Unit Nine

Kidney Function Test

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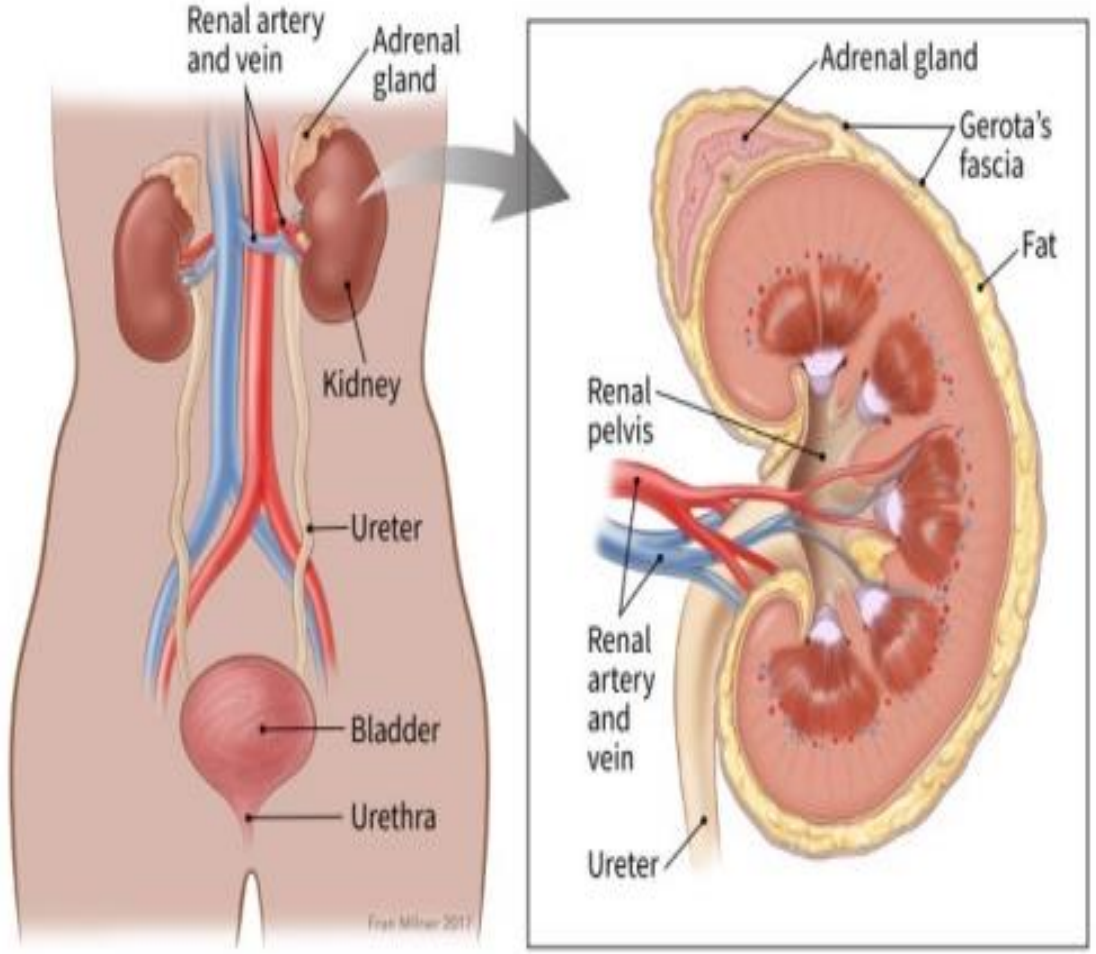
Unit 9. Kidney Function Test

Definition of Kidney

The kidneys are two reddish-brown bean-shaped organs found in vertebrates. They are located on the left and right in the retroperitoneal space, and in adult humans are about 12 centimetres in length. They receive blood from the paired renal arteries; blood exits into the paired renal veins. Each kidney is attached to a ureter, a tube that carries excreted urine to the bladder. The nephron is the structural and functional unit of the kidney. Each adult human kidney contains around 1 million nephrons. Filtration occurs in the glomerulus: one-fifth of the blood volume that enters the kidneys is filtered.



