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Review article

Understanding Kidney Health: Physiology, Diagnostic Markers, and Pathological Conditions

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Abstract

The kidney is a vital organ responsible for several essential functions, including waste elimination, fluid and electrolyte balance, blood pressure regulation, and hormone production. Structurally, it consists of the cortex and medulla, with nephrons as the fundamental functional units responsible for plasma filtration and homeostasis maintenance. The kidney plays a crucial role in metabolic processes, with glomerular filtration rate (GFR) as a key indicator of renal function. Various biochemical markers, such as blood urea nitrogen (BUN), creatinine, uric acid, sodium, and potassium, are used to assess kidney health and diagnose potential disorders. Kidney stone formation, a common disorder, results from the supersaturation of minerals in urine, leading to different types of calculi such as calcium oxalate, uric acid, and struvite stones. Advanced diagnostic techniques, including imaging and biochemical assays, aid in assessing kidney health and guiding treatment strategies. Understanding kidney physiology and pathology is crucial for the early detection, management, and prevention of renal diseases.

Keywords: Nephrons, GFR, BUN, creatinine, Kidney stone.

1. INTRODUCTION

The kidney performs several major functions: it eliminates toxins created by cellular or xenobiotic metabolism and regulates the homeostasis of the internal environment. The kidney also plays a hormonal role through the production of calcitriol, renin, and erythropoietin. Plasma filtration and reabsorption/secretion mechanisms, which occur in the various parts of the kidney's functional unit known as the nephron, are necessary for maintaining the body's homeostasis (hydric, ionic [sodium, potassium, calcium, phosphorus, etc.], or acid-base balance) (1).

2. KIDNEY ANATOMY

The kidney is composed of two regions: the cortex and the medulla. The cortex is composed of renal corpuscles, convoluted tubules, straight tubules, collecting tubules, collecting ducts, and vasculature. The medulla extends into the cortex through medullary rays, which are made up of collecting ducts and straight tubules. The medulla also contains the vasa recta, a network of capillaries integral to the countercurrent exchange system (2).

The kidney's functioning units are called nephrons. Each adult kidney contains about 2 million nephrons. The nephron consists of glomeruli, renal tubules (proximal tubules, loop of Henle, distal tubules, connecting segment, collecting ducts), interstitium, and juxtaglomerular apparatus (JGA).

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The glomerulus, which exists in the Bowman's capsule, is the first part of the nephron that filters plasma (3). An afferent arteriole supplies a network of capillary loops termed the glomerulus, which is surrounded by a double-layered epithelium, Bowman's capsule, to collectively form a renal corpuscle. An efferent arteriole becomes the vasa recta, which supplies the renal tubules after draining the glomerulus. The following are located in order distal to Bowman's capsule: the collecting tubule, cortical collecting duct, medullary collecting duct, papillary duct, minor calyx, major calyx, renal pelvis, ureter, proximal convoluted tubule, proximal straight tubule or thick descending limb of the loop of Henle, thin descending limb of the loop of Henle, thin ascending limb of the loop of Henle, distal straight tubule or think ascending limb of the loop of Henle, distal convoluted tubule, and renal pelvis. The tubules start in the cortex, rise toward the cortex close to their original renal corpuscle, descend into the medulla, and make a hairpin bend in the loop of Henle's thin limb (4)(5).

