

Introduction to Clinical Medicine
Assessment of Renal Function

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Kidneys are responsible for very wide variety of functions that are critical to maintain normal health. These include maintenance of plasma volume, regulation of sodium, potassium, calcium, phosphate, magnesium and most other electrolytes in normal concentrations, regulation of blood pressure both through changes in plasma volume and by secretion of renin, regulation of red blood cell mass through production of erythropoietin, and regulation of calcium homeostasis, bone health and, possibly, vascular health through metabolism of inactive vitamin D to the active form of vitamin D. As with any other function of the body, being able to assess and quantify levels of function or dysfunction is critical for assessing health and disease and for assessing the response to therapeutic interventions.

How to assess renal function

In general, all parameters of renal function, including glomerular filtration, tubular reabsorption and secretion and endocrine renal functions, change in parallel. As a result, any measure of these can be used to assess global renal function. Glomerular filtration is the easiest to measure, and is the most commonly (almost exclusively) used assessment of renal function.

The easiest way to measure the glomerular filtration rate (GFR) is with creatinine. This is a muscle breakdown product that is filtered almost completely at the glomerulus and undergoes no tubular reabsorption and, in general, little-to-no tubular secretion. As a result, the rate of creatinine removal is proportional to the concentration in the plasma and the rate of glomerular filtration.

The rate of creatinine addition to the body is proportional to body muscle mass.

Whenever the serum creatinine is constant, the rate of creatinine addition to the body is equal to the rate of creatinine removal.

Thus, changes in GFR are mirrored by reciprocal changes in the serum creatinine. Because serum creatinine multiplied by GFR equals the rate of creatinine production, a decrease in the GFR by 50% causes the serum creatinine to increase to ~200% of its basal level. This relationship is shown in Figure 2.

It is critical to recognize that a given change in the serum creatinine indicates quite different changes in the GFR that depend on the initial serum creatinine. Because of the inverse relationship between serum creatinine in GFR, it is proportional changes in creatinine are important, not absolute changes.

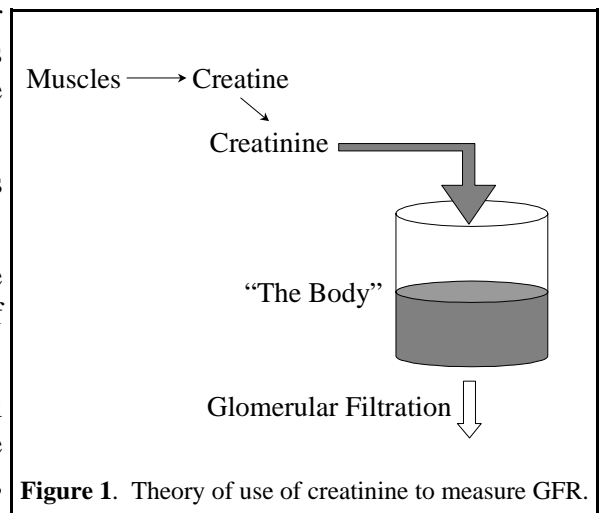


Figure 1. Theory of use of creatinine to measure GFR.

GFR can be estimated using either of two ways. Using only a serum creatinine measurement (S_{Cr}), the GFR can be estimated using a formula known as the “MDRD” formula (Equation 1). Quite obviously, this formula cannot be calculated without the use of an advanced calculator or, more commonly, by the use of web-sites that will calculate the formula.

The MDRD formula assumes that the person’s muscle mass is appropriate for their age, sex and race. If the person is cachectic, malnourished or is missing a limb then this formula overestimates actual GFR. Conversely, it underestimates GFR in the muscular patient.

The Cockcroft-Gault GFR formula is of historical importance, and is not as accurate as the MDRD formula.

If a 24-hour urine collection is available, the GFR can be estimated as the creatinine clearance (Equation 2). Amazingly, obtaining an accurate 24 hr urine collection is difficult (!?!). The MDRD generally is a more accurate way to estimate GFR than a single 24-hour urine creatinine collection.

