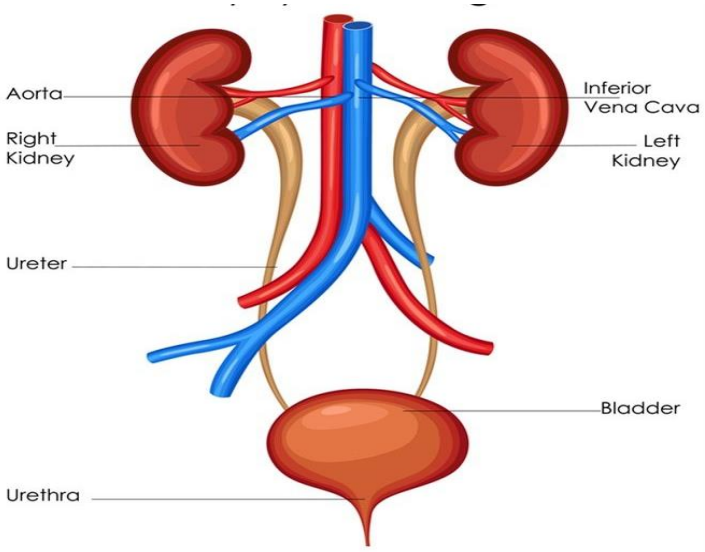
Unit 3

Kidney/ Renal Function Tests

Outlines:

- Anatomy of the Nephron
- Physiological functions of kidneys
- Urine formation
- Renal Function Tests
  a) Glomerular
  b) Tubular
- Acute Renal Failure
- Chronic Kidney Disease



Kidney structure and functions

Each kidney consists of one million Functional units: Nephron, each nephron can be divided into:-

a) The glomerulus (filtration)
b) Tubules (reabsorption & secretion)
   1. Proximal tubule (reabsorption)
   2. Loop of Henle (concentration)
   3. Distal tubule (secretion)
   4. Collecting duct (H_2O reabsorption)

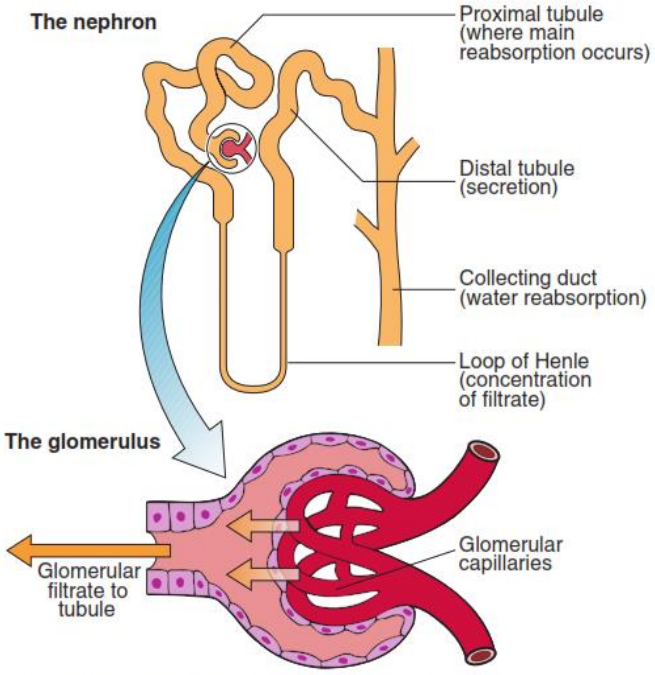


Fig 14.1 **Diagrammatic representation of a nephron.**

Functions of the Kidneys:

1) Excretory Functions:

- Removal of organic wastes products from body fluids (urea, creatinine, uric acid)
- Kidneys serve to rid the body of most of the undesirable waste products of metabolism , as well as any excess of inorganic substances
- The maximal excretory rate is limited or established by their plasma concentrations and the rate of their filtration through the glomeruli
- The maximal amount of substance excreted in urine does not exceed the amount transferred through the glomeruli by filtration except in the case of those substances capable of being secreted by the tubular cells

2) Regulatory functions (Homeostasis):