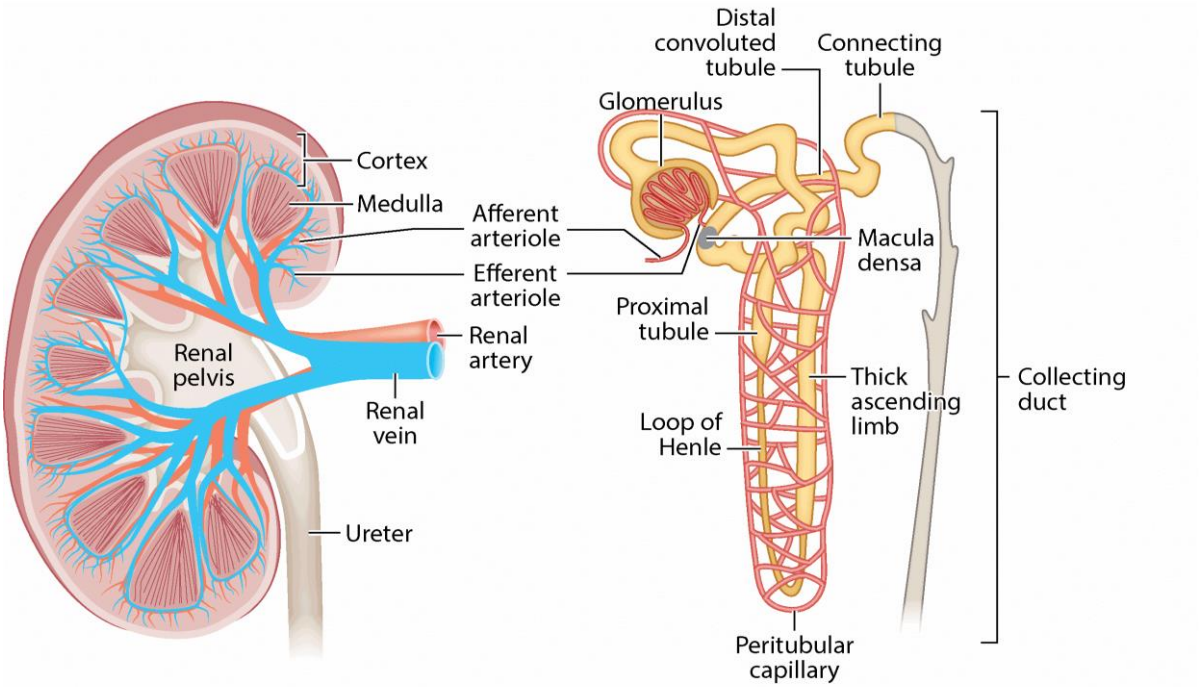


Figure (1): Structural anatomy of the kidney (6).

3. KIDNEY FUNCTION

The kidneys' main roles include: (1) maintaining and controlling the body's fluid and electrolyte levels; (2) maintaining the volume of extracellular fluid; (3) endocrine processes, including hormone production; (4) controlling blood pressure and pH; (5) eliminating waste products from metabolism; and (6) metabolic activities. About 10% of oxygen consumption takes place in the kidneys, and optimal kidney function is affected by adequate blood flow and perfusion. Measurement of kidney function is determined by glomerular filtration rate (GFR), which varies across species and pathologies in afferent and efferent arterioles (eg, drug-induced vasoconstriction) can affect GFR (7).

Kidney glomeruli are primarily responsible for filtering low-molecular-weight plasma waste

products into the urine while obstructing the passage of larger macromolecules, such as albumin, which are essential for maintaining good homeostasis. The glomerulus consists of a capillary tuft inside the Bowman's capsule, which is the nephron's most proximal portion. The tubular system that opens into the kidney medullary calyx is the glomerulus' distal portion. The glomerular filter residing in the capillary wall consists of three quite distinct layers: a fenestrated endothelium, a glomerular basement membrane (GBM), and a slit diaphragm located between the interdigitating foot processes of the epithelial podocytes (Figure 2).

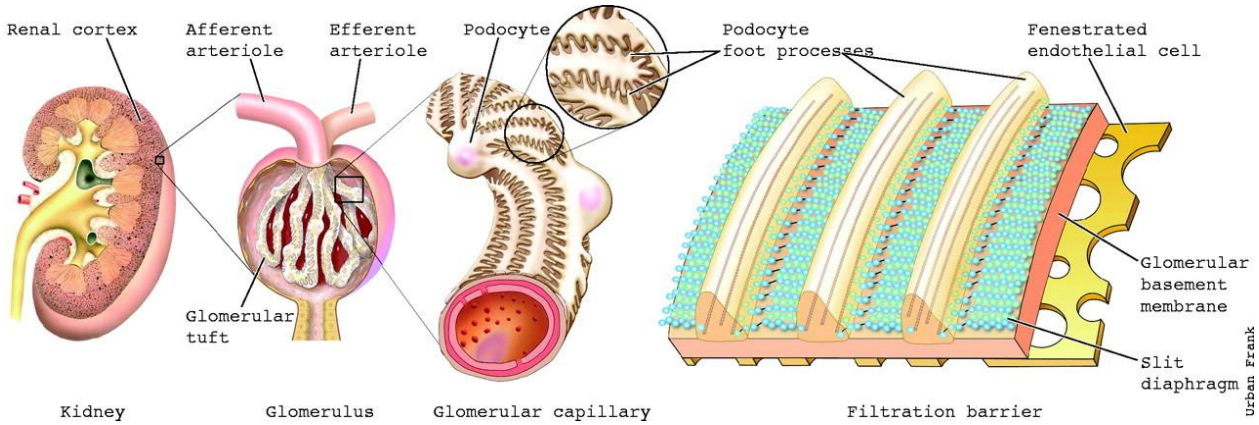


Figure (2): **Renal glomerular filtration system**, each human kidney has around one million glomeruli. The glomerular filter is made up of the walls of the capillaries (glomerular tuft) that an afferent arteriole branches into. While infiltrating blood is returned to the bloodstream, the primary urine, known as plasma filtrate, is guided to the proximal tubules. The filtration barrier contains fenestrated endothelial cells, the glomerular basement membrane (GBM), and podocytes with their interdigitating foot processes. The slit diaphragm is a porous filter construction with a uniform width that contains specific components (8).