Another commonly used measure of renal function is the BUN (blood urea nitrogen). Urea has many of the same characteristics as creatinine, with the exception that its blood level is ~10x higher. However, many factors change urea metabolism, which then causes the BUN to not accurately reflect renal function. In particular, glucocorticoids, gastrointestinal bleeding and intravascular volume depletion increase the BUN out-of-proportion to any changes in actual GFR.

Caveat!

The MDRD and Cockcroft-Gault formulae are accurate only when renal function and serum creatinine are stable and the muscle mass is normal. *When renal function is changing estimates of renal function based on the serum creatinine lag behind the actual GFR by approximately 2 to three days. Patients with abnormal, either elevated or decreased, muscle mass have parallel changes in the serum creatinine, which if unappreciated result in abnormal estimates of actual GFR.*

PROTEINURIA

A second essential renal function is to retain formed elements in the blood, such as proteins and cellular elements, despite filtering ~120 ml/min (~180 L/d) of blood. Under normal circumstances there should be no red cells, white cells or protein in the urine. The presence of any of these indicates a specific abnormality.

The presence of protein in the urine (proteinuria) almost always indicates damage to the glomerulus. Since the glomerulus is essentially an extremely large blood vessel with increased permeability, damage to the glomerulus that results in proteinuria predicts the presence of extra-

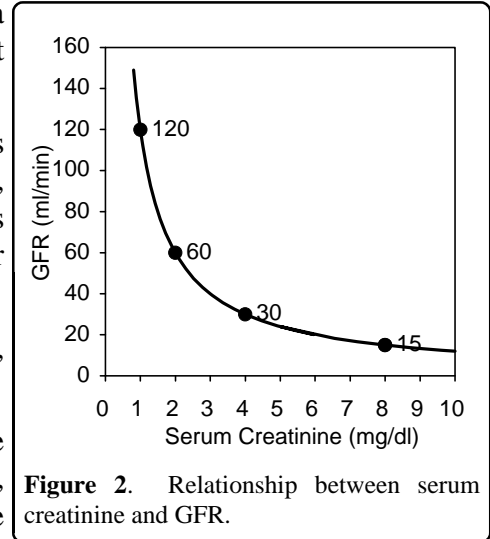


Figure 2. Relationship between serum creatinine and GFR.

$$eGFR = 186 \times S_{Cr}^{-1.156} \times Age^{-0.203} \quad (1)$$

$$= \times 0.742(\text{female}) \times 1.21(\text{AA})$$

$$Cl_{Cr} = \frac{U_{Cr} \times V}{S_{Cr}} \quad (2)$$

renal vascular disease, and is predictive of an increased risk of cardiovascular events. The immune response to a urinary tract infection can cause proteinuria in the absence of glomerular disease.

The major protein in the blood is albumin, and albumin comprises the majority of protein in the urine in patients with glomerular disease is albumin. One can screen for urinary albumin with the urine dipstick test; this provides a semi-quantitative assessment of urinary albumin excretion rates. Urinary albumin and protein can also be quantified with direct quantitative tests. In order to correct for variations in renal water reabsorption, the urinary protein or albumin is typically expressed as a ratio of the urine protein or urine albumin concentration to the urine creatinine concentration.

The average person excretes approximately 1000 mg (1 gm) per day of creatinine in the urine. As a result, a urine protein to creatinine ratio of 2 mg protein per milligram creatinine is predictive of a urine protein excretion rate of 2 g per day.

There is one specific circumstance in which the urine dipstick for protein does not identify urinary proteins. Multiple myeloma is a plasma cell neoplasm associated with monoclonal light or heavy chain immunoglobulin production. These proteins, particularly light chains, can be filtered by the glomerulus and detected in the urine by quantitative analysis. However, they will not be detected by the urine dipstick because the dipstick is an enzymatic test for albumin. As a result, identification of urinary protein by quantitative assay, but not by urine dipstick, suggests the presence of multiple myeloma.

