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# Kidney Disease and Kidney Function Tests: A Narrative Review

**[1] Margaret Chinazam Ibe, [2] Sunday Joyce Imbigbu, [3] Ezeoha Ifunanya Gloria, [4] Darlington Chukwuebuka Ejim, [5] Onyeaghala Santus Uchendu, [6] Esther Onyinyechi Nchuma, [7] Isuajah Chukwuka Emmanuel, [8] Onuabuchi Eucharia Uchenna, [9] Chibuzo Ngozi Christiana, [10] Williams Esther Ubong, [11] Obialor Oluchi Peace, [12] Chukwudi Precious Ofoedu, [13] Linda Chiemezie Ahanonu, [14] Okagu Bonaventure Chukwuemeka, [15] Anthony Chukwuemeka Egbo, [16] Jonathan Joshua Danjuma, [17] Ijezie Gabriel Izuchukwu, [18] Kadiatu Victoria Turay, [19] Henry Obinna Igbo, [20] David Kennedy Nkweke**

[1, 13] Department of Medical Laboratory Science, Ebonyi State University, Abakaliki, Ebonyi State, Nigeria
[2] Science Department, Plateau State Polytechnic Academy, Barkin Ladi Plateau, Nigeria
[3] Department of Food Science and Technology, Enugu State University of Science and Technology (ESUT), Enugu, Nigeria
[4, 8, 9, 12, 14, 15] Department of Medical Laboratory Science, University of Nigeria Enugu Campus, Enugu State, Nigeria
[5] Department of Medical Laboratory Science, Imo State University Owerri, lmo State, Nigeria
[6, 11] Department of Medical Laboratory Science, Abia State University, Uturu, Abia State, Nigeria
[7] Department of Clinical Pathology, College of Medicine, Lead City University, Ibadan, Nigeria
[10] Department of Medical Laboratory Science, University of Calabar, Calabar, Cross River State, Nigeria
[16] Department of Medical Laboratory Science, Bayero University Kano, Kano State, Nigeria
[17] Department of Microbiology, Kingsley Ozumba mbadiwe University, Orlu, Imo State, Nigeria
[18] Science Department, Kamabia Secondary School, Free- Town, Sierra Leone
[20] Department of Human Anatomy, University of Port Harcourt, Rivers State, Nigeria

Corresponding Author: **Margaret Chinazam Ibe**

**Abstract**

The kidney is a vital organ responsible for maintaining overall body homeostasis through its role in renal function. This function includes filtration, reabsorption, secretion, and excretion processes essential to the regulation of fluids, electrolytes, and waste products. The kidney's primary role is to filter blood through the glomerulus, removing toxins and metabolic byproducts while retaining necessary proteins and cells. This filtration process forms urine, which collects waste and excess substances, eventually excreted from the body. Additionally, the kidney balances electrolytes, including sodium, potassium, and calcium, and regulates blood pH through acid-base equilibrium. By releasing hormones like erythropoietin, which stimulates red blood cell production, and renin, which modulates blood pressure, the kidney plays a critical role in endocrine function. It also contributes to bone health through vitamin D activation, essential for calcium absorption. Impaired kidney function, from acute or chronic conditions, can disrupt these homeostatic processes, leading to systemic health issues, including hypertension, anemia, and mineral imbalances. Understanding renal function mechanisms is crucial in preventing and managing kidney diseases, enhancing patient outcomes, and improving quality of life.

**Keywords:** Kidney, Glomerulus, Erythropoietin, Renal Filtration, Renal Reabsorption, Renal Secretion

## Introduction

The kidneys are essential organs that serve a number of crucial purposes. Removal of waste and surplus substances from plasma, homeostasis (maintenance of equilibrium) of the body's water, electrolyte, and acid-base state, and involvement in hormonal regulation are the three main roles. Kidney function tests are used in the clinical laboratory to evaluate renal illness, water balance, acid-base disorders, and in cases of trauma, brain damage, surgery, and infectious disease. This chapter focuses on the architecture and physiology of the kidneys as well as the analytical techniques that can be used to detect, track, and treat kidney failure [1].

On either side of the spinal column, at the retroperitoneal point, are the kidneys, which are two bean-shaped organs. Each kidney is macroscopically enclosed by a fibrous capsule of connective tissue. Two distinct regions—an outer region known as the cortex and an interior region known as the medulla—can be seen when the brain is dissected longitudinally. The pelvis is also visible. The ureter's top end has a hollow that resembles a basin into which newly generated urine is expelled. The bilateral ureters, which have strong walls and link the kidneys and urine bladder, are vessels. The bladder serves as a temporary holding tank for urine until the urethra allows it to exit the body. The kidney's nephrons—functional units that can only be observed under a microscope—are arranged in the figure below. Approximately 1 million nephrons can be found in each kidney. Each nephron is a sophisticated device made up of five fundamental components.

- The glomerulus, a capillary tuft encircled by Bowman's capsule, the enlarged end of a renal tubule. An afferent arteriole carries blood into each glomerulus, and an efferent arteriole carries blood out. The tubule is supplied by peritubular capillaries, which branch off from the efferent arteriole.
- The cortical structure known as the proximal convoluted tubule.
-The long loop of Henle is made up of a region that is narrow and then thick, with a thin descending limb that spans the medulla and an ascending limb that is found in both the medulla and cortex.
- A cortex-based structure called the distal convoluted tubule.
- The duct that collects urine that drains from each nephron and is made up of two or more distal convoluted tubules as they travel back via the cortex and medulla. Eventually, collecting ducts combine and release their contents into the renal pelvis [1].

Fig 17 shows how the nephron processes three different chemicals in three different ways. Filtered substance A is secreted, but not reabsorbed; filtered substance B is partially reabsorbed; and filtered substance C is fully reabsorbed [1]. The regulation of particular compounds in this way to preserve homeostasis is described below.

The glomerulus, which is the nephron's initial segment, serves to filter incoming blood. Filtration is facilitated by several variables. The glomerular capillaries' abnormally high pressure, which results from their location in between two arterioles, is one contributing cause. A significant pressure difference across the walls results from this. The semipermeable glomerular basement membrane is another factor. Its molecular size cutoff value is roughly 66,000 Da, or about albumin's molecular size. This indicates that the basement membrane is permeable to water, electrolytes, and tiny dissolved solutes like glucose, amino acids, low-molecular-weight proteins, urea, and creatinine that enter the proximal convoluted tubule. Other blood components like albumin, many plasma proteins, cellular components, and protein-bound compounds like lipids and bilirubin cannot be filtered due to their size. Additionally, negatively charged molecules like proteins are rejected by the negatively charged nature of the basement membrane. The glomerulus removes 125–130 mL of glomerular filtrate, a fluid that is basically protein- and cell-free, from the 1200–1500 mL of blood that the kidneys receive per minute (or about 25% of the total cardiac output). Glomerular filtration rate (GFR), which is defined as the amount of blood filtered per minute, must be determined in order to assess renal function, as is covered in the section on analytical procedures [1].
[See Figures1 and 2].