4. KIDNEY FUNCTION TESTS

a) UREA

Urea, commonly referred to as blood urea nitrogen (BUN) when measured in the blood, is a product of protein metabolism. BUN is classified as an NPN (non-protein nitrogenous) waste product. Ammonia is created through the deamination of amino acids obtained from the breakdown of protein. After that, liver enzymes transform ammonia into urea. Therefore, the amount of protein consumed, the body's ability to catabolize protein, and the renal system's ability to adequately excrete urea all affect the concentration of urea.

Five enzymatic processes make up the urea cycle: the mitochondria host the first two, while the cytosol hosts the remaining ones. Other proteins, such as glutaminase, glutamate dehydrogenase, N-acetyl glutamate synthetase, mitochondrial aspartate/glutamate transporter, and mitochondrial ornithine/citrulline transporter, contribute to the pathway's efficient functioning in vivo in addition to the five enzymes mentioned above.

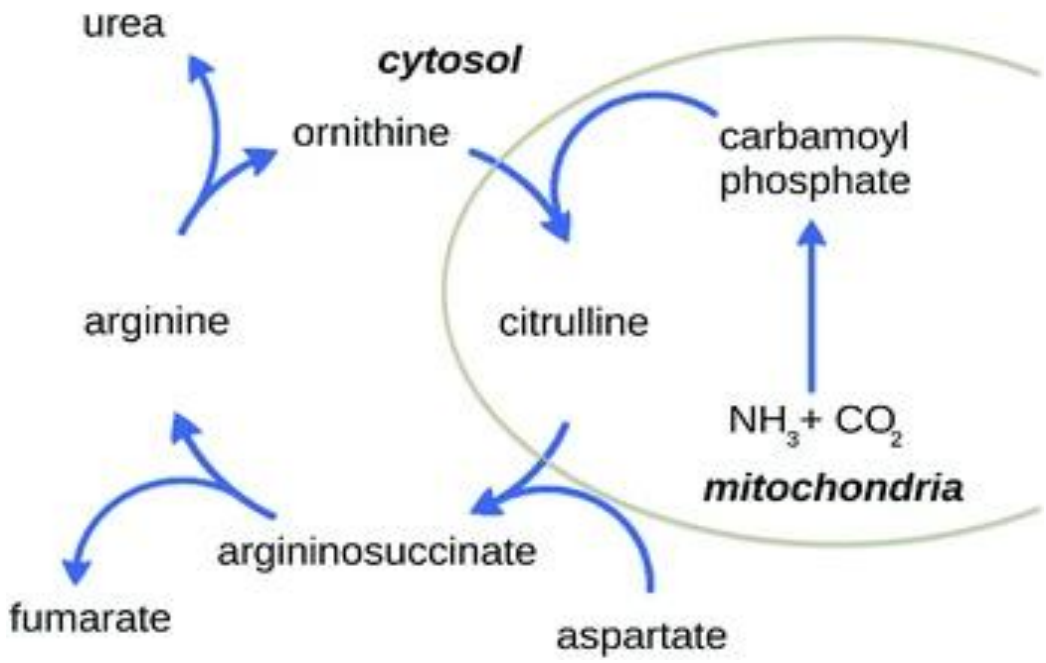


Figure (3): The urea cycle (11).

Urea nitrogen levels in blood or serum typically range between 5 and 20 mg/dl, or 1.8 and 7.1 mmol urea per liter. The range is wide because of typical variations caused by dietary protein intake, endogenous protein catabolism, hydration status, hepatic urea synthesis, and renal urea excretion. Over time, a variety of BUN analysis techniques have been developed. The majority of those currently in use are automated and produce results that are reproducible and clinically reliable.

Urea nitrogen can be measured using two general techniques. Photometry measures the yellow chromogen that is produced by the diacetyl, or Fearon, reaction with urea. It has been modified for use in auto analyzers and generally gives relatively accurate results. However, its specificity is still limited, as demonstrated by colorimetric interference from hemoglobin when whole blood is used and by misleading rises with sulfonylurea drugs (9-11).

The more specialized enzymatic techniques use the urease enzyme, which breaks down urea into carbonic acid and ammonia. These products are measured in a number of ways, some of which are automated, and are proportionate to the amount of urea present in the sample. One technique measures the drop in absorbance at 340 mm following the reaction of alpha-ketoglutaric acid with ammonia. The Astra system measures the rate of increase in conductivity of the solution in which urea is hydrolyzed.