- **This function is the main function of the kidney to maintain the constant optimal chemical composition of the body.**

1. **Retention of biologically active substances (glucose, amino acids , minerals and vitamins), by differential reabsorption throughout the tubules**
2. **Regulation of the total water and electrolytes body content (Water-Salt Balance)**
3. **Kidneys are responsible for keeping pH of the blood constant (Acid-Base Balance) by excreting H^+ ions and reabsorbing HCO_3^-**
4. **Blood pressure regulation via renin-angiotensin system**

3. Endocrine functions:

- **The kidneys act as endocrine glands and secrete a variety of hormones , (erythropoietin , renin vit-D_3) and are subject to control by others (ADH, Aldosterone, PTH)**

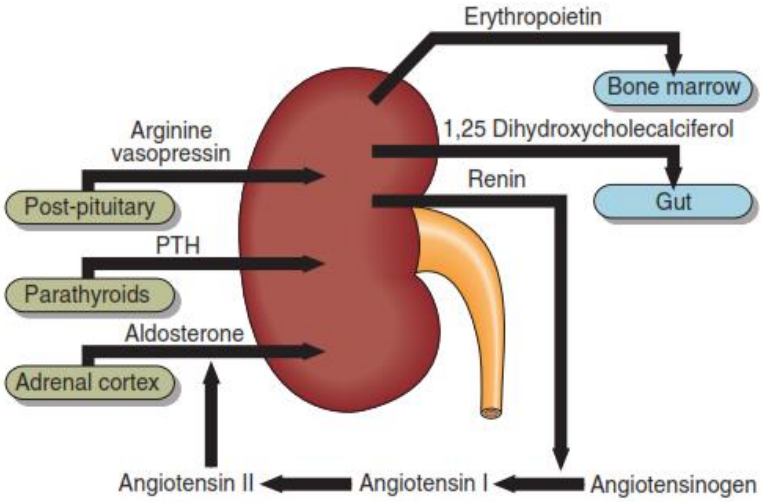


Fig 14.2 **Endocrine links in the kidney.**

Urine formation

- **Urine is a sterile fluid composed of.**

1. **Water (95%)**
2. **Nitrogen containing waste (Urea, Uric acid , Ammonia, and Creatinine)**
3. **Electrolytes**

- **Urine is formed in nephron by 3 processes ;**

1. Glomerular Filtration: process by which cells and large proteins are filtered from the blood to make an ultra-filtrate that will become urine.

2. Tubular Reabsorption: it is the transport of molecules needed by body from ultra-filtrate into the blood e.g. Glucose and amino acids.

3. Tubular Secretion: it is the reverse process of reabsorption, in which molecules are transported from blood directly to the urine through tubules

1. Glomerular Filtration:

- **Filtration is a passive process (no need for energy) in which cells and large proteins are filtered from the blood to make an Ultra filtrate that will eventually become urine**
- **The glomeruli act as filters which are permeable to water and Low Mw substances, but impermeable to macromolecules.**
- **This impermeability is determined by both size and charge, with proteins smaller than albumin (68 kDa) being filtered, and +ve charged molecules being filtered more readily than those with a -ve charge.**

The filtration rate is determined by

1) The differences in blood pressure in the glomerular (55 mmHg) capillaries and the hydrostatic pressure (15 mmHg) in the lumen of the nephron,