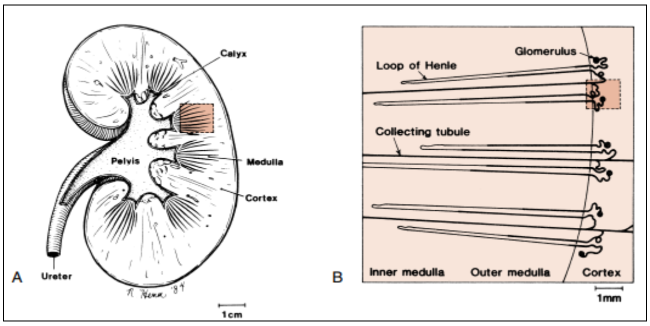


**Fig 1:** Anatomy of the Kidney[1]

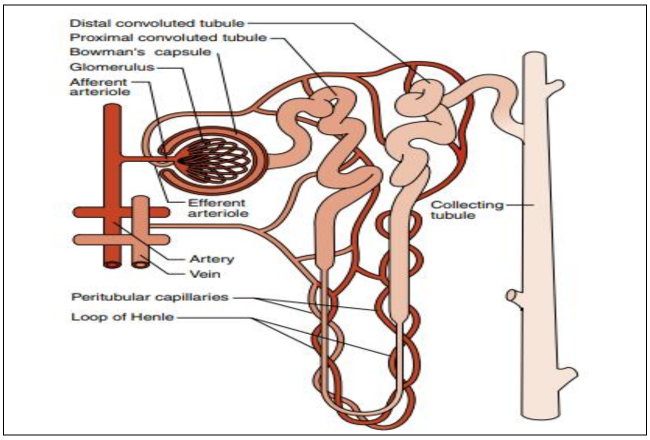


**Fig 2:** The nephron and its blood supply [1]

**Tubular Function**

**1. Proximal Convoluted Tubule**

The next area of the nephron to receive the blood, which is now essentially protein- and cell-free, is the proximal tubule. This filtrate comprises both waste products that are beneficial to the body and compounds that are poisonous to it above a particular concentration. Returning the majority of each important substance back to the blood circulation is one of the proximal tubule's functions. As a result, various amounts of urea, uric acid, and ions like magnesium, calcium, potassium, and bicarbonate are reabsorbed along with 75% of the water, sodium, and chloride, 100% of the glucose (up to the renal threshold), and practically all of the amino acids, vitamins, and proteins. Nearly all (98–100%) of the waste product uric acid is actively reabsorbed before being secreted at the distal end of the proximal tubule. Tubular reabsorption is the process by which chemicals are transferred from the tubular lumen to the peritubular capillary plasma. The mechanism, which involves the tubular epithelial cells using energy to bind and transport the chemicals through the plasma membrane to the blood, is active with the exception of water and chloride ions. The related transport systems usually contain enough reserve for effective reabsorption, but they are saturated. The substance is then expelled in the urine when the concentration of the filtered substance exceeds the transport system's capacity. The renal threshold is the plasma concentration at which the chemical manifests in urine, and its assessment is helpful in evaluating both tubular function and non-renal illness conditions. Water is constantly passively carried through diffusion down a concentration gradient, hence there is no renal threshold for it. In this case, sodium diffuses first, then chloride ions. The proximal tubule's ability to release hydrogen ions and medications like penicillin as byproducts of kidney tubular cell metabolism is its second function [1].

There are two ways to refer to tubular secretion:

- The transfer of chemicals from peritubular capillary plasma to the tubular lumen is known as tubular secretion.
- Tubular secretion also refers to the process by which tubule cells release byproducts of their own cellular metabolism into the filtrate in the lumen of the tubule.

Once more, transport occurs either actively or passively across the cell membrane. Countercurrent Loop of Henle Multiplier System Water, salt, and chloride are more easily reabsorbed when the osmolality in the medulla in this region of the nephron increases continuously from the corticomedullary junction inward. The loop of Henle, a hairpin-like loop between the proximal tubule and the distal convoluted tubule, continuously maintains the hyperosmolality that develops in the medulla. A countercurrent flow is defined as the opposing flows in the loop, which are the upward flow in the ascending limb and the downward flow in the descending limb. It is best to first examine what transpires in the ascending limb in order to comprehend how the hyperosmolality is maintained in the medulla. The entire length of the ascending limb experiences active and passive resorption of sodium and chloride into the medulla interstitial fluid. The medulla interstitial fluid becomes hyperosmotic in comparison to the fluid in the ascending limb because little water follows the ascending limb since it is relatively impervious to water. The ascending leg is frequently referred to as the diluting segment because as sodium and chloride ions are reabsorbed without the loss of water, the fluid there becomes hypotonic or diluted. In contrast to the ascending limb, the descending limb has a high water permeability and does not reabsorb sodium and chloride. The physical force accelerating the reabsorption of water from the filtrate in the interstitial medulla is the high osmolality of the fluid in the surrounding area. Because of the ascending limb's continued infusion of salt and chloride ions, interstitial hyperosmolality is kept at a constant level. Hypoosmolal urine is created as a result of the interplay between water leaving the descending loop and salt and chloride leaving the ascending loop to maintain a high osmolality within the kidney medulla. The countercurrent multiplier system is the name of this procedure [1].

[Fig 3].

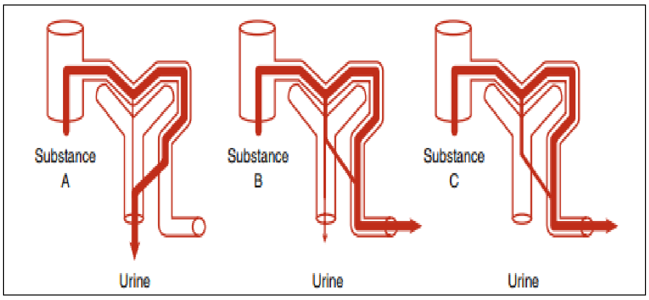


**Fig 3:** Filtration, reabsorption and secretion processes of the renal system [1]

## 2. Distal Convoluted Tubule

The distal convoluted tubule has two or three coils that link to a collecting duct and is considerably shorter than the proximal tubule. This region of the nephron receives filtrate that is nearly finished. 90% of the water and 95% of the sodium and chloride ions from the original glomerular filtrate had already been reabsorbed. The distal tubule's job is to make minor modifications to maintain acid-base and electrolyte equilibrium. Antidiuretic hormone (ADH) and aldosterone both exert hormonal control over these modifications [1]. The figure below describes these hormones act [Fig 4].

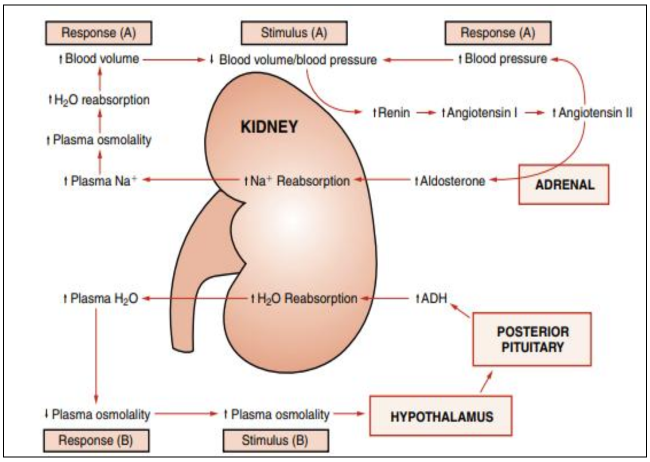


**Fig 4:** ADH and aldosterone control of the renal reabsorption of water and $Na^+$ (Bishop *et al*., 2010) [1]

### 1.) Antidiuretic Hormone (ADH)

The posterior pituitary releases ADH, a peptide hormone, mostly in reaction to elevated blood osmolality. ADH is also released when blood volume drops by more than 5%–10%. Even with a drop in plasma osmolality, significant blood volume reductions will promote ADH secretion. 3 ADH promotes the reabsorption of water. Similar to the ascending loop of Henle, the walls of the distal collecting tubules are typically impervious to water; but, in ADH, they become so. Water passively diffuses from the tubule lumen, producing more concentrated urine and lower plasma osmolality [1].

### 2.) Aldosterone

The adrenal cortex produces this hormone under the control of the renin-angiotensin system. Reduced blood flow or blood pressure in the afferent renal arteriole as well as decreased plasma sodium cause it to secrete. Aldosterone promotes potassium and hydrogen ion secretion in addition to sodium reabsorption in the distal tubules. Ammonia secretion and bicarbonate regeneration, both of which take place in this location, are related to hydrogen ion secretion. Small amounts of chloride ions are reabsorbed along with these ions [1].

## 3. Collecting Duct

The final location for either concentrating or diluting urine is the collecting ducts. To regulate the reabsorption of water and sodium, the hormones ADH and aldosterone work on this section of the nephron. Additionally reabsorbed here are urea and chloride. The renal medulla's hyperosmolality is maintained in large part by urea. Urea diffuses along its concentration gradient out of the tubule and into the medulla interstitium because the collecting ducts in the medulla are extremely permeable to urea, increasing its osmolality [2].