The name BUN is still used by convention, despite the fact that the test is now performed mainly on serum. Because sodium fluoride inhibits urease, the specimen shouldn't be collected in tubes containing fluoride. Additionally, it has been noted that guanethidine and chloral hydrate raise BUN levels (9-11).

b) CREATININE

Creatinine, also a NPN waste product, is produced from the breakdown of creatine and phosphocreatine and can also serve as an indicator of renal function. Creatine is synthesized in the liver, pancreas, and

kidneys from the transamination of the amino acids arginine, glycine, and methionine. Following its circulation throughout the body, creatine undergoes phosphorylation in the brain and skeletal muscle to become phosphocreatine. The majority of the creatinine is produced in the muscles. Consequently, the patient's muscle mass affects the plasma creatinine concentration. Compared to BUN, creatinine is less affected by diet and more suitable as an indicator of renal function.

The normal serum creatinine (sCr) varies depending on the measurement method and the subject's body muscle mass. For the adult male, the normal range is 0.6 to 1.2 mg/dl, or 53 to 106 µmol/L by the kinetic or enzymatic method, and 0.8 to 1.5 mg/dl, or 70 to 133 µmol/L by the older manual Jaffé reaction. According to the enzymatic technique, the normal range for an adult female's typical lower muscle mass is 0.5 to 1.1 mg/dl, or 44 to 97 µmol/L.

To determine drug levels and diagnostic chemicals in urine samples, as well as to evaluate kidney function, a reliable creatinine measurement is required. The Jaffe principle of alkaline creatinine-picric acid complex color synthesis is the basis of the most widely utilized techniques. However, Jaffe creatinine values may be impacted by other substances that are frequently present in serum and urine. To eliminate or account for these interfering chemicals, numerous laboratories have modified the basic procedure. This appendix will summarize the basic Jaffe method, as well as a modified, automated version. A high-performance liquid chromatography (HPLC) technique that isolates creatinine from contaminants before direct UV absorption quantification is also described. Finally, a method for accurately quantifying creatinine in any sample using stable isotope dilution is given for liquid chromatography-tandem mass spectrometry (LC-MS/MS). Experts in the field advise using this last strategy to standardize all quantitative creatinine methods against an accepted reference (9,10,12).

c) URIC ACID

It is a weak organic acid that under physiologic conditions exists mainly as a monosodium salt, produced mostly in the liver, is the end product of dietary and endogenous purine metabolism. Glycidic metabolism produces ribose-5-phosphate, which the enzyme PRPP synthetase transforms into phosphoribosyl pyrophosphate (PRPP) and inosine monophosphate. This intermediate compound yields adenosine monophosphate (AMP) and guanosine monophosphate, the purinic nucleotides used in DNA and RNA synthesis, as well as inosine. The purine nucleoside phosphorylase transforms the latter into hypoxanthine. Xanthine oxidase (XO), an enzyme inhibited by allopurinol, converts hypoxanthine to xanthine and subsequently xanthine to uric acid (13,14).

In a normal population, a statistical range may be used to identify the upper limit of plasma uric acid. In the United States, epidemiologic studies have generally accepted an upper limit of 7.0 mg/dl for adult males and 6.0 mg/dl for females.

Uric acid levels are influenced by age and sex. Males and females have an average blood uric acid level of 3.6 mg/dl before puberty. Values rise to adult levels after puberty, with women typically having 1 mg/dl less than men. This lower level in women appears to be due to estrogen-related enhancement of renal urate clearance, and it disappears during menopause. Temporary variations in uric acid levels can be caused by a variety of other factors, such as nutrition, medication, exercise, and the amount of hydration.

There are now two commonly used techniques for measuring uric acid. A colorimetric method depends on uric acid's ability to reduce a chromogen, like sodium tungstate, to generate a measurable color change. This technique has been commonly employed in automated hospital screening (SMA systems). The method measures

materials other than urate, such as ascorbic acid. The normal range is typically 1 mg/dl higher than the more specific enzymatic methods, and colorimetric measurements are typically thought to overestimate actual uric acid levels. When uricase specifically oxidizes uric acid, it transforms its substrate into allantoin, which leads to the enzymatic determination of uric acid. The differential absorbance of these substances at 293 nm allows quantification (14).

d) SODIUM

Extracellular fluid's primary cation is sodium [ECF2 (1 mmol, or molar equivalent, corresponding to 23 mg of sodium)]. The average adult male's sodium content is 92 g, of which 46 g are found in the ECF at a concentration of 135–145 mmol/L, approximately 11 g are found in the intracellular fluid at a concentration of approximately 10 mmol/L, and approximately 35 g are found in the skeleton. By using the energy provided by ATP to move sodium and potassium, respectively, from inside to outside the cell and vice versa against the concentration gradient, the sodium–potassium pump activity maintains the concentration gradient between the intracellular fluid and the extracellular fluid (15).

Serum sodium concentration abnormalities are frequently observed in hospitalized patients and might give the physician important clues about the kind or severity of the underlying disease process. The conceptual significance of distinguishing between the sodium content of the body and the sodium concentration in bodily fluids must be highlighted. Active, energy-requiring processes at the cell boundary exclude sodium from the intracellular compartment and, for practical purposes, confine it to the extracellular fluid. The amount of water added or removed from the extracellular compartment controls its concentration there. Variations in the salt level cause water to be added or removed, which in turn affects the extracellular fluid's volume.