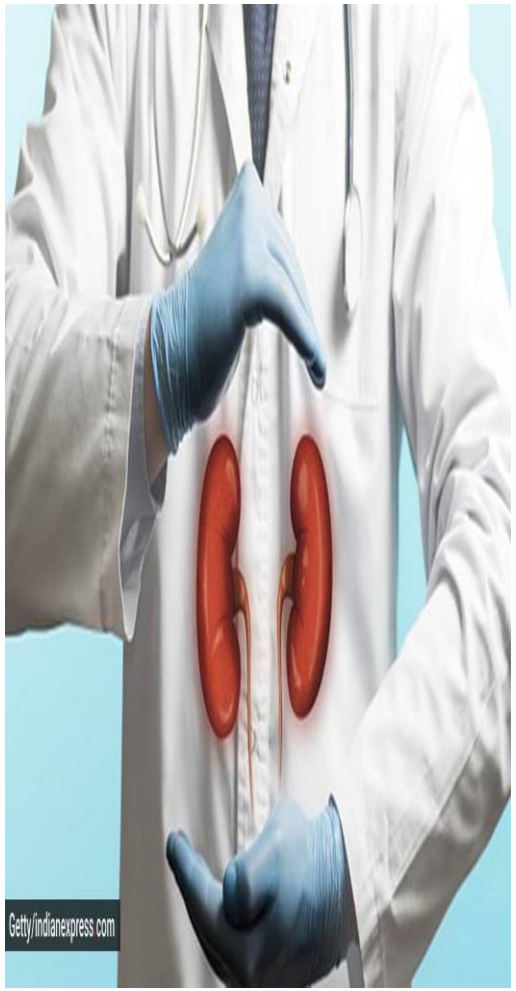
Unit 9. Kidney Function Test

Functions of Kidney

The major renal functions are:

1. Excretion of urea and other waste products, such as creatinine, uric acid and metabolites of xenobiotics.
2. Maintaining water balance.
3. Excretion of sodium (effect on BP).
4. Excretion of potassium (effect on heart).
5. Excretion of hydrogen ions (maintenance of pH).
6. Activation of vitamin D (effect on bone).
7. Production of erythropoietin (effect on RBCs).
8. Filtration: 180 liters/day of water with all sodium, chloride, sugar and amino acids.
9. Reabsorption: 178.5 liters reabsorbed; all glucose and amino acids reabsorbed; most of sodium and chloride reabsorbed.

A decrease in kidney function is due to a reduction in the performance of nephrons. The functional unit of the kidney is the nephron, which is composed of the Bowman's capsule with the glomerular tuft of capillaries, the proximal convoluted tubule (PCT), loop of Henle, distal convoluted tubule (DCT) and collecting tubules.