### Elimination of Nonprotein Nitrogen Compounds

The body creates nonprotein nitrogen compounds (NPNs) as waste products when proteins, amino acids, and nucleic acids are broken down in a process called degradative metabolism. The kidneys play a crucial role in the excretion of these substances. Urea, creatinine, and uric acid are the three main substances. See Chapter 11 for a more thorough discussion of their biology and illness connections. Urea As a result of the oxidative catabolism of protein, the majority (more than 75 percent) of the NPN waste ejected daily is urea. The liver is where urea is made. Amino acids, which are produced from the breakdown of proteins, are deaminated to produce ammonia. Since urea is easily formed from ammonia, toxicity is avoided. The kidney is the only important pathway for urea excretion. Given that it has a molecular weight of 60 Da, the glomerulus can easily filter it. Urea is reabsorbed in the collecting ducts in amounts between 40 and 60 percent. One of the previously stated mechanisms of urine concentration, excessive osmolality in the medulla, is a result of the reabsorbed urea (see Loop of Henle). For the quick synthesis of adenosine triphosphate, creatine phosphate, a high-energy substance, is present in muscle (ATP). This reaction, which is the first source of metabolic energy used in muscle contraction, is catalyzed by creatine kinase (CK) [1]. As illustrated below, creatine is converted into creatinine.

$$\text{Creatine phosphate} + \text{ADP} + \text{H}^+ \xrightarrow{\text{CK}} \text{creatine} + \text{ATP} \xleftarrow{\text{nonenzymatic}} \text{creatinine}$$

Up to 20% of the total amount of muscle creatine (and its phosphate) dehydrates spontaneously each day and cycles to generate the waste substance creatinine. Therefore, unless muscle mass or renal function changes, creatinine levels are a function of muscle mass and are roughly constant from day to day in an individual. Because creatinine has a molecular weight of 113 Da, the glomerulus can easily filter it. Creatinine is not reabsorbed by the tubules like urea is. However, at high serum concentrations, a little quantity of creatinine is released by the renal tubules.

As for uric acid, it is the main byproduct of purine metabolism. Adenine and guanine, two types of purines, are the building blocks for the nucleic acids guanosine triphosphate (GTP) and ATP, respectively. The molecular weight of uric acid is 168 Da. Similar to creatinine, it is easily filtered by the glomerulus, but as it travels through the nephron, it goes through a complicated cycle of reabsorption and secretion. Only 6–12% of the uric acid that was originally filtered is ultimately expelled. At urine pH 5.75, uric acid is present in its ionized and more soluble form, typically sodium urate (the first pKa of uric acid). It is non-dissociated at pH 5.75. This information is clinically significant for the progression of gout and urolithiasis (the creation of calculi) [1].

**Water and Electrolyte Balance**

Water loss or conservation by the kidney, which is controlled by the hormone ADH, contributes to the body's overall water balance. Osmolality and intravascular volume fluctuations are the main triggers for ADH response. ADH production from the posterior pituitary is stimulated by either decreased intravascular volume or elevated plasma osmolality. Then, as a result of ADH increasing the distal convoluted tubules' and collecting ducts' water permeability, more water is reabsorbed and more concentrated urine is excreted. Contrarily, thirst is the main mechanism controlling water intake, and it appears that the same factors that cause ADH secretion also cause thirst. In dehydrated conditions, the renal tubules reabsorb water at their maximum rate, producing a tiny volume of highly concentrated urine (1200 mOsmol/L urine osmolality). 7 When there is an overabundance of water in the body, the tubules can only reabsorb water at a very slow rate, which causes a considerable amount of extremely diluted urine to be excreted (urine osmolality is as low as 50 mOsmol/L) [3, 4, 5]. The body's fluid balance is precisely controlled as a result of the ongoing fine-tuning that is feasible between these two extreme states (Fig 5).

**Electrolyte Equilibrium**

The important ions involved in maintaining the electrolyte balance within the body are listed briefly below.

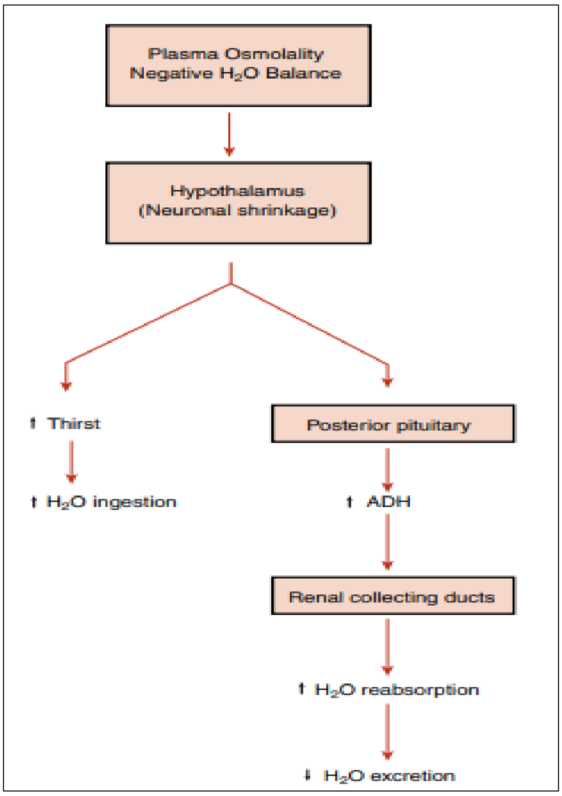


**Fig 5:** Mechanism of thirst control by ADH [1]

**1.) Sodium**

The human body's main extracellular cation, sodium, is primarily eliminated through the kidneys. The sole way to regulate the body's sodium balance is through excretion. The primary mechanism for controlling sodium balance is the renin-angiotensin-aldosterone hormonal system.

**2.) Potassium**

The body's primary intracellular cation is potassium. Cellular metabolism depends heavily on the careful management of its concentration, which is mostly managed by renal mechanisms. Similar to sodium, it is aggressively reabsorbed throughout the entire nephron after being freely filtered by the glomerulus (except for the descending limb of the loop of Henle). Potassium can be reabsorbed and excreted through the distal convoluted tubule and the collecting ducts, and aldosterone regulates this excretion. In the proximal convoluted tubule, potassium ions can compete with hydrogen ions for sodium, which allows the body to conserve hydrogen ions and make up for metabolic alkalosis situations [1].

### 3.) Chloride

The major extracellular anion, chloride, is important for maintaining the proper balance of extracellular fluids. The glomerulus easily filters it, and when sodium is passively reabsorbed in the proximal convoluted tubule, it is reabsorbed as a counter ion. A separate chloride "pump" that also actively reabsorbs sodium reabsorbs potassium in the ascending limb of the loop of Henle. By inhibiting this pump, loop diuretics like furosemide can be used. The same forces that control sodium also influence chloride, as one might predict [3].

### 4.) Phosphate, Calcium, and Magnesium

In internal surroundings as opposed to external fluid conditions, the phosphate ion is present in larger amounts. Homeostatic balance is primarily determined by proximal tubular reabsorption, which is regulated by parathyroid hormone; it can either be protein-bound or not (PTH). The most significant inorganic messenger in the cell is calcium, which is the second-most prevalent intracellular cation. It can be found in both states—protein-bound and unbound—as well. If calcium is not protein-bound, it is either ionized, where it is physiologically active, or it is non-ionized, where it is complexed to tiny, diffusible ions like phosphate and bicarbonate. Under the control of PTH, the ionized form is freely filtered by the glomerulus and reabsorbed in the tubules. The primary mode of regulation, however, is not renal control of calcium concentration. More significant than renal secretion or reabsorption is the regulation of calcium absorption from the gut and bone reserves under the control of PTH and calcitonin. Magnesium, a significant intracellular cation, plays a crucial role as an enzyme cofactor. Similar to phosphate and calcium, it can be in an ionized or protein-bound state. Under the effect of PTH, the glomerulus quickly filters the ionized portion, which is then reabsorbed in the tubules [3].

### 5.) Creatinine Clearance and Glomerular Filtration Rate

As a common laboratory procedure, calculating creatinine clearance now determines GFR. The serum creatinine concentration and the urine creatinine concentration excreted over a period of time, typically 24 hours, are mathematically related to get this result. Therefore, a 24-hour urine specimen and a serum creatinine value, ideally obtained at the halfway point of the 24-hour urine collection, must both be included in the specimen collection. Throughout the collection process and the ensuing storage time until a laboratory analysis can be done, the urine container (clean, dry, and devoid of pollutants or preservatives) must be kept chilled. The amount of urine is carefully measured, and the formula for calculating the creatinine clearance is as follows:

$$\frac{U_{Cr}\ (\text{mg/dL}) \times V_{Ur}\ (\text{mL/24 hour})}{P_{Cr}(\text{mg/dL}) \times 1440\ \text{minutes/24 hours}} \times \frac{1.73}{A}$$

where $P_{Cr}$ is the serum creatinine concentration, $C_{Cr}$ is creatinine clearance, $U_{Cr}$ is urine creatinine clearance, $V_{Ur}$ is urine volume excreted in a 24-hour period, and 1.73/A is the normalization factor for body surface area (1.73 is the generally accepted average body surface in square meters and A is the actual body surface area of the individual determined from height and weight). This body mass correction must be used in the formula if the patient's body surface area differs significantly from the average (for instance, if they are obese or a child).