When flame photometry was developed in the late 1940s, measuring the sodium content became an acceptable and accurate laboratory test. The management of the plasma sodium level and the pathogenesis of changes in its value have been better understood thanks to studies that were encouraged by increasing clinical experience with abnormalities in sodium concentration. The flame photometer has been replaced by automated methods using ion-specific sodium electrodes that provide equally or more reliable measurement of the plasma sodium concentration (16).

e) POTASSIUM

The most abundant cation in the body is a metallic inorganic ion with an atomic weight of 39. Only a minor portion of potassium is found in the extracellular space; the majority is found in the intracellular compartment. Normal serum potassium is 3.5 to 5.5 mEq/L; however, plasma potassium is 0.5 mEq/L lower. Serum potassium concentration is unaffected by age or sex, although total body potassium is lower in older patients and females.

There are multiple ways to maintain potassium homeostasis. In response to changes in intake, the kidney modifies renal excretion of potassium to determine the total body potassium content. Under normal conditions, insulin and beta-adrenergic tone are essential for preserving potassium's internal distribution. Disorders of disturbed potassium homeostasis are widespread, even though homeostatic pathways are designed to keep potassium levels within the normal range. The ubiquitous Na+-K+ ATPase exchanger found in all cells pumps K+ into the cell and Na+ out, creating a K+ gradient across the cell membrane (K+in > K+out), which helps to maintain the membrane potential. The ability to maintain this gradient is essential for the normal functioning of excitable tissues, including nerve and muscle (17,18).

An ion-selective electrode or flame photometer is used to measure serum potassium. The procedure is

rapid, simple, and reproducible. It should be remembered when interpreting serum potassium that any maneuver that would cause a small amount of intracellular potassium to be released will incorrectly raise serum potassium because the intracellular potassium concentration is about forty times greater than the extracellular concentration. These include: (1) a tight tourniquet; (2) vigorous exercise of the extremity during blood drawing; (3) hemolysis due to vigorous shaking of the test tube; (4) thrombocytosis (platelet count greater than 600,000); and (5) leukocytosis (WBC greater than 200,000). In the last two situations, the increase in serum potassium will be larger the longer the blood stands (17,18).

f) GFR

The volume filtered through the glomerular capillaries and into the Bowman's capsule per unit of time is known as the GFR. The difference in high and low blood pressure produced by the afferent (input) and efferent (output) arterioles, respectively, determines the kidney's filtration. When a substance is neither secreted nor reabsorbed by the kidneys, its clearance rate is equal to the GFR. The mass of the substance excreted during urine collection is equal to the urine concentration times the urine flow for that given substance (19).

GFR is an essential part of clinical practice, research, and public health. In clinical practice, GFR is used to interpret symptoms, signs, and laboratory abnormalities that may indicate kidney disease; to modify drug doses; and to identify, evaluate, and treat acute kidney diseases and disorders (AKD) and chronic kidney disease (CKD). In clinical research, GFR is used as an exposure, outcome, or characteristic in stratification or adjustment, and in public health, GFR is used to estimate the burden of kidney disease.

According to several studies, the typical GFR for healthy young individuals ranges between roughly 100 and 125 mL/min per 1.73 m2 of body surface area (BSA). Hemodynamics, sympathetic tone, food, time of day, activity, body size, pregnancy, and medications are known to affect GFR. Within-person variability in mGFR is widespread, even under steady conditions, and is likely to contribute to random measurement error in GFR evaluation (19-21).

g) CREATININE CLEARANCE

A quick and economical way to evaluate renal function is to measure creatinine clearance (CrCl), which is the amount of blood plasma cleared of creatinine per unit of time. Urine creatinine, serum creatinine, and urine volume during a specific time can all be used to quantify CrCl and GFR.

The breakdown result of dietary meat and skeletal muscle creatine phosphate is creatinine. The production of creatinine in the body is dependent on muscle mass. Creatinine is not eliminated extra-renally, and under steady-state conditions, urinary excretion equals creatine production, regardless of the serum creatinine concentration. Since creatinine is freely filtered by the glomerulus, the CrCl rate approximates the GFR estimate. However, the peritubular capillaries also secreted it, which results in a 10%–20 % overestimation of the GFR by CrCl. Because measuring CrCl is simple, it is a recognized technique for determining GFR despite the marginal inaccuracy (19).