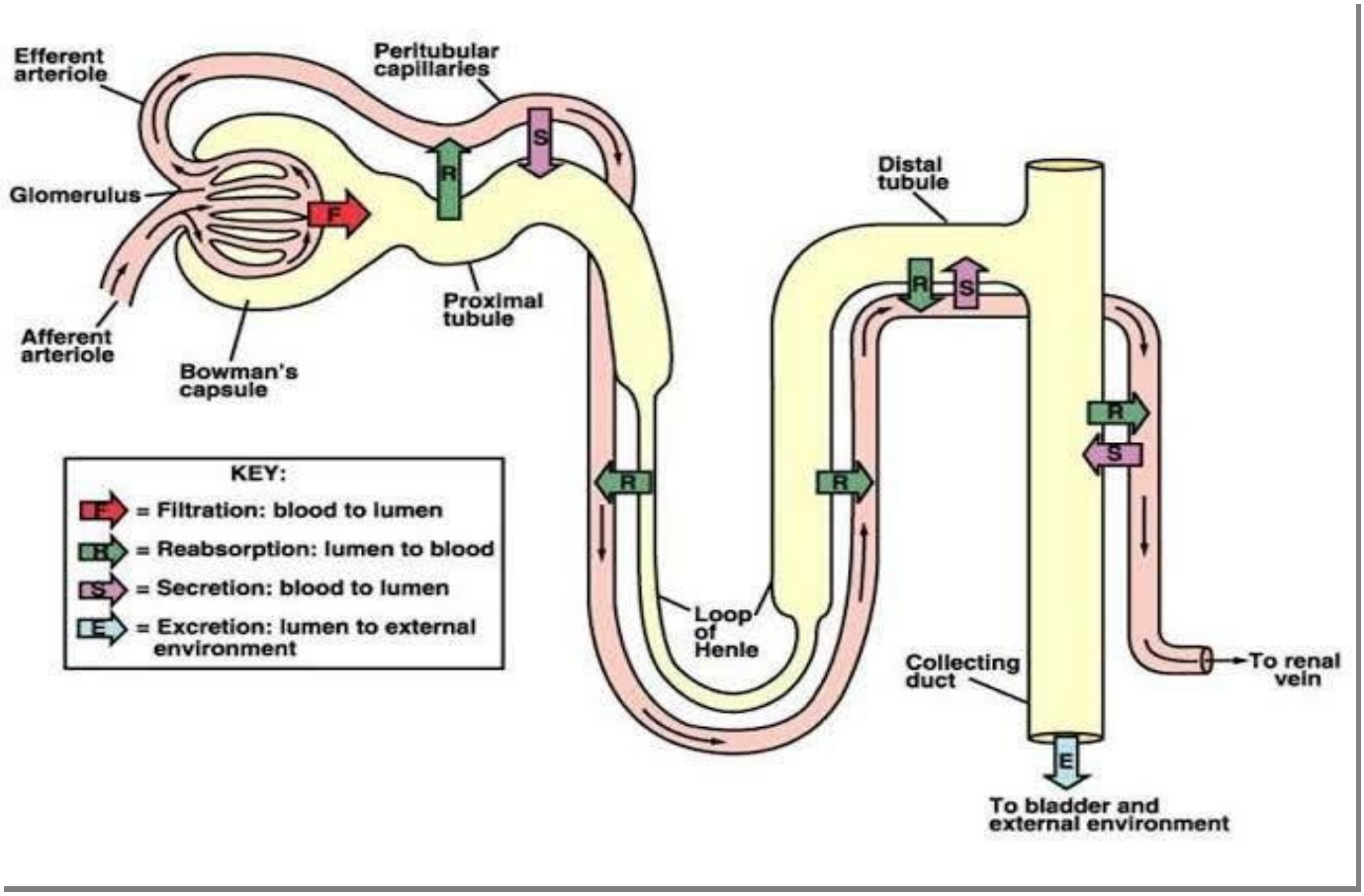
2) By the nature of the glomerular basement membrane.

3) By the total glomerular area available for flirtation.

- **The volume of blood that filtered through the glomeruli each minute is called the Glomerular Filtration Rate (GFR).**
- **It varies with body size so it is corrected to body surface area (BSA) of 1.73 m^2**
- **In the normal adult, GFR is about 120 ml/min/1.73 m^2 (about 180 liters/Day), (12 times the typical ECF volume and 70 times of the plasma volume), and has a composition similar to plasma except that it is almost free of protein.**

2. Tubular Reabsorption and secretion:

- **Reabsorption of water and solute occurs throughout entire length of tubule. Approximately 99% of all water goes back into the body. Thus the 180 liters that have been filtered become 1.5 -2 liters of urine per day**



Renal Function Test is

- They are a collective of individual tests help to determine f the kidneys are preforming their tasks adequately
- These tests are done on urine samples, as well as on blood samples.