***Reference Ranges for Creatinine Clearance Males***: between 97 and 137 mL/min per 1.73 $m^2$. For females, the range is from 88 to 128 mL/min per 1.73 m2. Normal aging results in a reduction in creatinine clearance of about 6.5 mL/min per 1.73 m2 for each decade of life [1].

### 6.) Estimated Glomerular Filtration Rate

When a serum creatinine level is recorded, it is advised by the National Kidney Foundation to estimate GFR (eGFR). The formula, which predicts GFR without the need of a urine creatinine, is based on serum creatinine, age, body size, gender, and race. The computation should be used more frequently than the conventional creatinine clearance because it does not call for timed urine collection, which will lead to earlier detection of chronic kidney disease [6].

$$\text{GFR (mL/min)} = \frac{(140 - \text{Age}) \times \text{Weight(kg)}}{72 \times S_{Cr}(\text{mg/dL})} \times (0.85 \text{ if female})^*$$

### 7.) Urea

One of the first assays for clearance was urea clearance. At the glomerulus, urea is freely filtered, and the tubules reabsorb around 40% of it. It is no longer frequently utilized and does not offer a complete clearance assessment because of this. Older clearance assays measured glomerular filtration or tubular secretion by administering inulin, sodium [125I] iothalamate, or p-aminohippurate. Due to their length, cost, and difficulty in administration, these tests have mostly been abandoned (Lab Test Online).

### 8.) Cystatin C

A protein with a low molecular weight called cytostatin C is created by nucleated cells. The glomerulus freely filters it, and the proximal tubule reabsorbs and catabolizes it. If kidney function is normal, levels are consistent because they are produced at a constant pace. Gender, ethnicity, age, and muscle mass don't seem to have any impact on plasma concentrations. According to studies, measuring cystatin C is at least as helpful for spotting early changes in kidney function as measuring blood creatinine and creatinine clearance. Before a quantifiable decline in GFR or an increase in creatinine, a rise in cystatin C is frequently perceptible. Immunoassay techniques can be used to quantify cystatin C.).

Individual homeostatic setting points frequently differ when the same test is administered to several persons, as shown by the fact that the mean of each person's results is not the same. The definition of biologic variation is the random variation surrounding a homeostatic setting point [7]. This comprises variances between the homeostatic setting points of different individuals, also known as between subject biologic variations, as well as fluctuations around the homeostatic setting point for a single individual, also known as within-subject biologic variation. When it comes to creatinine, an individual's levels change slightly over time, and the mean values across all people differ noticeably from one another. As a result, just a small percentage of the population-based reference interval is covered by each person's data. Therefore, the within-subject biologic variation for creatinine is lower than the between-subject biologic variation. A particular analyte is said to exhibit marked individuality when this is the case. Interestingly, compared to creatinine, the between-subject biologic variance is substantially lower for cystatin C, indicating that population-based reference values are more helpful for cystatin C. When compared to creatinine, the within-subject variation for cystatin C is larger. As a result, whereas cystatin C may be more useful for detecting modest renal impairment, creatinine is more helpful in monitoring renal function over time for a given individual [1].

## Pathophysiology

### Glomerular Diseases

At least initially, conditions or illnesses that directly harm the renal glomeruli may show normal tubular function. However, when the condition worsens over time, the renal tubules are also affected. The following syndromes are distinguishable by their patterns of clinical laboratory findings and have distinct symptoms [4].

### Acute Glomerulonephritis

The glomerulus is largely affected by pathologic lesions in acute glomerulonephritis. A study of the tissue's histology reveals enlarged, inflammatory glomeruli with a reduced capillary lumen. Rapid onset of hematuria and proteinuria (usually albumin, and typically 3 g/day) are two common abnormal laboratory results. Common symptoms include a rapidly declining GFR, anemia, increased blood urea nitrogen (BUN), elevated serum creatinine, oliguria, salt retention, hypertension, and occasionally congestive heart failure. On UA, many hyaline and granular casts are frequently observed. It is thought that the actual RBC casts are very symptomatic of this disease. Group A -hemolytic streptococci infections that have recently occurred are frequently linked to acute glomerulonephritis. According to one theory, circulating immune complexes cause the glomerular basement membrane to have a significant inflammatory response, directly injuring the glomerulus. Acute kidney infections brought on by other bacterial (and possibly viral) agents, drug-related exposures, and other systemic immune complex disorders such systemic lupus erythematosus (SLE) and bacterial endocarditis are additional potential causes [1].

### Chronic Glomerulonephritis

Long-lasting glomerular inflammation may result in glomerular scarring and eventually the loss of functional nephrons. Because only moderate declines in renal function first occur, and because only mild proteinuria and hematuria are seen, this process frequently goes undiagnosed for prolonged periods of time. The first indicator of this process may be the gradual onset of uremia (or azotemia, excess nitrogen molecules in the blood).

### Nephrotic Syndrome

Numerous illnesses that damage the glomerular basement membrane and increase its permeability can result in nephrotic syndrome (Fig 6). Numerous aberrant results, including extensive proteinuria (>3.5 g/day) and the ensuing hypoalbuminemia, are virtually usually produced by this abnormality. The transfer of bodily fluids out of vascular and into interstitial spaces as a result of the following fall in plasma oncotic pressure results in a widespread edema. Moreover, lipiduria and hyperlipidemia are other symptoms of this disease. Oval fat bodies appear as a result of lipiduria in the urine. These entities are reabsorbed lipoprotein-containing deteriorated renal tubular cells. The states of glomerular disease are intimately related to primary causes [4].

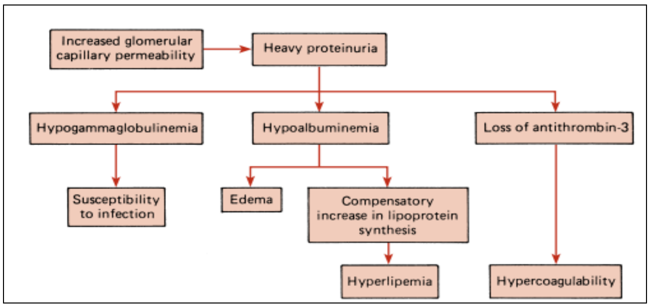


**Fig 6:** Pathophysiology of Nephrotic Syndrome [1]

### Tubular Diseases

All renal disorders proceed to some extent with tubular abnormalities when the GFR decreases. But occasionally, this component of the broader dysfunction takes center stage.Reduced urine concentrating capacity or decreased excretion/reabsorption of specific compounds are the outcomes. Renal tubular acidosis (RTA), the major tubular disease influencing acid-base balance, is the clinically most significant abnormality. Depending on the type of tubular abnormality, this disease can be divided into two categories:

- Distal RTA, a condition in which the renal tubules fail to maintain the critical pH gradient between the blood and tubular fluid.
- Proximal RTA, which causes hyperchloremic acidosis due to reduced bicarbonate reabsorption.

In general, excessively low blood levels of phosphorus and uric acid, as well as glucose and amino acids in the urine, are signs of decreased reabsorption in the proximal tubule. There may also be some proteinuria (typically 2 g/day). Acute inflammation of the tubules and adjacent interstitium can also result from methicillin hypersensitivity reactions, renal transplant rejection, analgesic medication or radiation toxicity, viral, fungal, or bacterial infections, or methicillin hypersensitivity reactions. Leukocyte casts in the urine, decreased urinary concentrating capacity, decreased metabolic acid excretion, and improper sodium balance regulation are common clinical findings in these instances [4].

### Urinary Tract Infection/Obstruction

#### 1.) Infection

The urinary bladder or the kidneys (pyelonephritis) may be the location of infection (cystitis). In either location, a microbiologic colony count of more than 105 colonies/mL is generally regarded as diagnostic for infection. The most typical aberrant laboratory findings in these situations are bacteriuria, hematuria, and pyuria (leukocytes in the urine, as demonstrated by a positive leukocyte esterase dipstick finding for some pathogens). WBC (leukocyte) casts in the urine, in particular, are thought to be a sign of pyelonephritis [4, 8].