Previously widely used, the Cockcroft-Gault (C-G) formula predicts CrCl (mL/min) based on a patient's weight (kg) and gender. The resulting CrCl is multiplied by 0.85 if the patient is female to correct for the lower CrCl in females. Age is the main predictor of CrCl in the C-G formula. The formula is as follows:

$$CrCl = [(140 - Age) \times Mass\ (kg) \times 0.85\ \text{if female}] / 72 \times [\text{Serum Creatinine } (mg/dL)]$$ (19).

h) URINE

Information on renal function and the function of various organs can be obtained by urinalysis. It helps

evaluate urine concentrating and diluting ability, glomerular barrier function, tubular function, proteinuria, discolored urine, urolithiasis, and neoplasia. Blood urea nitrogen and serum/plasma creatinine values must be interpreted.

On visual inspection, normal urine is usually transparent and yellow or amber in color. The yellow color is primarily caused by two pigments: urobilin and urochrome. The colorless urochromogen undergoes oxidation to produce urochrome, which contains sulfur. Hemoglobin breaks down to produce urobilin. While diluted urine may be transparent or light yellow in color, highly concentrated urine is amber in color due to the ongoing 24-hour urinary output of urochrome.

For accurate specific gravity measurement and chemical analysis, urine must be at room temperature. These tests are usually done before centrifugation; however, if urine is discolored or turbid, it may be beneficial to perform these tests on the supernatant. Although it is frequently not done, urine sediment examination by microscopy is a great tool for clinicians to understand underlying pathology.

The patterns and appearances of many crystals are distinguishable. Crystals may provide information on underlying disease pathology. Drug-related crystalluria, metabolic syndrome, hypercalciuria, hyperuricemia, and hyperoxaluria are frequently linked conditions. When choosing therapeutic actions, such as dietary modifications or the prescription or discontinuation of drugs, accurate urine crystal identification might be helpful. Given the significant prevalence of nephrolithiasis, patient morbidity can be reduced by properly diagnosing and treating risk factors (22,23).

A sign of urinary supersaturation with different chemicals is the production of crystals in the urine. Medication side effects, metabolic abnormalities, and hereditary conditions can all result in crystals. Since uric acid, calcium oxalate, calcium phosphate (CaP), and drug-induced crystals can all be seen under normal physiological conditions, the presence of crystals in the urine is not always a sign of an abnormal metabolic or renal state. Examining the urine sediment and accurately identifying the associated urinary crystals can help indicate the diagnosis of some monogenetic disorders, including cystinuria, primary hyperoxaluria, and adenine phosphoribosyl transferase deficiency.

Although it may not always result in nephrolithiasis, urinary crystal formation always comes before renal stone formation. Acute kidney damage, obstructive uropathy, hydronephrosis, renal colic, pyonephrosis, and urosepsis can all result from kidney stones. Acute kidney injury, progressive chronic kidney disease, and end-stage kidney disease can all be brought on by urinary crystals and renal crystal deposition disease (22,23).

5. KIDNEY STONES

Mineral deposits in the renal calyces and pelvis that are either free or connected to the renal papillae are known as kidney stones. They are created when the urine gets supersaturated with a mineral and contain both organic and crystalline components. The majority of stones are composed primarily of calcium oxalate, and many of them develop on the surface of renal papillaries where Randall's plaques, a calcium phosphate base, are found.

Mineral concretions in the renal calyces and pelvis (FIG. 4) that are either free or connected to the renal papillae are known as kidney stones (calculi). Nephrocalcinosis, on the other hand, is the term for diffuse renal parenchymal calcification. Nephrolithiasis, often referred to as urolithiasis, is the development of stones in the urinary tract caused by overly supersaturated urine with respect to a mineral, which causes crystal formation, growth, aggregation, and retention inside the kidneys. Calcium oxalate (CaOx) combined with calcium phosphate (CaP) makes up about 80% of kidney stones worldwide. Uric acid, struvite, and cystine-

based stones are also prevalent and make up roughly 9%, 10%, and 1% of all stones, respectively. Certain relatively insoluble medications or their metabolites can also cause urine to become supersaturated, which can result in crystallization (iatrogenic stones) that form in the renal collecting ducts. For example, nephrolithiasis is a danger for HIV patients receiving treatment with protease inhibitors such as indinavir and atazanavir. Kidney stones develop as a result of the liver's metabolism of indinavir and atazanavir, with a significant amount of the medication being eliminated in the urine unaltered. Atazanavir has the potential to crystallize in the urine and cause kidney stones, even when taken in combination with other drugs (24,25).

