Diagnosis can be made with plain film and/or computed tomography, which will show air in the renal parenchyma, bladder, or surrounding tissue.[19] Treatment of emphysematous UTI is usually by systemic antibiotics.[19][20] Percutaneous drainage might be necessary for pyelonephritis.

Chronic kidney diseases are not uncommon. Approximately 16.8% of the US population has chronic kidney disease (CKD).[21] CKD is the presence of kidney damage with urinary albumin excretion of over 29 mg/day or decreased kidney function with GFR less than 60mL/min/1.73m^2 for three or more months. CKD is classified based on the six GFR stages and the three albuminuria stages. Clinical manifestations include edema and hypertension although some patients can be asymptomatic. Laboratory testings are essential in the diagnosis of CKD. An increase in serum creatinine and urea concentration are very common findings. Hyperphosphatemia, hyperkalemia, hypocalcemia, elevated parathyroid hormone, and metabolic acidosis may also be present in the lab findings. When CKD is suspected, ultrasound, urinalysis with microscopy, and albumin to creatinine ratio are necessary. Ultrasound will help rule out any form of obstruction.[22] Urinalysis with microscopy will help rule out glomerulonephritis in the absence of albuminuria, RBC cast or dysmorphic RBC. Urinalysis can also help rule out interstitial nephritis when sterile pyuria is negative. Once urinalysis is deemed normal, the patient needs evaluation for renovascular disease. If there is no evidence of renovascular disease as a causative factor, a kidney biopsy might be conducted, then evaluation for renal replacement therapy can be done.[23] Management of CKD involves treatment of reversible causes, preventing or slowing the progression of renal disease, treatment of the complications of the renal failure, medication adjustment, and proper education of a patient on the renal disease and on the possibility of needing renal replacement therapy.[24][25]

Nephrolithiasis is another pathology commonly seen in the renal system. Nephrolithiasis is the presence of crystallized calcium, magnesium, cystine, or uric acid in the renal system. Calcium stones are known to cause eighty percent of nephrolithiasis. Calcium stone has two forms: calcium oxalate which is the most common and the calcium phosphate.[26][27] Several risk factors lead to nephrolithiasis including high oxalate diet, prior history of nephrolithiasis, family history of nephrolithiasis, recurrent UTI, and enhanced enteric oxalate absorption caused by gastric bypass procedures, bariatric surgery, and short bowel syndrome.[28][29] Approximately seventy percent of the patients with nephrolithiasis are symptoms free.[30] The most common symptoms associated with nephrolithiasis are waves of waxing and waning unilateral flank pain that lasts 20 to 60 minutes. Hematuria is also a common symptom seen in nephrolithiasis. As the diagnosis of nephrolithiasis is under consideration, other possible pathologies need to be ruled out. For instance, pyelonephritis frequently presents with flank pain, although it also presents with a fever, which is not usually present with nephrolithiasis. Ectopic pregnancy can be mistaken for renal colic. In this case, a renal and pelvic ultrasound can help to clarify.[31] Once symptomatic ureteral stone is clinically suspected, non-contrast renal CT should follow. Pain management should also commence. If urosepsis is present, emergent decompression should be conducted. If urosepsis is absent, the size of the stone should undergo evaluation. Observation, symptomatic treatment, alpha-blocker, and urine straining is appropriate for patients with a stone size of less than 10 mm.

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Extracorporeal shock wave lithotripsy or ureteroscopy can potentially help patients with stones greater than 10 mm.[32]

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