#### 2.) Obstruction

One of two ways, renal blockages can result in illness. The intratubular pressure may progressively increase until the nephrons die and chronic renal failure develops, or they may put the urinary tract at risk for recurrent infections. There could be obstructions in either the upper or lower urinary tract. A restricting lesion below a dilated collecting duct is the defining feature of blockages in the upper tract. Remaining urine in the bladder after micturition (urination) stops indicates lower tract obstructions; symptoms include slow voiding both at the beginning and throughout urination. Neoplasms (such as prostate/bladder carcinoma or lymph node tumors compressing ureters), acquired illnesses (such as urethral strictures or renal calculi), and congenital abnormalities of the lower urinary system can all result in blockages. Reduced urine concentrating ability, impaired metabolic acid excretion, decreased GFR, and decreased renal blood flow are clinical signs of a progressing obstructive condition. Urinalysis, urine culture, BUN, serum creatinine, and CBC are laboratory tests that can help diagnose the type of obstruction. Typically, radiologic imaging methods are used to make the final diagnosis [3].

**3.) Renal Calculi**

Kidney stones, also known as renal calculi, are created when a number of crystallized compounds, which are detailed in Table 11 below, come together. The majority of these stones are calcium oxalate stones, especially in the tropics and subtropics. It is generally thought that a number of factors, primarily a decreased urine flow rate (linked to a decreased fluid intake) and saturation of the urine with significant amounts of practically insoluble chemicals, induce calculi to recur in susceptible individuals. Finding the underlying cause of the ailment often requires chemical examination of the stones. For this, specialized x-ray diffraction and infrared spectroscopy methods are frequently employed. Of course, the clinical signs are comparable to those of other obstructive processes, including hematuria, urinary tract infections, and the typical abdominal pain [4, 8].

***Renal Failure***

**Acute Renal Failure**

Acute renal failure, defined as occurring when the GFR is lowered to less than 10 mL/minute, is a sudden, severe reduction in renal function as a result of an acute toxic or hypoxic insult to the kidneys. Depending on where the precipitating defect is located, there are three different kinds of this condition. Failure of the blood supply before it reaches the kidneys is referred to as prerenal failure. Failure of the cardiovascular system and the ensuing hypovolemia are possible causes.

- Primary renal failure: The kidney is harmed. Acute tubular necrosis is the most frequent cause, however glomerulonephritis and vascular obstructions/inflammations are also involved.
- Postrenal failure: The problem is in the urinary tract after the kidneys have stopped producing urine. A lower urinary tract obstruction or bladder rupture are the two most common causes of acute renal failure.

Acute renal failure can be brought on by toxic assaults to the kidney that are severe enough to cause hemolytic transfusion responses, myoglobinuria from rhabdomyolysis, heavy metal/solvent poisonings, antifreeze consumption, and toxicities from aminoglycoside and analgesic drugs. The renal tubules are harmed immediately by these diseases. Hypoxic insults include diseases including septic/hemorrhagic shock, burns, and heart failure that severely impair renal blood flow. Oliguria and anuria (400 mL/day) are the symptoms of acute renal failure that are most frequently seen. Peripheral edema, hypertension, and congestive heart failure are caused by the extracellular fluid volume being significantly increased as a result of the decreased ability to eliminate electrolytes and water. The beginning of the uremic syndrome, or ESRD, which is characterized by elevated blood creatinine and BUN values coupled with the aforementioned symptoms, is what stands out the most. Either healing from this condition will occur, or if irreversible kidney damage occurs, it will develop to chronic renal failure [4].

**Chronic Renal Failure (Chronic Kidney Disease)**

When renal function slowly deteriorates over time, a clinical illness known as chronic kidney disease (CKD) develops (Fig 7). One in nine American adults has chronic kidney disease (CKD), and another 20 million are at risk, according to the 2007 U.S. Renal Data System (USRDS) Annual Data Report. In order to stop the development of ESRD and consequences such coronary vascular disease, early detection and treatment are required. Guidelines for earlier illness detection, treatment, and prevention have been developed by the National Kidney Foundation. The five stages of CKD are listed in Table 12. The categories are based on GFR and indications of renal injury measured by proteinuria or other indicators [9]. Chronic renal failure may result from the same causes that cause acute renal failure [1]. In Table 13, a number of additional causes for this syndrome are described.

**Increasing Incidence of Chronic Kidney Disease**

Incidence of CKD is rising in the United States as a result of rising diabetes rates, an aging population, obesity, and metabolic syndrome. The renal system may have significant repercussions from diabetes mellitus. In those with type 1 diabetes, there is a shortage of insulin. Within 15 to 20 years of diagnosis, 45 percent of people with type 1 diabetes will experience gradual decline in kidney function (diabetic nephropathy). Those who already have type 2 diabetes are less likely to develop this illness. The consequences, which are largely glomerular in nature but may also impact all kidney structures, are thought to be brought on by the persistently abnormally hyperglycemic milieu that surrounds the vascular system [4]. Diabetes typically has an impact on the kidneys by making them glucosuric, polyuric, and nocturic. These conditions are brought on by the kidneys having to work extremely hard to dilute the hyperosmotic urine. In addition, between 10 and 15 years after the first diagnosis, a moderate proteinuria (microalbuminuria) frequently appears. The following symptom is frequently hypertension, which makes the kidney damage worse. Nephrotic syndrome or chronic renal insufficiency may eventually develop, and each can be recognized by its distinctive symptoms and laboratory results. Early diabetes management that prioritizes strict blood glucose control and high blood pressure control may delay the onset of chronic renal failure. The main predictor of CDK, outside diabetes and hypertension, is age. The percentage of the population aged 65 or older is anticipated to rise from 12.4 percent in 2000 to 19.6 percent in 2030 as a result of the drop in fertility and increase in average life span, according to the U.S. Census Bureau. This ongoing increase over the past ten years and those to come has had a substantial impact on the rising prevalence of CKD. Obesity and CKD and ESRD are linked by epidemiologic research. However, given that obesity is a risk factor for both diabetes and hypertension, the two leading causes of CKD and ESRD, diabetes mellitus and hypertension have potential confounding roles. Recent research indicates that obesity itself raises the risk of kidney damage [10]. The number of nephrons does not change as a person acquires weight, but the GFR does, in order to meet the higher metabolic demands, which leads to kidney damage. At least three of the risk factors listed below must be present in order for there to be a metabolic syndrome:

- Abdominal obesity
- High blood pressure,
- low levels of HDL cholesterol,
- hypertriglyceridemia,
- or hyperglycemia.

In a population study using a representative sample of the general American population, the probability of CKD and microalbuminuria gradually rose with the presence of more metabolic syndrome risk factors [11]. When compared to people without metabolic syndrome, those with it had a 2.6-fold higher chance of getting CKD [11]. The risk of CDK may be decreased by interventions that focus on the biochemical elements of metabolic syndrome [1].
[Fig 7].