HEMATURIA

Red cells in the urine, also known as hematuria, is always abnormal and indicates the presence of bleeding someplace in the genitourinary tract, anywhere from the glomerulus to the ureters to the bladder to the urethra. Red cells are generally detected initially by urine dipstick testing that identifies the presence of hemoglobin. They may be also be detected by urine microscopy. The latter may be helpful in differentiating between glomerular origin of hematuria and non-glomerular origin.

Hematuria of glomerular origin frequently results in red cells with a crenated or dysmorphic morphology. This probably results from the severe deformation of the red cells in order for them to traverse the glomerular basement membrane. On occasion, red cells that originate from glomerulonephritis will “stick together” during their travel through the renal nephron. When viewed under the microscope in the urine, they will form a “cast” of the renal nephron; they are termed a “RBC cast.” This finding is essentially diagnostic of glomerulonephritis.

Urinary RBCs can indicate cancer in the genitourinary tract. They may also occur in response to bladder trauma and urinary tract infections. Patients with persistent hematuria in the

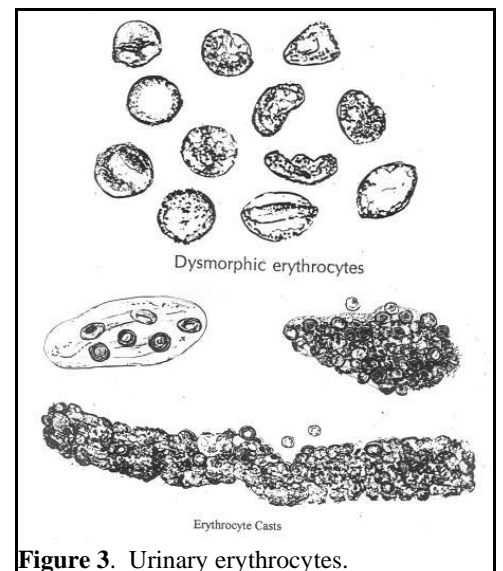


Figure 3. Urinary erythrocytes.

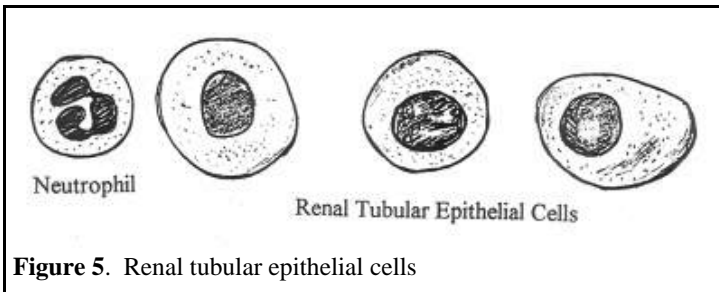
absence of demonstrated trauma or urinary tract infection should be evaluated for cancer in the kidneys, ureters or bladder.

OTHER CELLULAR ELEMENTS IN THE URINE

A variety of other cellular elements may be observed in the urine and one should be able to differentiate these from erythrocytes.

White blood cells in the urine, termed *leukocyturia*, should be easy identifiable by the presence of their multi-lobed nucleus. The presence of leukocyturia strongly suggests a urinary tract infection. A WBC cast suggests that the cells originate in the kidney and suggests the presence of pyelonephritis.

If there is damage to renal tubular cells, most often occurring in the presence of hypotension or renal toxins, damaged and detached *renal tubular epithelial cells* may be visible in the urine. These are characterized by a size ~50%



larger than a RBC or WBC and a single lobed nucleus that is ~50% of the diameter of a cell. When seen they suggest the diagnosis of acute tubular necrosis in a patient with acute renal failure.