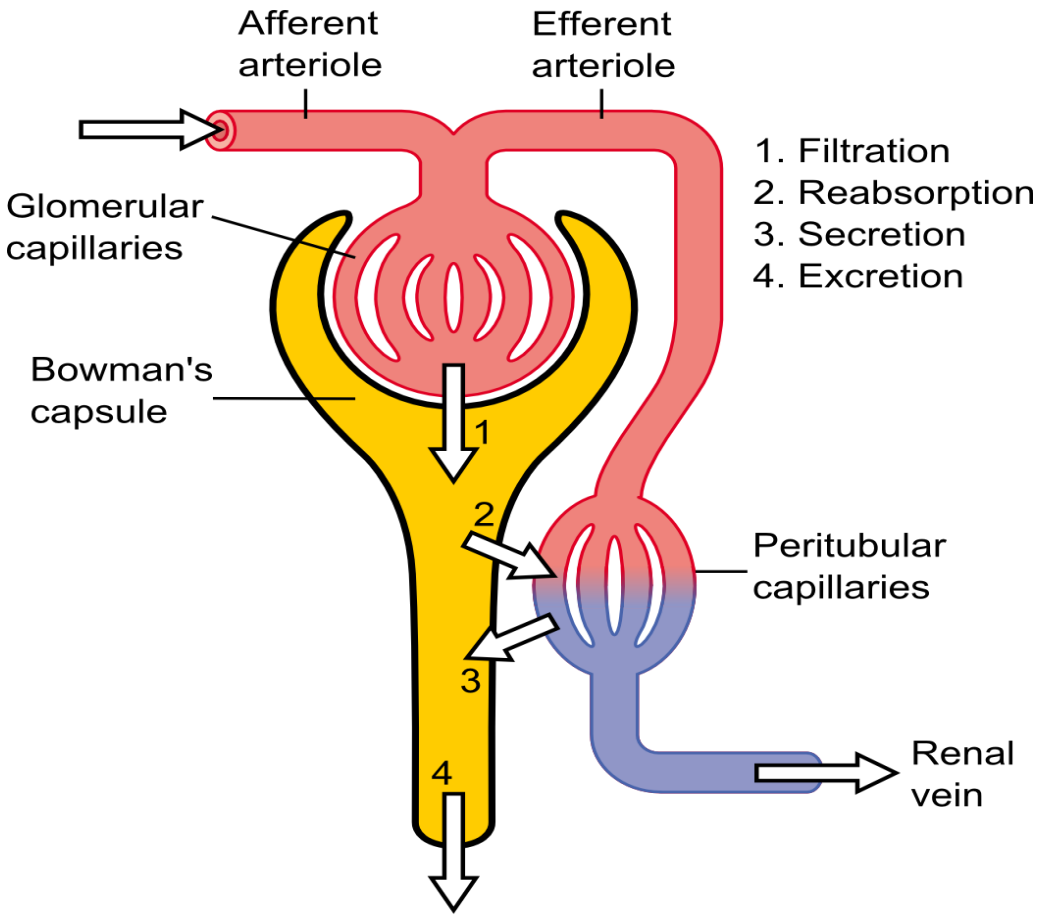
Unit 9. Kidney Function Test

Glomerular Function

When the blood is perfused through the Bowman's capsule, an ultra-filtrate of the blood is produced in glomerulus, while the cells and proteins are retained in the blood. The sieves of the glomeruli are such that albumin is passed through to be excreted in urine, while hemoglobin is retained in the blood. Therefore, the earliest manifestation of the a abnormal function of the glomeruli is the appearance of albumin in urine.