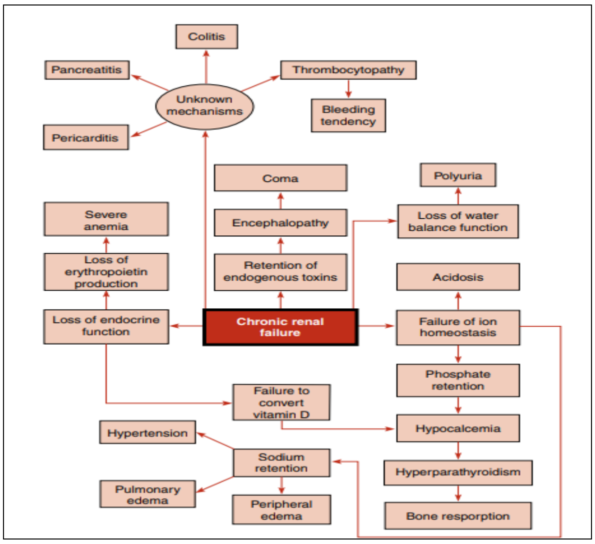


**Fig 7:** Pathophysiology of Chronic Kidney Disease [1]

## Renal Hypertension

Reduced perfusion to the entire or a portion of the kidney can be the cause of hypertension brought on by renal illness (ischemia). Traumatic injury, artery narrowing, or narrowing of the intrarenal arterioles can all lead to a lack of perfusion. Nephron dysfunction and eventual necrosis are the results of chronic ischemia in any form. The renin-angiotensin-aldosterone system is activated as a result of the alterations in blood and body fluid volumes within the kidney, leading in vasoconstriction and chronic hypertension. Serum aldosterone, Na+, and renin levels can be monitored to assess renal hypertension. Aldosterone will increase serum Na+, decrease serum K+, and increase urine K+ as a result of its impact. Treatment for Urgent Renal Failure Dialysis Uremic symptoms, uncontrolled hyperkalemia, and acidosis have historically been signs of acute renal failure in patients, indicating the need for dialysis as a substitute for the kidneys' inability to eliminate waste products from the body. However, dialysis is frequently started earlier than this. There are several types of dialysis, but they all utilize a semipermeable membrane encircled by a dialysate solution. Traditional hemodialysis uses a synthetic membrane that is external to the body to remove waste from blood. High rates of pumping (150–250 mL/min for arterial blood and 500 mL/min for dialysate, respectively) are utilized. The dialysate is discarded and the blood is put back into the venous circulation. This procedure favors the diffusion of low-molecular-weight solutes (< 500 Da) into the dialysate, but it is insufficient for clearing mid-molecular-weight solutes (500-2000 Da). The rate of creatinine clearance is 150–160 mL/min. The peritoneal wall serves as the dialysate membrane in peritoneal dialysis, and gravity is employed to introduce and remove the dialysate. There are two varieties of this type: continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis. In all cases, the process is ongoing and is carried out around-the-clock, seven days a week. This approach is less strict than the conventional approach. In comparison to the conventional approach, small solutes (such as potassium) have much reduced clearance rates; however, more big solutes are cleared, and steady-state levels of blood analytes are preserved. The slow continuous renal replacement therapies were created to treat acute renal failure in critically ill patients in intensive care settings. They include continuous venovenous hemofiltration, continuous arteriovenous hemofiltration (ultrafiltration of blood), continuous venovenous hemofiltration, and continuous venovenous hemodialysis. The semipermeable barrier is once more outside the body when using these techniques. The first two techniques filter water and solutes up to 5000 Da (the pore size of the membranes) from the blood slowly (10 mL/min) and continuously, with no impact on plasma osmolality. Parenteral feeding and intravenous medicines are two ways to replace volume loss. The last two techniques are comparable to filtration techniques, but instead of filtering the dialysis fluid through the membrane, they continuously diffuse it, tripling the amount of urea clearance [1].

## Therapy of End-Stage Renal Disease

The only two treatment choices for patients with irreversible renal failure are dialysis and transplantation. When the GFR drops to 5 mL/min (10-15 mL/min in individuals with diabetic nephropathy), either treatment is started.

## Dialysis

The options include peritoneal dialysis, high-efficiency hemodialysis, or traditional hemodialysis. A hemodialysis facility's clinical laboratory must be able to effectively assess procedural efficiency over a broad spectrum of domains. Basic objectives of renal dialysis should be evaluated by certain laboratory tests, which should be carried out [1].

## Transplantation

Only 10–12 percent of the small solute clearance of two healthy kidneys is achieved by the most effective hemodialysis procedures, and the removal of bigger solutes is far less. Even well-dialyzed patients can experience physical limitations and a decline in quality of life. The best opportunity for a complete recovery and return to a healthy, active life is through kidney transplantation. The severe lack of organ donors places restrictions on this approach. Patients with ESRD may have to wait anything from a few months to many years for an organ donation. A recipient with irreversible renal failure receives a kidney transplant from a compatible donor. The organ may come from a live person or a cadaver (80 percent and 20 percent, respectively, of all kidney transplants in the United States). The body's immunological reaction to the transplanted organ must be controlled for this treatment to be successful. As a result, the donor and recipient are thoroughly examined for their ABO blood group, HLA compatibility, and presence of HLA antibodies. The main barrier to transplantation is the HLA system. Despite the fact that kidney transplants can last for many years, the average half-life of a cadaveric transplant is about seven years. In comparison to hemodialysis, the mortality rate is not considerably different. Between 65 to 85 percent of three-year transplants survive, with live grafts performing better. Hemodialysis, CAPD, and cadaveric kidney transplantation have all been shown to have the same patient survival rates. Compared to other ESRD treatment options, live related-donor transplantation is associated with a higher patient survival rate [1].

**Antiretroviral Drug-Induced Nephrotoxicity**

Although ART-associated nephrotoxicity is rare, it is anticipated that it will become more common as HIV-infected people' life expectancies rise and comorbidities become more common. The main causes of renal toxicity from antiretroviral medications include mitochondrial toxicity, vascular lesions, crystal precipitation at the tubular level, and functional abnormalities of transport proteins in epithelial cells of the proximal convoluted tubule. Protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs), particularly tenofovir (TDF), are the medications most commonly involved in kidney damage (PIs). Although this clinical effect is debatable, some PIs, including atazanavir (ATV) and lopinavir (LPV), have been linked to a higher risk of a decline in the eGFR. This interaction between ritonavir (RTV) and TDF when taken at the same time may be the cause of this clinical effect [12, 13, 14, 15, 16, 17, 18]. When it comes to NRTIs, TDF is the primary medication that causes nephrotoxicity, and its excretion is handled by the actions of transport proteins, which assist in removing the medication to the tubular lumen so it can be seen in the urine. By blocking these proteins, nephrotoxicity and drug accumulation in renal tubular cells may be facilitated [19, 20].

TDF poisoning has the potential to proceed to CKD by causing proximal tubular dysfunction and acute tubular necrosis. Phosphaturia, glucosuria with normoglycemia, renal tubular acidosis with a normal anion gap, aminoaciduria, tubular proteinuria, and medium-term renal failure are all symptoms of proximal tubular dysfunction, also known as Fanconi's syndrome. Phosphoruria, metabolic acidosis, and glucosuria are the early symptoms. When the medicine is stopped, TDF toxicity is typically reversible, however recovery might not be complete [21]. Renal toxicity in PIs (mostly indinavir [IDV] and ATV) is brought on by the medicines' low solubility in urine under specific pH circumstances, which results in crystalluria and tubular blockage. IDV, which is currently only very seldom used, is more likely to cause crystal-induced toxicity because it is soluble in acidic urine but comparatively insoluble in alkaline urine, the latter of which favors the formation of crystals [22]. Crystal precipitation in urine has also been recorded with darunavir (DRV) [23]. Some brand-new antiretroviral medications block the active tubular production of creatinine. Rilpivirine (RPV), dolutegravir (DTG), and the pharmacokinetic enhancer cobicistat (COBI) have all been linked to interactions with creatinine transport [24, 25]. According to Moss and Koteff, RPV and DTG mostly inhibit the renal organic cation transporter type 2 (OCT2) [24, 25], whereas COBI primarily inhibits the multidrug and toxin extrusion protein transporter type 1 (MATE1) [26]. The eGFR may drop as a result of this interaction with the transporters involved in the tubular secretion of creatinine, even if there may be only small increases in serum creatinine [25, 27]. Although there haven't been any indications in the majority of clinical trials conducted to date that the co-administration of these drugs significantly raises the risk of developing tubular toxicity with TDF, the information on the renal safety of these combinations is still scarce, and there might be variations between the various drugs. Tenofovir, emtricitabine, cobicistat, and elvitegravir (TDF/FTC/COBI/EVG) and tenofovir, emtricitabine, atazanavir, and ritonavir (TDF/FTC/ATV/r) patients in the TDF/FTC/COBI/EVG group (n=701) and two patients in the comparison group (n=355) who received In the first 48 weeks, there were 7 discontinuations in the TDF/FTC/COBI/ EVG group and 1 in the TDF/FTC/ATV/r group [28, 29].

Similar to prior reports of TDF, the renal toxicity profile seen with TDF/FTC/COBI/EVG predominantly comprised of proximal tubulopathy, which is typically curable with medication discontinuation. Two of the four patients with Fanconi's syndrome in trial GS-236-0103 (estimated creatinine clearance [CrCl] 70 ml/min) had a baseline renal function abnormality [28, 29].

**Non-antiretroviral drug-induced nephrotoxicity**

Other potentially nephrotoxic medications may be administered to HIV-infected patients at some time over the course of their condition's clinical manifestations. Direct nephrotoxicity, which must be avoided in patients with renal failure or for which a dose adjustment is necessary (iodinated contrasts, aminoglycosides, amphotericin B, vancomycin, pentamidine, foscarnet), hemodynamic mechanisms (NSAIDs or angiotensin-converting enzyme inhibitors [ACE inhibitors]/angiotensin receptor blockers [ARBs] in certain situations such as decreased GFR), and crystalluria are The list of non-antiretroviral drugs that may be nephrotoxic is summarized in Table 14 along with the mechanism of kidney injury. In some clinical circumstances, the administration of ACE inhibitors or ARBs may be linked to renal decline. On the other hand, these medications are especially helpful for treating high blood pressure or cases of proteinuria. Additionally, NSAIDs may worsen hemodynamics in individuals with impaired renal function if they are taken for extended periods of time, in conjunction with other medications that may affect glomerular hemodynamics, or with potentially nephrotoxic medications like TDF. In individuals with normal renal function who do not also take medications that affect glomerular hemodynamics, NSAIDs may be given if they are absolutely essential and only for brief periods of time. When administered to patients with renal failure, these medications must be administered with extreme caution, their dosages must be carefully regulated, and the development of renal function must be properly watched [30].