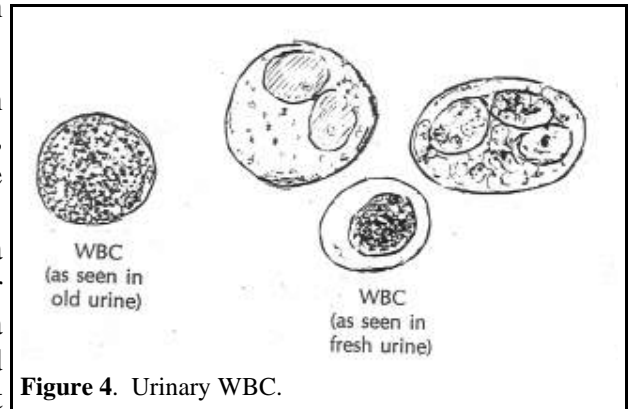


Figure 4. Urinary WBC.

Occasionally *squamous epithelial cells* from the patient's perineum will be visible. They are characterized by a large and irregular shape and a very small nucleus, resulting in a very low nucleus-cytoplasmic ratio. They indicate the presence of external skin contamination of the urine. When examining a patient for a possible urinary tract infection, the presence of squamous epithelial cells in the urine should indicate that the samples is **not** an accurate assessment of bladder cellular elements, and should not be used for determining whether the patient has a urinary tract infection.

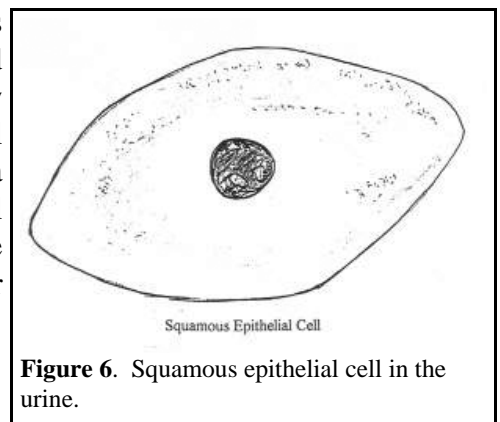


Figure 6. Squamous epithelial cell in the urine.

OTHER COMPONENTS OF THE URINALYSIS

The routine urinalysis is a routine screening test for a variety of conditions.

The urine's *specific gravity (sp.gr.)* indicates the relative concentration of the urine. The normal range is 1.002 - 1.030. One can predict the urine osmolality by taking the last two digits of the sp.gr. and multiplying by 30. For example, a sp.gr. of 1.010 predicts an osmolality of ~300. When interpreting other urine tests, one should consider the degree of concentration of the urine.

A urine protein by dipstick of 100 mg/dl with a sp.gr. is 1.030 may indicate less proteinuria than a dipstick protein of 30 mg/dl with a sp.gr. of 1.005.

The urine *leukocyte esterase* and *nitrite* assays test for activation of WBC in the urine, and their presence suggests an ongoing urinary tract infection.

The urine dipstick for *hemoglobin* is an enzymatic test for hemoglobin, and is frequently used as a screening test for RBC in the urine. Myoglobin will cross-react with this assay. Patients with significant muscle damage, known as rhabdomyolysis, will have the myoglobin filtered by the glomerulus and detected by urine dipstick, but will not have RBC identified on urine microscopy. This pattern should strongly suggest a diagnosis of rhabdomyolysis.

Diabetes mellitus, particularly if poorly controlled, can sufficiently elevate the plasma glucose that the filtered glucose load exceeds the renal tubules ability to reabsorb glucose. However, the urine dipstick for glucose should NOT be used for dosage adjustments in insulin or other diabetes-related medications.

RENAL IMAGING

In many conditions it is important to image the kidneys. This may be important either in the evaluation of renal masses, exclusion of urinary tract obstruction as a cause of acute renal failure or investigation of renal artery stenosis.

Renal ultrasound is the most commonly used renal imaging modality. It is noninvasive, widely available, and does not involve either the use of potentially nephrotoxic radiocontrast agents or exposure of the patient to radiation. The figure to the left shows a normal renal ultrasound. A smooth contoured kidney is easily identifiable. The renal cortex is less echogenic than the liver. The renal medulla mostly comprises fat and has an increased echogenicity as compared to the cortex.