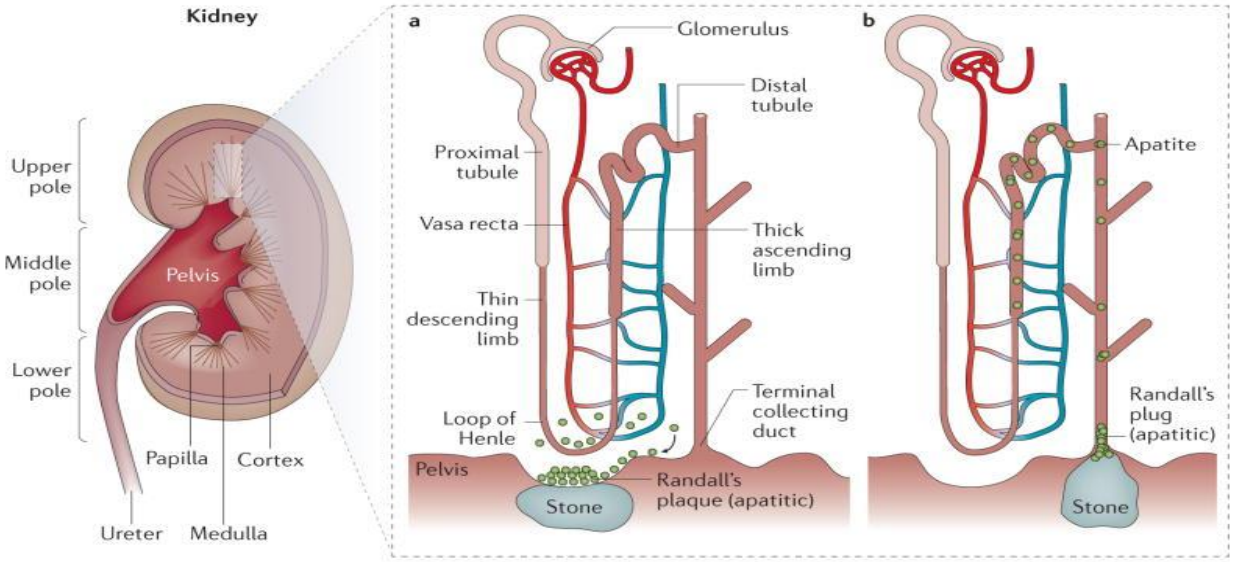
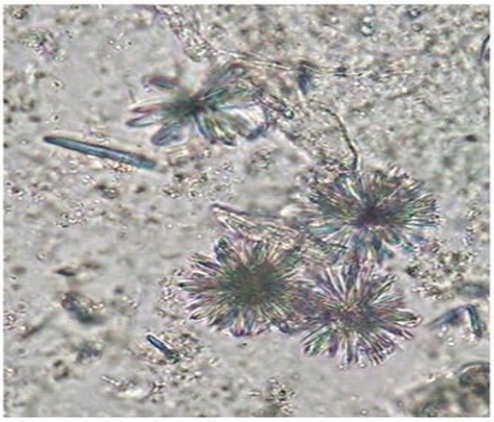


Figure (4): Kidney stones (24).

Most stones contain calcium (Ca) combined with oxalate, phosphate or occasionally uric acid in the form of calcium oxalate ($CaC_2O_4 \cdot H_2O$), calcium phosphate [$Ca_{10}(PO_4)_6 \cdot 2H_2O$], calcium carbonate ($CaCO_3$), brushite ($CaHPO_4 \cdot 2H_2O$), gypsum ($CaSO_4 \cdot 2H_2O$) and/or dolomite [$CaMg(CO_3)_2$]. As a calcium salt of oxalic and dicarboxylic acids, calcium oxalate crystallizes into two distinct chemical and crystallographic forms: calcium oxalate dihydrate (also known as weddellite, $CaC_2O_4 \cdot 2H_2O$) and calcium oxalate monohydrate (also known as whewellite, $CaC_2O_4 \cdot H_2O$). Every Calcium stone is radiopaque (26).

Unlike radiopaque Ca stones, uric acid stones are radiolucent and radiographically transparent until combined with struvite or Ca crystals. Even in the absence of elevated blood or urine uric acid concentrations, uric acid can precipitate out in acidic urine and salt out calcium oxalate. As with all stones, certain drugs can make them more likely to form. For uric acid stones, these drugs include hyperuricosuric agents like thiazides, probenecid, and low-dose salicylates (26).



Calcium Phosphate Nephrolithiasis.