## The Most Common Renal Diseases in HIV-infected Patients

HIV-positive individuals may experience a variety of glomerular, vascular, tubulointerstitial, and obstructive nephropathies as a result of the virus itself, medications taken, and/or coinfection.

### Glomerular and vascular nephropathies

The range of glomerular pathology in HIV-positive patients depends on race, the way the virus is managed, and whether or not other infections, such HCV, are present or not. This has undoubtedly changed in recent years as evidenced by the observation of a higher prevalence of classic focal and segmental hyalinosis and a lower incidence of HIVAN, both of which are linked to older age and a greater number of CVR variables [31].

### HIV-associated nephropathy

The most well-known form of glomerular involvement is this one. Compared to Caucasian patients, Black patients experience it far more frequently (12:1) [32]. Although the earliest reports linked the development of HIVAN to severe stages of the HIV infection, it can also happen in patients who are asymptomatic. High proteinuria, which often exceeds 2-3g/24 hours and frequently reaches nephrotic range (>3.5g/24 hours), is the primary symptom of HIVAN [32]. Despite this, patients with patients with other causes of nephrotic syndrome experience proteinuria with less clinical consequence (edema, hypoalbuminemia, and hyperlipidemia). Although minor microhematuria and leukocyturia are often seen in patients, the urine sediment is generally unremarkable. Although HBP is frequently present in Black individuals with renal disorders, it is not usually accompanied by the HIVAN nephrotic syndrome. The size of the kidneys is normal or even expanded during ultrasound testing, and there is a distinct and recognizable hyperechogenicity. Without ART, HIVAN has an unfavorable clinical outcome, with a high death rate, rapid development of renal failure necessitating dialysis within the first year of diagnosis, and rapid development of renal failure [30]. Clinical course has improved after the introduction of combination ART [31]. Collapsing localized glomerulosclerosis with extensive tubulointerstitial involvement and dilated renal tubules, which occasionally produce real pseudocysts, is its histological substrate64. Immunoglobin M (IgM) and C3 deposits are typically non-specifically detected in renal immunofluorescence. The absence of immune complex deposits is crucial for the differential diagnosis. Regarding the pathophysiology, it is believed that HIV itself directly contributes to the development of glomerular cell abnormalities65. Along with this, the relationship between HIVAN and the Black population is explained by a recently discovered genetic mutation (locus MYH9-APOL1), which is particularly prevalent in African Americans [33]. ART appears to lower the risk of developing HIVAN and improve the prognosis of patients who have already experienced this nephropathy, according to observational study data [31, 34, 35, 36]. Despite the lack of controlled. blocking the renin-angiotensin system with ACE inhibitors or ARBs causes an antiproteinuric and renoprotective effect in HIVAN patients that is comparable to that seen in other nephropathies and may prevent the progression of renal failure [37]. In HIVAN patients receiving steroids, certain studies have indicated a reduction in proteinuria and a propensity to halt the progression of renal impairment. However, steroid therapy may result in significant and common side effects, especially in patients with severely compromised immune systems [30].

ART, ACE inhibitors or ARBs, and glucocorticoids are used to treat HIVAN. If there is proteinuria or high blood pressure, ACE inhibitors or ARBs are advised [37]. Although several small clinical trials have demonstrated their usefulness, corticosteroids are not regularly used in these individuals, and they must only be offered to patients who have worsening renal failure despite the use of ART, an ARB, or an ACE inhibitor [30]. The biopsy's histology may reveal details regarding parameters that call for steroid treatment. In the case of crescents, this is demonstrated [30].

### Immune complex-mediated glomerulonephritis

Other glomerulonephritis (GN), whose pathophysiology is typically related to glomerular immune complex deposits, as well as HIVAN, are more common in HIV-infected patients. In contrast to HIVAN, immune complex-induced GN is not more common in the Caucasian population than the Black population, and cases of this glomerulonephritis have primarily been reported in European nations [30, 38]. These individuals' renal histology was incredibly diverse and included proliferative (10%–80%), lupus-like, and mixed proliferative and sclerotic forms. They can also be connected to other coinfections, such as those brought on by HBV or HCV, which can be linked to a wide range of renal disorders, including membranoproliferative GN with cryoglobulinemia or membranous nephropathy. One of the most frequent immune complex-mediated nephropathies in HIV-infected patients in Europe is immunoglobulin (IgA) nephropathy (IgA deposit-induced mesangial GN). Immune complex-mediated GN typically has extremely obvious clinical indications (macroscopic hematuria, edema, ARF, severe HBP), however there are also instances of less obvious manifestations that are discovered by accident (for example, non-nephrotic proteinuria, microhematuria or slowly progressive deterioration of renal function). In some cases of membranoproliferative GN, purpura, digestive symptoms, and even alveolar hemorrhage are clinically evident extrarenal signs of cryoglobulinemia.

These patients may develop ARF with hematuria and proteinuria, and a renal biopsy reveals cryoglobulin deposits in the lumens of glomerular capillaries in addition to the usual lesions of membranoproliferative GN. Typically, HCV-related cryoglobulins are mixed (IgG-IgM). In the majority of cases, circulating cryoglobulins are found associated with elevated rheumatoid factor and reduced complement, notably C4. This clinical-serological picture closely resembles patients without HIV infection who have membranoproliferative GN associated with HCV. These are thought to be GN pathogenically generated by HCV, without concomitant HIV playing a significant pathogenic role [39, 40]. Although clinical presentation may help us determine the kind of GN (Table 15), a renal biopsy may occasionally be necessary for a conclusive diagnosis. The need for a biopsy must always be determined on an individual basis, taking into account both the procedure's risk and potential clinical advantages for the patient. There is a dearth of information on the management of immune complex-mediated GN in HIV-positive patients. There is still very little knowledge of the natural history, and it is unknown whether treatments performed on patients who do not have HIV can change it (steroids, immunosuppressants, calcineurin inhibitors). It is mostly unknown how interferon (IFN) and ribavirin therapy affects the clinical progression of HCV-associated nephropathies in HIV-infected patients. Therapeutic suggestions are based on knowledge gained from treating patients with monoinfection who have membranoproliferative GN associated with HCV. There are numerous instances when an effective antiviral treatment (long-term clearance of HCV ribonucleic acid [RNA] in plasma) was followed by a reduction in renal symptoms [40, 41]. Cryoglobulinemia, however, may last for extended periods of time after the RNA of HCV has been cleared from the plasma and may remain asymptomatic. Rituximab, an anti-CD20 monoclonal antibody, has improved renal symptoms in patients with membranoproliferative GN who were monoinfected with HCV but lacked virological control of the virus [41].

**Diabetic nephropathy and hypertensive nephropathy**

End-stage renal disease brought on by diabetic nephropathy and hypertensive nephroangiosclerosis has become more common in the general population over the past 20 years, accounting for 70% of all end-stage renal disease diagnoses. The metabolic side effects of ART (dyslipidemia, changes in body composition, insulin resistance, and diabetes) as well as the aging of the infected population raise the possibility that kidney impairment brought on by DM and HBP may become more significant in HIV-infected patients [42]. Diabetes nephropathy has been documented in some series of renal biopsies of HIV-infected patients in 6% of cases and hypertension nephropathy with nephroangiosclerosis in 4% of instances [43, 44]. A rising incidence of diabetic nephropathy and hypertensive nephropathy is anticipated in HIV-infected patients over the coming years due to the high prevalence of albuminuria (an established predictor of cardiovascular disease [CVD] and renal disease) in these patients and the close association between the amount of albuminuria and traditional CVR factors like insulin resistance and HBP82 [30].