Glomerular tests	Tubular tests
1) Urine analysis 2) Serum NPN (BUN, creatinine uric acid) 3) Creatinine clearance 4) Cystatin C 5) Albumin in urine	1) Osmolality (plasma and urine) 2) Water deprivation test 3) Urine pH 4) α1 and β2 microglobulins in urine 5) Glycosuria 6) Aminoaciduria

Glomerular Function Tests

1) Urine analysis

a) The physical examinations: which include volume; color, odor, specific gravity, reaction, and aspect.

b) Chemical examinations; for abnormal constituents: which include proteins, glucose, ketone bodies, bile salts, bilirubin, and blood.

C) Microscopic examinations:

1. **Cells and casts normally urine does not contain any red blood cells, pus cells and casts. In case of glomerulonephritis the urine will contain red blood cells; pus cells and casts (hyaline or granular casts).**

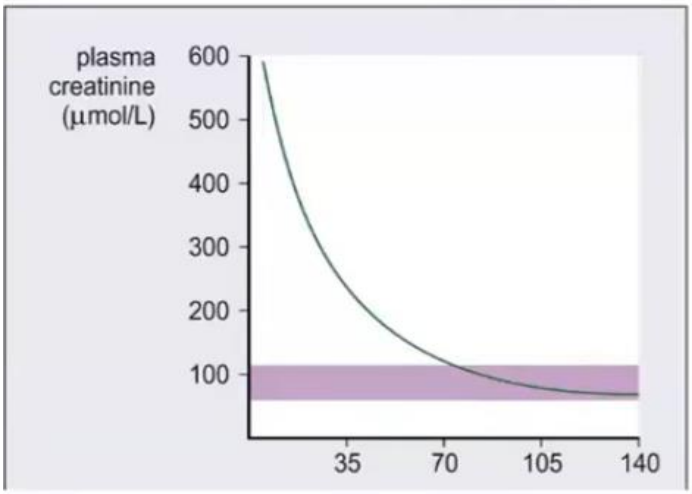
2. **Crystals: the urine may contain one or more of the following crystals, uric acid, calcium oxalate, phosphates and cysteine crystals (in case of inborn error of cysteine metabolism).**

2) Serum NPN compounds

- **Plasma concentrations of NPN (creatinine, urea and uric acid) are inversely related to the GFR.**
- **Creatinine is the most reliable simple biochemical test of glomerular function. Creatinine is produced irreversibly from dehydration of creatine and completely filtered from the blood by glomeruli and not reabsorbed or secreted by renal tubules**
- **However, serum creatinine is insensitive index of renal function as GFR can decrease by 50% before plasma creatinine concentration rises beyond the normal range , a normal plasma creatinine does not necessarily imply normal renal function, although a raised creatinine does usually indicate impaired renal function**
- **Endogenous creatinine production is proportional to muscle mass therefore the plasma level of creatinine in adult males is greater than female.**
- **Meat-rich diets can increase plasma creatinine, so ideally blood samples should be collected after an overnight fasting**
- **Strenuous exercise also causes a transient, slight increase in plasma creatinine concentrations**
- **N.B: normal serum creatinine is 1.5 mg % (133 µmol/L) , When serum level reaches 8 mg% (700 µmol/L) or more , *patient will require renal dialysis***

3) Creatinine Clearance

- **Clearance tests measure the amount of blood which could be completely cleared of a substance per minute.**
- **Creatinine clearance is the amount of blood which could be completely cleared of creatinine per minute.**
- **It is the best measurement of GFR**
- **Normal value is about of 120 ml/min**
- **Minimum level of creatinine clearance that is needed to maintain life without need of renal dialysis is 10 ml/min**



- **The test is done by comparing serum creatinine levels and amount of excreted creatinine in 24 hours urine, it can be calculated from the following equation:**

$$\frac{U \times V}{P}$$

U = Urinary creatinine by mg%
V = Urine flow rate (ml/min)
P = Plasma creatinine by mg%