Tubules Functions

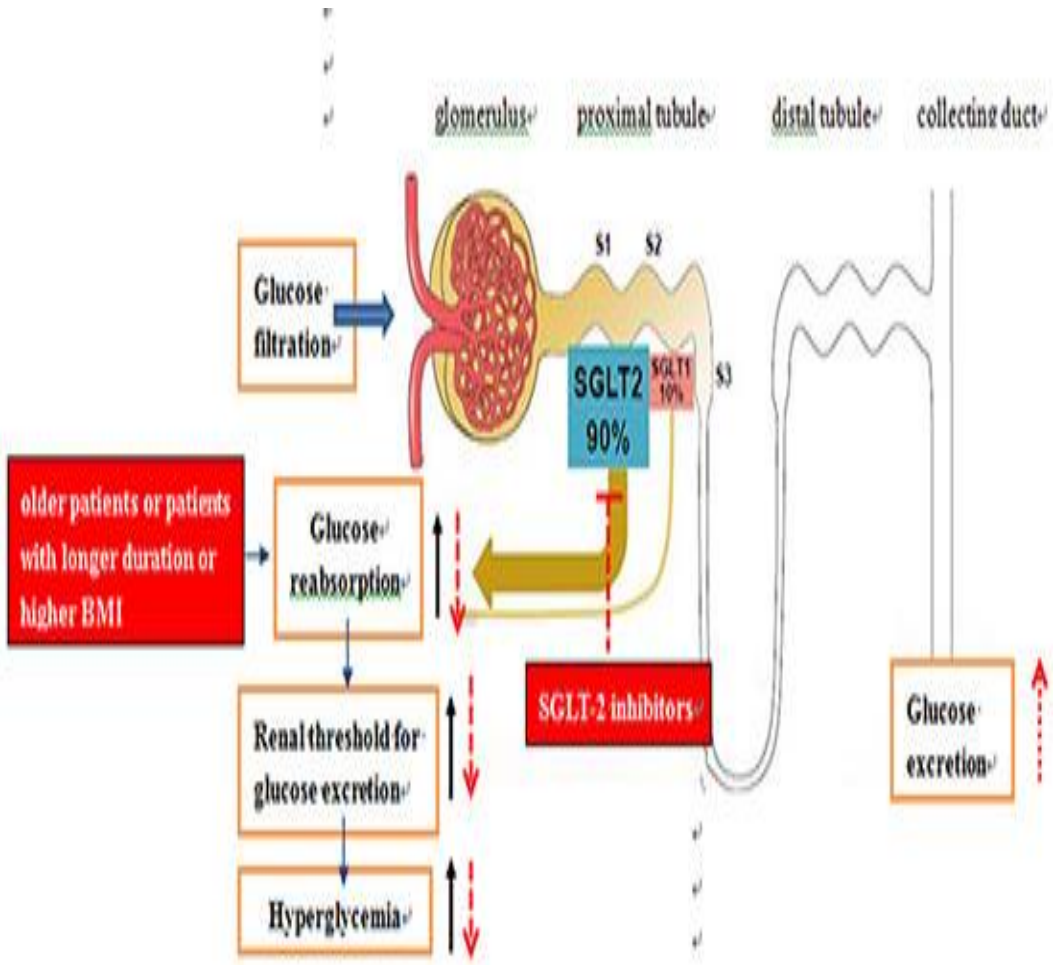
When the glomerular filtrate is formed, it contains almost all the crystalloids of plasma. In the proximal convoluted tubules, about 70% water, sodium and chloride as well as 100% glucose, amino acids and potassium are reabsorbed. Urea, phosphate and calcium are partially absorbed. The major processes occurring in renal tubules are the reabsorption or secretion of solutes and reabsorption of water.



Unit 9. Kidney Function Test

Renal Threshold and Tubular Maximum

Compounds whose excretion in urine are dependent on blood level are known as threshold substances. At normal or low plasma levels, they are completely reabsorbed and are not excreted in urine. But when the blood level is elevated, the tubular re-absorptive capacity is saturated, so that the excess will be excreted in urine. The renal threshold of a substance is the plasma level above which the compound is excreted in urine. The maximum re-absorptive capacity of the substances is known as the tubular maximum (Tm). For glucose, the renal threshold is 180 mg/dL and Tm is 375 mg/ min. In other words, glucose starts to appear in urine when blood level is more than 180 mg/dL, and all the glucose molecules above 375 mg are excreted in the urine. In abnormal conditions, the renal threshold may be lowered so that even at lower blood levels, compounds are excreted in urine, e.g. renal glycosuria (glucose); and renal tubular acidosis (bicarbonate).