**Thrombotic microangiopathy**

HIV-infected patients are more likely than the general population to develop thrombotic microangiopathy (TMA), which can impact the kidneys and/or the nervous system [37, 45]. Since TMA commonly manifests in HIV-infected test animals and a number of HIV proteins have been shown to directly damage endothelial cells and induce apoptosis84, we hypothesize that HIV may play a significant role in TMA-associated endothelial damage87. The prognosis is grim and the clinical course is aggressive. Similar symptoms are seen in TMA cases in patients who do not have HIV [30, 37, 45]. The majority of patients are young and male, and the hematological symptoms that characterize TMA include thrombocytopenia, elevated lactate dehydrogenase (LDH), reduced haptoglobin, and anemia with schistocytes in peripheral blood. Although hemolytic-uremic syndrome symptoms and a distinct and rapidly worsening decline in renal function are present in the majority of cases, there may also be significant neurological manifestations, as in thrombotic thrombocytopenic purpura. If there are no concurrent glomerular processes, deteriorating renal function may show as increasing oligoanuria with modest proteinuria and moderate urogenital problems. Contrarily, in some instances, macroscopic hematuria and nephrotic-range proteinuria can be seen. Similar changes to those of idiopathic TMA can be seen in the renal biopsy. Renal failure is usually permanent, and mortality is very high. The recommended treatments for hemolytic-uremic syndrome are plasmapheresis, the administration of fresh plasma, and more recently eculizumab, a particular inhibitor of the complement attack complex. However, there is no information on the effectiveness of these therapies in TMA caused by HIV infection [30].

**Malignant hypertension**

Very high blood pressure (BP) readings coupled with grade III or IV hypertensive retinopathy are referred to as malignant hypertension. It has been linked to a number of glomerular disorders in HIV-infected patients, including IgA-induced nephropathy, membranoproliferative GN, membranous nephropathy, and focal glomerulosclerosis, according to reports by Gerntholtz and Morales [46, 47]. It is commonly recognized that TMA and hypertensive emergencies are related. Hypertensive emergency may accompany TMA, and TMA may be brought on by hypertensive emergency. Renin-angiotensin system blockers (ACE inhibitors or ARBs) are introduced early and in high dosages, allowing for a reduction in the ARF that is present in the majority of hypertensive emergency patients [48]. The prognosis of a hypertensive emergency related to HIV infection is far worse, though.

**Tubular and interstitial nephropathies**

Patients with HIV may experience a wide range of tubular and interstitial nephropathies. The following paragraphs provide descriptions of the main forms.

**Acute tubular necrosis**

Acute tubular necrosis may arise in many cases of prerenal ARF related to coexisting illnesses when the underlying cause is not promptly and appropriately treated. Likewise, people with HIV infection may develop tubular necrosis as a result of the intrinsic tubular nephrotoxicity of some drugs and radiographic iodinated contrasts. Depending on the severity of the damage, recovery can take days or even weeks, albeit it is not always successful. When a patient is septic and/or hemodynamically unstable, when there is progressive ARF, normally (but not always) with diuresis maintained, or when any of the medications that could be involved, such as iodinated contrast or NSAIDs, angiotensin receptor blockers, aminoglycosides, trimethoprim-sulfamethoxazole, pentamidine, amphotericin B, foscarnet, cidof [30].

**Drug-induced tubular nephropathies**

The most well-known clinical manifestation of the malfunction and destruction to the proximal tubular cells of the kidney is Fanconi's syndrome. The most severe form is distinguished by an overall deficit in reabsorption in the proximal tubule, favoring urine loss of substances including phosphate, calcium, urate, amino acids, glucose, and bicarbonate, among others. This can manifest as disproportionate levels of phosphaturia and uricosuria, the emergence of hypophosphatemia and hypouricemia, aminoaciduria, glucosuria despite normoglycemia, type II renal tubular acidosis (metabolic acidosis with normal anion gap), tubular proteinuria (typically less than 2g/day), hypokalemia, and polyuria and polydipsia because of the inability to concentrate urine. When structural damage and apoptosis occur in the proximal tubular cell in addition to functional damage, there is tubular necrosis and renal failure, which, if it lasts for an extended period of time due to the original damage being maintained, may develop into chronic renal failure. However, the symptoms of the condition typically only manifest partially, primarily as fluctuating hypophosphatemia, normoglycemic glucosuria, and proteinuria. Fanconi's syndrome can have two primary types of causes: congenital, which manifests in infancy, and acquired, which manifests primarily in adulthood and is linked to paraproteinemias, tubulointerstitial disorders, medications, or toxic substances (Table 16). 84 percent of patients with HIV, who have Fanconi's syndrome most frequently associated with TDF, were taking PIs at the same time, frequently supplemented with RTV92. Additionally, several haplotypes of the genes ABCC2 (MRP2) and ABCC4 (MRP4), which encode TDF transport proteins in proximal renal tubule cells, have been linked to an increased risk of nephrotoxicity when using this medication [49, 50, 51].

**Immunoallergic interstitial nephritis**

Some medications may also result in ARF due to an immunoallergic reaction that manifests as a diffuse interstitial infiltration enriched in eosinophils, in addition to direct tubular injury. In patients with ARF whose cause is unclear, the presence of peripheral eosinophilia, skin rash, and fever must suggest this diagnosis, especially when non-nephrotic proteinuria, leukocyturia, and leukocyte casts are present, there is no urinary infection, and when a new treatment has just been introduced [52]. The only way to make a diagnosis is by a kidney biopsy, albeit older patients or those with serious comorbid conditions frequently choose empirical treatment instead [52]. The mainstay of treatment is the swift discontinuation of the offending substance. Additionally, a brief course of steroids (between 4 and 6 weeks) favors the full restoration of renal function [53]. Immunoallergic nephritis is most frequently brought on by NSAIDs and antibiotics, however it can be brought on by any medication, including antiretroviral medications [54].

**Crystal deposition-induced intrarenal obstructive nephropathy**

After receiving therapy with medications that are poorly soluble in urine, especially at high doses and at certain pH levels, there is a mass accumulation of crystals and a potential obstruction in the tubules [23]. Patients with HIV may be given high dosages of sulfadiazine, IDV, ATV, foscarnet, and acyclovir. IDV and ATV have both been linked to nephrolithiasis as a result of a buildup of the ejected crystals. Although patients receiving DRV111 have been recognized to have crystalluria, there have not yet been any recorded instances of obstructive nephropathy brought on by crystal deposition in individuals receiving this PI. Although this issue is typically treatable with enough hydration, the inflammatory response brought on by the crystals themselves may result in variable degrees of long-lasting chronic tubulointerstitial damage [30].

**Rhabdomyolysis**

HIV-positive individuals frequently have acute muscle injury from drug use, ischemia leading to compartment syndrome, sepsis, or water and electrolyte imbalances. Characteristic ARF symptoms include dark urine, a sharp rise in muscle enzymes, renal tubular blockage and necrosis caused by myoglobin casts, and myoglobin secreted and filtered in the glomerulus.

***Non-specific chronic renal failure***

A high incidence of CKD, marked by GFR decreases of varying severity without being accompanied by significant proteinuria or sediment abnormalities that are suggestive of glomerular disease, has recently been reported in HIV-infected patients in addition to glomerular and tubulointerstitial processes, whose clinical manifestations are typically very obvious. The cause of CKD in these patients is likely multifactorial; in some, it may be the result of prior ARF episodes that have not fully resolved, and in others, it may be the result of certain treatments that were continued for years, such as some antiretroviral medications, which have nephrotoxic side effects. According to De Francisco, the clinical-laboratory profile of this type of CKD in HIV-positive patients is very similar to that of "silent" or "occult" CKD, which has a high incidence in elderly patients but is otherwise normal, with rates ranging from 10% to 33% in those over the age of 70. This "occult CKD epidemic" in the general population has been linked to long-term conditions (HBP, DM) and renal alterations brought on by aging. These elements might affect HIV-positive people at a younger age through as-yet-unidentified processes [55]. It is interesting to note that this significant CKD prevalence has also been documented in HIV-infected patient groups who have not received ART, without HBP or DM giving adequate explanations [56].

**Conclusion**

The kidney plays a central role in maintaining the body's overall health by regulating essential physiological processes. Its primary functions include filtering blood, removing waste products, balancing electrolytes, and regulating fluid levels, all of which are crucial for homeostasis. Beyond filtration, the kidney is also integral in producing hormones that control blood pressure, support bone health, and stimulate red blood cell production. Renal function, therefore, is vital not only for waste elimination but also for broader systemic balance and cellular function. Any impairment in kidney function can lead to significant health issues, including hypertension, metabolic imbalances, and chronic kidney disease. Understanding the intricacies of renal physiology highlights the importance of early detection and management of kidney-related health issues. With advancements in medical science, treatment options continue to improve, underscoring the critical role of kidney health in promoting overall well-being and quality of life.

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