- **Creatinine clearance in adults is normally of 120 ml/min, corrected to a standard body surface area of 173 m^2.**
- **The accurate measurement of creatinine clearance is difficult especially in outpatients, as it is necessary to obtain a complete and accurately timed sample of urine.**
- **The usual collection time is 24 h. but patients may forget the time or forget to include some urine in the collection. Patients may add water or some other person's urine to their own collection. Thus, measurements of creatinine clearance are potentially unreliable and no longer recommended in practice.**
- **Alternative methods should be used if a reliable calculation of GFR is required (Estimated GFR or eGFR)**
- **This approach has the advantage that a urine collection is not required**
- **Several formulae have been derived from the Modification of Diet in Renal Disease (MDRD) to calculate eGFR.**
- **The "four-variable" formula is: (Cr, Age, Sex, Race)**
- **A six-variable formula includes serum urea and albumin in addition.**

4) Cystatin C

- **This low molecular weight peptide is produced by is nucleated cells**
- **It is cleared from the plasma by glomerular filtration and its plasma concentration reflects the GFR more accurately than creatinine as it is not influenced by gender or muscle mass**
- **Measurement may have a role in the detection of early renal impairment.**

5) Albumin in urine:

- **The glomerular basement membrane does not usually allow passage of albumin and large proteins.**
- **A small amount of albumin is found in urine (<25 mg/day) . When larger amounts (> 250 mg/day) ⟶ severe damage of glomerular membrane**

Renal tubular tests

- Renal tubular dysfunctions are less commonly than that of glomerular.
- Specific disorders affecting the renal tubules may affect
  1. The ability to concentrate urine
  2. To excretes an appropriately acidic urine,
  3. Impaired reabsorption of amino acids, glucose, phosphate
- There are no easily performed tests that quantitatively measure tubular function
- Many tests rely on the detection of increased quantities of substances in the urine that are normally reabsorbed by the tubules (glucose, amino acids, H_2O).
- In some conditions , these defects occur singly , in others , multiple defects are present

Tubular fiunction tests

1) Osmolality measurements (plasma and urine)

- Urine Osmolality serves as general marker of tubular function. Because the functioning tubules have the ability to concentrate urine.
- Normal Plasma Osmolality is 280-295 mOsml/kg (Milliosmoles per kilogram)
- A 24 hour urine osmolality should be 2-3 times the plasma osmolality (500-800 mOsm/Kg) this means Urine / plasma osmolality ratio-2-3 If
- If Urine / plasma osmolality ratio = 1 ⟶ indicate tubules are not reabsorb H_2O

2) Water deprivation test: It is the test for renal concentration ability

- The normal physiological response to water deprivation is water retention which minimizes the rise in plasma osmolality. this response depends on:
  a) Normal ADH releasing mechanism
  b) Normal tubular response to the released ADH
- Fluid is restricted overnight (8 pm 10 am) and measure the osmolality of urine voided in the morning. Normally, the urine osmolality must be raised.
- if the urine osmolality fails to rise ⟶ indicates Diabetes Insipidus
- To differentiate between Neurogenic and Nephrogenic DI Desmopressin (DDAVP) which is a synthetic analogue of AVP, is administered and subsequent urine osmolality measurement

3) Urine pH

- The normal urine pH is slightly acidic (pH= 5). Only fresh urine sample is used for determination of pH (if not fresh, urease-splitting bacteria may alkalinize the urine)
- The normal response to metabolic acidosis is to increase H^+ excretion and urine pH will be less 5.3

- **If pH >5.3 ⟶ indicate that the cause of <u>metabolic acidosis</u> is tubular dysfunction (Renal Tubular Acidosis or RTA) that is 4 types:**

a) <u>Type I :</u> inherited or acquired defect in tubular secretion of H^+

b) <u>Type II</u>: reduced tubular HCO_3 reabsorption

C) <u>Type III</u>: pediatric variant of type I

d)<u>Type IV</u> reduced tubularHCO_3,reabsorption due to ↓ aldosterone, aldosterone receptors defects, or aldosterone antagonists

4) α1and ß2 microglobulins in urine:

- **α1 and β2 microglobulins are small proteins that are <u>normally filtered</u> through the glomeruli and reabsorbed by the tubules**
- **An increased concentration o these proteins in urine is a sensitive indicator of renal tubular cell damage**