Unit 9. Kidney Function Test

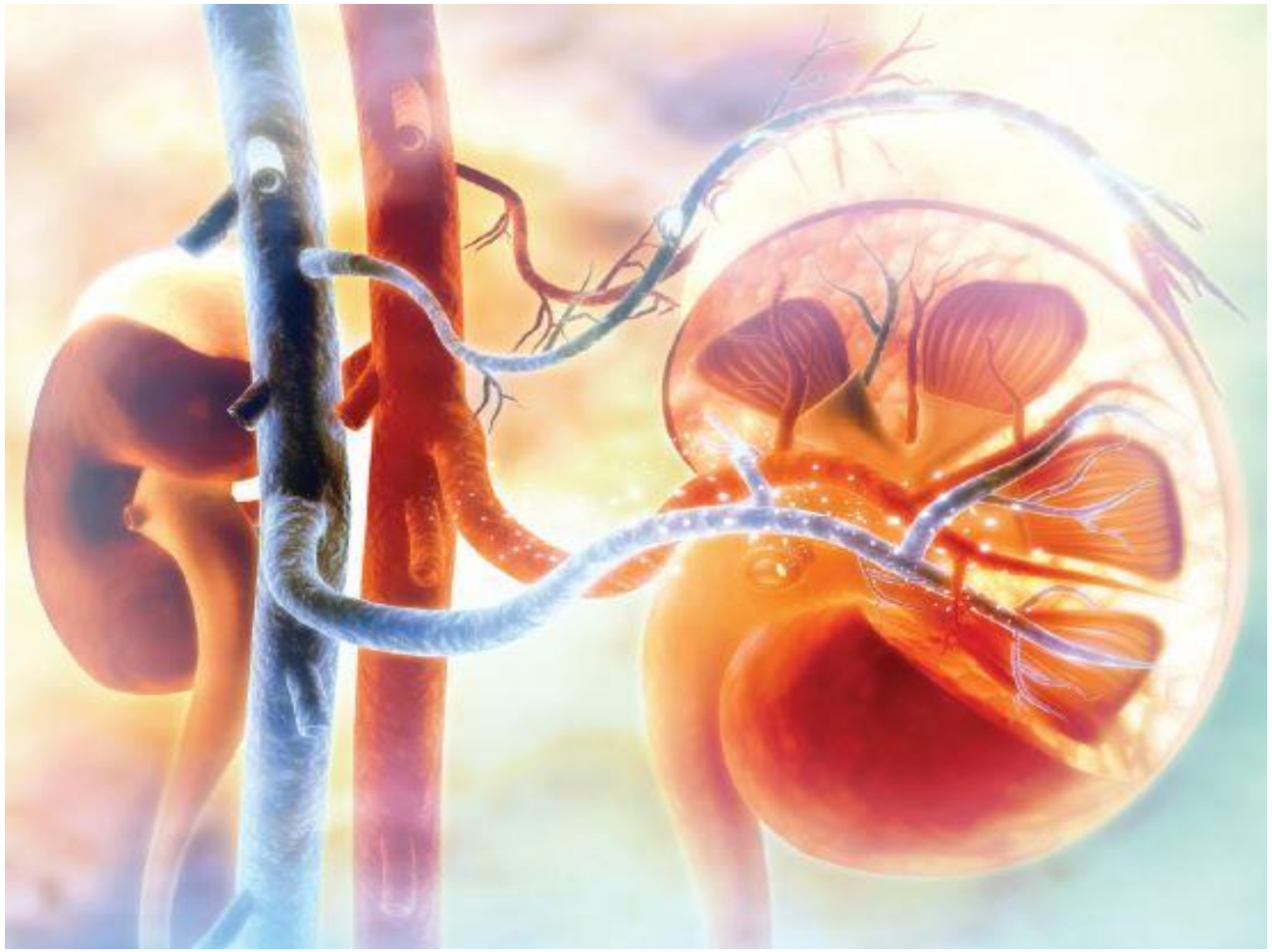
Classification of Renal Function Tests

1. Screen for Kidney Disease: Complete urine analysis, Plasma urea and creatinine and Plasma electrolytes.

2. Assess Renal Function:

a. Assess Glomerular Function: Glomerular filtration rate (GFR), Clearance tests, Glomerular permeability and Proteinuria.

b. Assess Tubular Function: Reabsorption studies, Secretion tests, Concentration and dilution tests and Renal acidification.