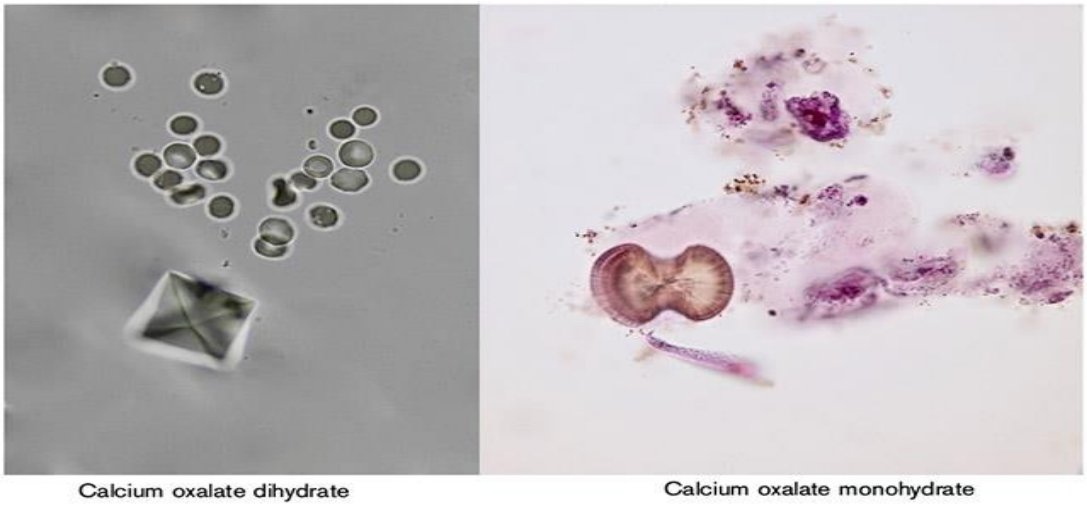


Figure 5: a) Calcium Phosphate Nephrolithiasis, b) Calcium oxalate dihydrate, c) Calcium oxalate monohydrate (26).

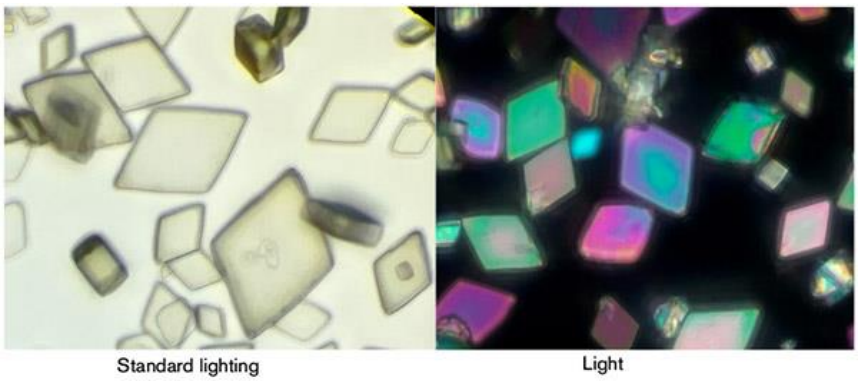


Figure 6: Uric Acid Nephrolithiasis (26).

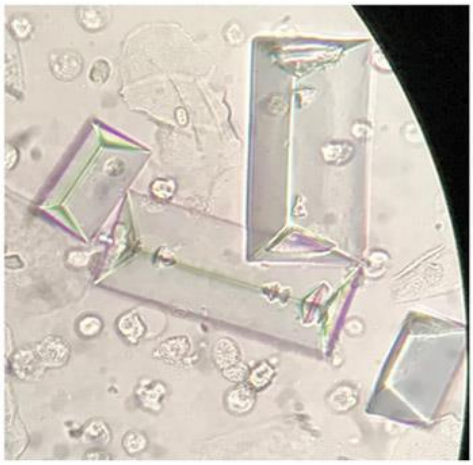


Figure 7: Magnesium-Ammonium-Phosphate (Struvite) (26).

Struvite (triple phosphate stones), also known as infection stones, is a crystalline substance composed of magnesium ammonium phosphate. According to radiography research, struvite stones are big, laminated, and gnarled. Admixed struvite/apatite stones often have a coarse, granular surface and are light brown in color. White and light-brown layers are typically blended inside these stones. Struvite stones form when bacteria-produced urease and trivalent phosphate are present in alkaline urine, which has a high ammonium content. In addition to struvite stones, Kajander and Ciftcioglu (1998) noted that Ca-based stones might have an infectious origin (26).

The current techniques utilized for the analysis of kidney stones are: (1) chemical analysis, (2) thermogravimetry, (3) polarization microscopy, (4) scanning electron microscopy (SEM), (5) powder X-ray diffraction (XRD), and (6) spectroscopy.

Thermogravimetric analysis (TG or TGA) has been used by several authors to analyze stones, with the respective authors confirming its ability to produce fast and accurate quantitative results (Rose and Woodfine 1976; Rose 1982). In addition to being the most effective physical technique for analyzing calcium oxalate monohydrate and dihydrate salt, it may also yield information that aids in determining the stones' age (Rose and Woodfine 1976; Rose 1982). When combined with uric acid or magnesium ammonium phosphate, this technique offers a substitute for XRD and Fourier transform infrared spectroscopy (FT-IR) in the quantitative assessment of each calcium oxalate hydrate (Kaloustian et al. 2003) (25,26).

6. Diabetic Nephropathy: Diabetes, particularly when poorly controlled, can lead to a range of serious complications, such as Diabetic Nephropathy, in which Kidney damage results in chronic kidney disease and potential progression to renal failure (27).

Conflict of interest: NIL

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