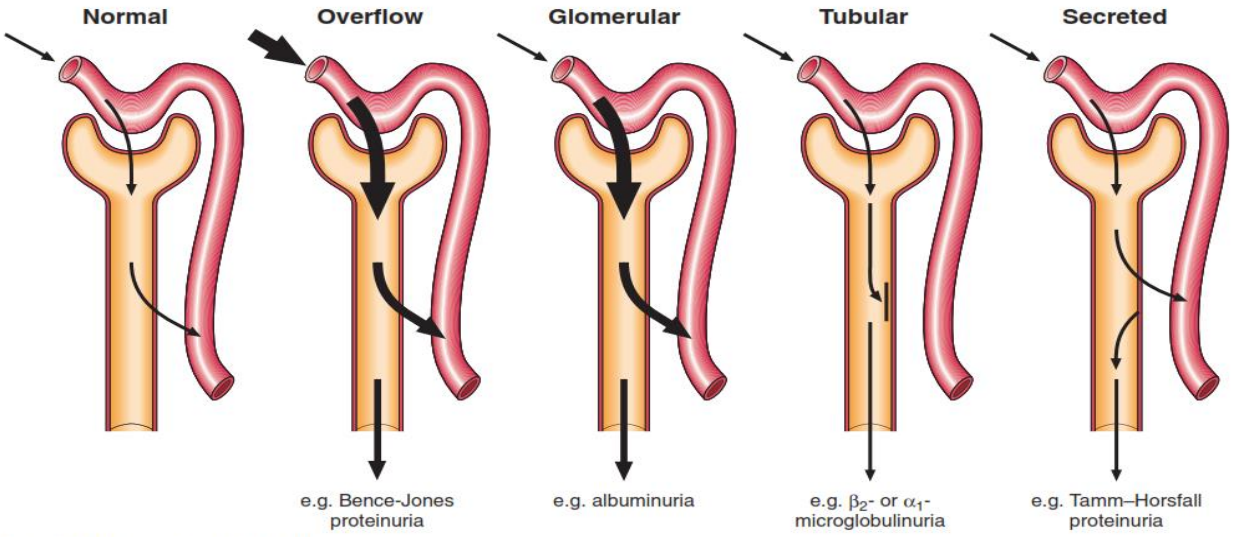


Fig 17.1 **Mechanism of proteinuria.**

5) Glycosuria:

- **Renal threshold is the capacity for the renal tubules to reabsorb a substance The presence of glucose in urine when blood glucose is normal usually reflects the inability of tubules to reabsorb glucose. This is called renal glycosuria.**

6) Aminoaciduria

- **Normally amino acids in the glomerular filtrate are reabsorbed in the tubules. Presence of amino acids in urine may be due to :**

a) Plasma concentration exceeds the renal threshold (cystinuria)

b) Renal tubular damage

❖ **Fanconi syndrome: is generalized tubular defects leads glycosuria . aminoaciduria, tubular proteinuria and RTA Caused by heavy metal poisoning**

Renal Failure

❖ **Renal failure is the cessation of the kidney function. There are 2 types**

a) Acute Renal Failure (ARF) (recently known as AKI):

- **The kidneys fail over a period of ihours or days. ARF may be reversed**
- **It usually presents as a sudden deterioration of renal function indicated by rapidly rising serum urea and creatinine levels.**
- **Urine output falls to less than 400 ml/day (oligouria) or may pass no urine at all (anuria)**

b) Chronic Renal Failure (CRF) [recently known as CKD):

- **The kidneys fail over a period of months or years and leads to end-stage renal failure (ESRF) . CRF is irreversible.**
- **It usually presents as a progressive irreversible destruction of the kidney**