With chronic kidney disease, there is increased fibrosis of the renal cortex. Fibrous tissues reflect sound waves, and causes increased echogenicity on renal ultrasound. The fibrosis also causes the kidney to shrink. Under normal circumstances, kidneys are 10-12 cm in length. A kidney less than 10 cm should suggest chronic scarring resulting in shrinking of the kidney and indicate a diagnosis of chronic kidney disease. If a kidney is less than 7 cm in size, one should consider renal agenesis. Enlarged kidneys, >12-13 cm, should suggest the presence of acute inflammatory process in the kidney, such as acute interstitial nephritis, or the presence of lymphoma to us involvement of the kidney.

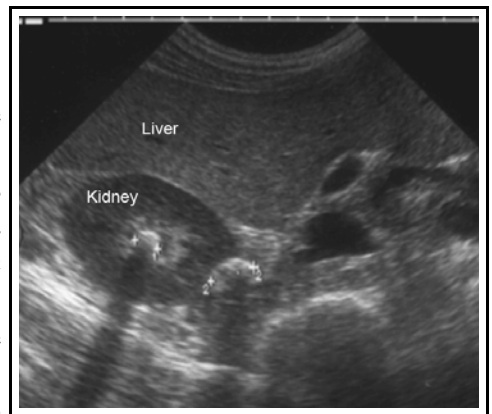


Figure 7. Normal renal ultrasound of the right kidney.

Increased echogenicity shows up as increased “whiteness” on renal ultrasound. An easy to use internal standard to use is the liver. Under normal circumstances, the renal cortex is of less echogenicity than the liver, while in chronic kidney disease the kidney has greater echogenicity.

Obstruction of urine drainage from the kidney (“obstructive uropathy”) is a common cause of acute renal failure. Failure of urine drainage leads to dilation of the renal pelvis. Water-based fluids do not reflect ultrasound, and appear as black on ultrasound images. The dilated renal pelvis is easily visible in obstructive uropathy, and is termed “hydronephrosis.”

Renal CT scan is used when greater resolution is required to image the kidneys. An important limitation of renal CT scan is the need for radiocontrast agents. All radiocontrast agents have some degree of renal toxicity. This toxicity is greater in kidneys which are already diseased. The second limitation is that CT scan involves irradiation, although this is not typically an important limiting factor in its use.

In patients in whom renal CT scanning cannot be performed, *magnetic resonance imaging* may be considered. Magnetic resonance imaging may also be used for noninvasive imaging of the renal arteries in considering the possibility of renal artery stenosis.

The most direct imaging of the renal arteries involves *renal angiography*. This is typically performed when considering renal artery stenosis as a cause of either renovascular hypertension or ischemic nephropathy. In most institutions this involves the use of nephrotoxic radiocontrast agents, which have limitation as described previously. At the University of Florida, our radiologists have developed a technique of using CO₂ as a radiocontrast agent; CO₂ is not nephrotoxic and is less expensive than conventional radiocontrast dye. However, CO₂ requires specialized equipment to use and is not widely available.

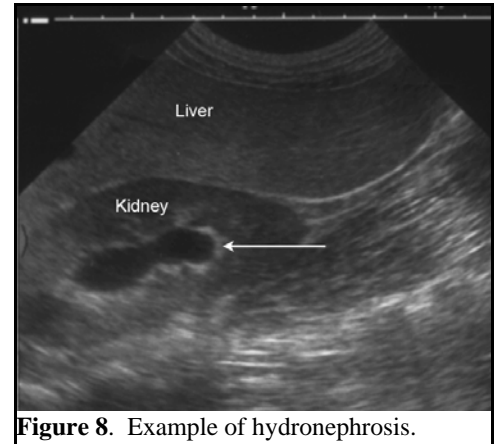


Figure 8. Example of hydronephrosis.