Unit 9. Kidney Function Test

Glomerular Filtration Rate (GFR)

Glomerular filtration rate (GFR) is an important indicator of the filtering capacity of kidneys and is considered the best overall index of renal function currently used. Estimated glomerular filtration rate (eGFR) is the most important variable in the assessment of patients with suspected or known kidney disease in clinical practice. GFR measures the rate at which the kidneys' two million glomeruli filter plasma in order to process it and remove waste products from it.

GFR is decreased when BP is below 80 mm of mercury. The GFR is reduced when there is obstruction to the renal flow (calculi, enlarged prostate, etc.). It also decreases with age. The renal blood flow is about 700 mL of plasma or 1200 mL of blood per minute. The glomerular filtration rate (GFR) is 120–125 mL per minute in a person with 70 kg body weight. Glomerular filtrate formed is about 170 to 180 liters per day, out of which only 1.5 liters are excreted as urine. This means that most of the water content of glomerular filtrate is reabsorbed. Furthermore, guidelines recommend that clinical laboratories compute and report estimated GFR by using estimating equations, such as the Modification of Diet in Renal Disease (MDRD) corrected for Body Surface Area (BSA) equation:

GFR (mL/min/1.73 m²) = 186 × Serum Creatinine$^{-1.154}$ × age$^{-0.203}$ × 1.212 (if subject is black) × 0.742 (if subject is woman)

**** Serum creatinine level (mg/dL) does not increase significantly until the GFR is reduced to less than 50% of its normal value because of increased tubular secretion of creatinine.**

Unit 9. Kidney Function Test

Creatinine Clearance (CrCl)

Creatinine clearance (CrCl) is the volume of blood plasma cleared of creatinine per unit time. It is a rapid and cost-effective method for the measurement of renal function. Both CrCl and GFR can be measured using the comparative values of creatinine in blood and urine. The CrCl rate approximates the calculation of GFR since the glomerulus freely filters creatinine. However, it is also secreted by the peritubular capillaries, causing CrCl to overestimate the GFR by approximately 10% to 20%. However, because a small amount of creatinine is released by the filtering tubes in the kidneys, creatinine clearance is not exactly the same as the GFR. In fact, creatinine clearance usually overestimates the GFR, particularly in patients with advanced kidney failure. Furthermore, CrCl was calculated by the Cockcroft-Gault equation:

CrCl (mL/min) = (140 – age) × Weight (Kg) × 0.85 (if subject is woman) / (72 × Serum Creatinine mg/dL)

From the other hand, obstruction within the kidney or dysfunction from another disease such as congestive heart failure may play a pivotal role in decreasing CrCl level. Moreover, CrCl overestimates GFR due to the secretion of creatinine from the tubules in normal individuals. In patients with CKD, there is increased extra-renal and decreased urinary elimination of creatinine leading to overestimation of GFR from serum creatinine.

Unit 9. Kidney Function Test

Measurements of Cystatin C

It is a marker which has advantages over serum creatinine. Cystatin C is a 13 kD (120 amino acids) non-glycosylated protein. Normal blood level of cystatin is 0.8 to 1.2 mg/L. It is seen in high concentrations in biological fluids, such as breast milk, tears, saliva and semen. It is expressed in virtually all organs of the body. Creatinine is the most widely used biomarker of kidney function. But sometimes, it is inaccurate in detecting mild renal impairment. The tubular secretion contributes approximately 20% of the total creatinine excretion by the kidney, and this contribution can increase as GFR decreases. Serum creatinine does not increase until the GFR has moderately decreased. This insensitivity to moderate decreases in GFR is called creatinine blind GFR area (40–70 mL/min/1.73 m2). So, serum creatinine may not be a good parameter for determination of GFR, especially at lower levels of glomerular function. On the other hand, Cystatin C is produced at a constant rate and is freely filtered by kidney glomeruli. It is completely reabsorbed; but degraded in the tubules; thus making it an excellent GFR marker. The blood levels are not depended on age, sex, muscle mass or inflammatory processes. It is sensitive to changes in the so-called creatinine blind area of GFR (40–70 mL/min/1.73m2). So, serum level of cystatin is a better test for kidney function (GFR) than serum creatinine levels. Since, there is no tubular secretion of Cystatin C, it is extremely sensitive to minor changes in GFR in the earliest stages of chronic kidney diseases. Cystatin C concentration contributes independently in predicting the risk of cardiovascular death or myocardial infarction.