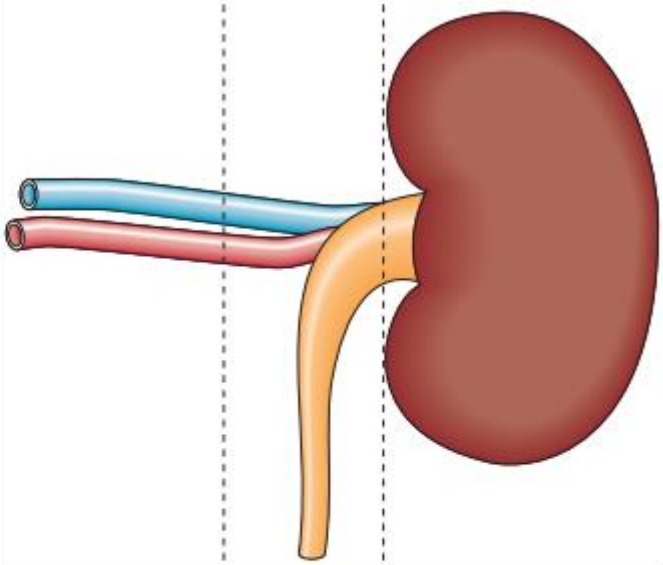
Classification:	Pre-renal	Post-renal	Renal
			
Mechanism:	Reduced renal perfusion	Ureteric/ urethral obstruction	Intrinsic kidney tissue damage
Examples:	Blood loss and hypovolaemia	Stones or malignancy	Glomerulonephritis or nephrotoxins

Fig 18.1 **The classification of acute renal failure.**

Acute Renal Failure

Aetiology:

a) Pre-renal

The kidney fails to receive a proper blood supply due to reduced ECF (blood loss, burns , prolonged vomiting or diarrhea, CHF , hepatic failure occlusion of the renal artery

b) Post-renal:

The urine flow of the kidneys is impaired by an obstruction (renal stones or cancer of prostate or bladder). The effective filtration pressure at the glomeruli is reduced due to the back pressure caused by the blockage

c) Renal:

Intrinsic damage to the kidneys; this may be due to a variety of diseases (glomerulonephritis or nephrotoxic drugs) of be a consequence of post-renal problems

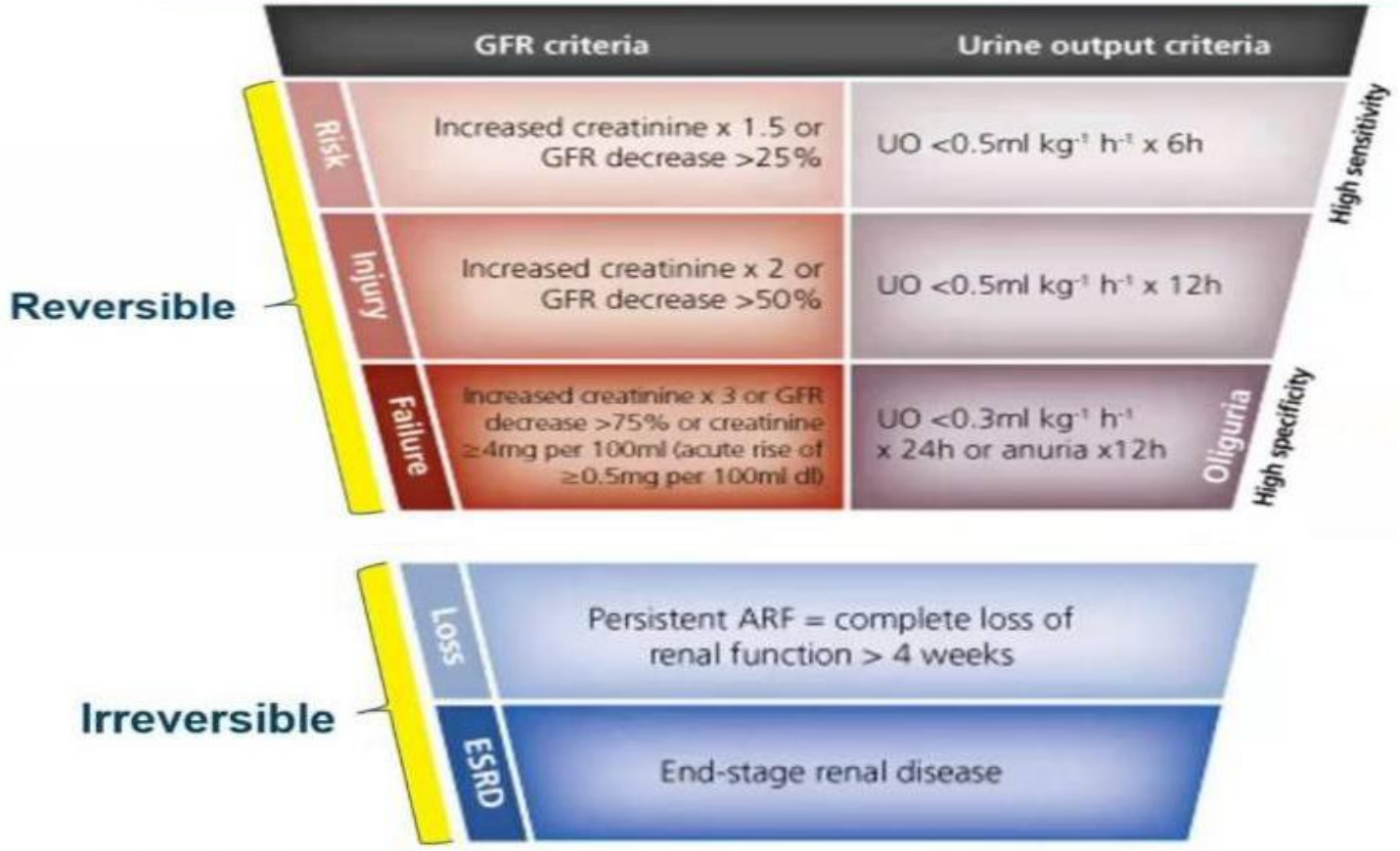
Biochemical findings:

1. **Reduced GFR**
2. **increased AVP and Aldosterone secretion**
3. **Low urine output (oliguria or anuria) with high osmolality**
4. **increased serum urea and creatinine**
5. **Metabolic acidosis**
6. **Hyperkalemia (most sensitive)**

Grades of AKI	Creatinine increase	GFR decrease%	Urine output
Risk	1.5 times	> 25	<0.5 ml/kg/h x 6 h
Injury	2 times	>50	<0.5 ml/kg/h x I2 h
Failure	3 times	> 75	<0.5 ml/kg/h x 24 h or anuria x12 h
Loss	Persistent ARF(Complete loss of renal function for >4 weeks)		
ESRD	End stage renal disease		

AKI: Acute kidney injury, RIFLE: Risk (R), injury (1), and Failure (F) and two outcome classes , Loss (L) and End stage kidney disease (E) , ARF Acute renal failure

Proposed by the Acute Dialysis Quality Initiative (ADQI) group



Aetiology:

- **The aetiology involves any kidney diseases leading to loss of functioning nephrons.**
- **The CRF patients may have not any symptoms until the GFR falls below 15 ml/min.**
- **If CRF not treated by dialysis or transplant, will result in the death.**

Stages of CKD according to GFR

Stage	Description	GFR (ml/min)	Comments
1	Kidney damage with normal or increased filtration	> 90	Proteinuria, haematuria , or other kidney abnormality by imaging
2	Kidney damage with mild decrease in kidney function	60-89	Proteinuria, haematuria , or other kidney abnormality by imaging
3	Moderate decrease in kidney function	30-59	Many patients are asymptomatic
4	Severe decrease in kidney function	15-29	Most patients are symptomatic
5	Established Kidney failure	< 15	Renal dialysis or transplant usually required

Biochemical findings:

1) **Kidneys lose their ability to reabsorb H_2O (polyuria) while retain the ability to reabsorb sodium**

2) **Hyperkalemia (when GFR is very low)**

3) **Metabolic acidosis develops as GFR decreases**

4) **Hypocalcaemia and hypophosphatemia (as kidneys cannot activate Vit- D)**

5) ↑ **PTH secretion (in response to hypocalcaemia)**

6) **Anemia (due to decreased erythropoietin synthesis)**

Increased	Decreased
Urea	Sodium
Creatinine	Bicarbonate
Potassium	Calcium
Hydrogen ions	
Phosphate	
Magnesium	