Unit 9. Kidney Function Test

Measurements of Microalbuminuria

The glomeruli of kidney are not permeable to substances with high molecular weight so plasma proteins are absent in normal urine. When glomeruli are damaged or diseased, they become more permeable and plasma proteins may appear in urine. The smaller molecules of albumin pass through damaged glomeruli more readily than the heavier globulins. Albuminuria is always pathological. Large quantities (a few grams per day) of albumin are lost in urine in nephrosis. Small quantities are seen in urine in acute nephritis, strenuous exercise and pregnancy.

Microalbuminuria (MAU) is also called minimal albuminuria or paucialbuminuria. It is identified, when small quantity of albumin (30–300 mg/day) is seen in urine. The test is not indicated in patients with overt proteinuria (+ve dipstick). Early morning midstream sample is preferred. MAU is an early indication of nephropathy in patients with diabetes mellitus and hypertension. Hence, all patients who are known diabetics and hypertensive should be screened for MAU. It is an early indicator of onset of nephropathy. The test should be done at least once in an year. It is expressed as albumin-creatinine ratio; normal ratio being:

Males < 23 mg/g of creatinine & Females < 32 mg/g of creatinine

Patients showing higher values on more than one occasion are considered to have MAU. Confirmed by overnight urine collection and calculation of albumin excretion rate. A value more than 20 mg/min confirms MAU. The selectivity of the membrane provides an assessment of glomerular damage.

Unit 9. Kidney Function Test

Chronic Kidney Disease (CKD)

GFR < 60 mL/min/1.73m² for 3 months or more with or without kidney damage indicates CKD. CKD is a silent killer, incidence is increasing worldwide and is the progressive loss of renal function which is a growing problem that affects approximately 12 % of the adult population. Kidney disease is very common, but silent, and progresses very slowly. Major risk factors of CKD are diabetes mellitus, hypertension, glomerular nephritis, urinary tract infection, autoimmune diseases, kidney stones and toxic effects of some drugs. The early symptoms of kidney failure are Polyuria (passing more urine), Nocturia (passing more urine during night), Pedal edema (puffiness of face), High blood pressure, Unexplained anemia, Fatigue (lassitude and tiredness), Microalbuminuria and Mild elevation of serum creatinine.

Stage	Grade	GFR
Minimal damage with normal GFR	**1**	**90-119**
Mild damage with slightly low GFR	**2**	**60-89**
Moderately low GFR	**3**	**30-59**
Severely low GFR	**4**	**15-29**
Kidney Failure (End Stage Renal Disease "ESRD") which need for Dialysis/Kidney Transplantation	**5**	**< 15**

Unit 9. Kidney Function Test

Acute Kidney Injury (AKI)

AKI is the abrupt kidney dysfunction, usually due to renal tubular cell injury. It is characterized by rapid rise of serum creatinine and low urine output. Onset of AKI can be swift and often deadly. In AKI, serum creatinine, the current standard for assessing kidney function, can take hours or days to respond to acute kidney damage. Novel biomarkers of tubular injury, such as neutrophil gelatinaseassociated lipocalin (NAGL), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (LFABP), and interleukin-18 (IL-18) may enable the early detection of acute kidney injury before or in the absence of a change in GFR. Out of these, urinary neutrophil gelatinase-associated lipocalin (uNGAL) is found to be the best to predict acute kidney injury. The uNGAL could be most useful when sCr is in the middle range. NAGL is a small molecule (molecular weight 25 kDa). It is found in neutrophils as well as in renal tubular epithelium, where its expression is dramatically increased in ischemic or nephrotoxic injury.