Kidney Function Tests

The kidneys have three major functions:

1. Excretion of waste products

2. Maintenance of extracellular fluid (ECF) volume and composition, including acid-base balance

3. Hormone synthesis (renin, erythropoietin and calcitriol)

4. Contribute to glucose supply in the fasting state through gluconeogenesis.

Each kidney comprises approximately one million functional units, called **nephrons**. The glomerular filtrate is an ultrafiltrate of plasma; that is, it has a similar composition to plasma except that it is almost free of large proteins. Proteins with molecular weights lower than that of albumin (68 kDa) are filterable. Almost all the protein in the glomerular filtrate is reabsorbed and catabolized by proximal convoluted tubular cells, with the result that normal urinary protein excretion is <150 mg/24 h.

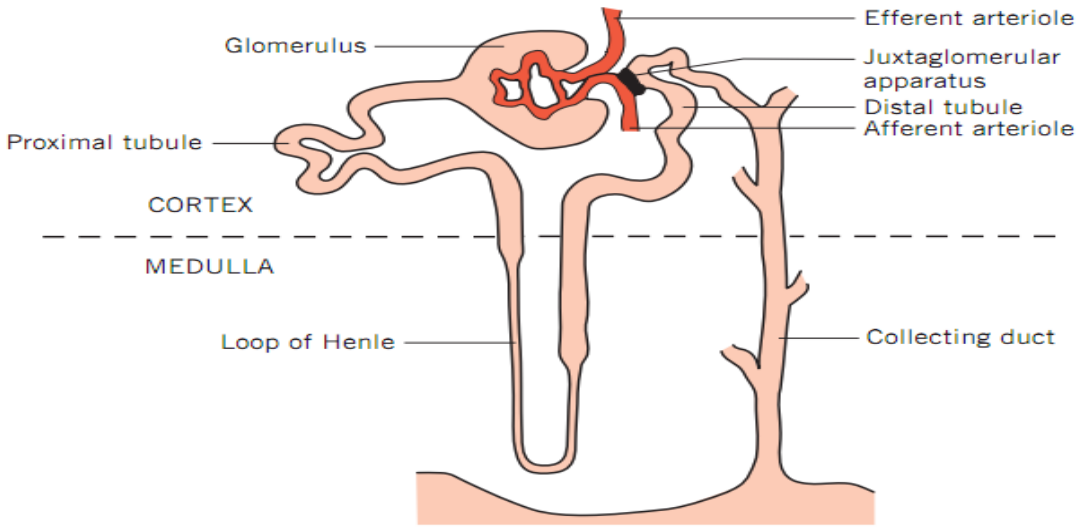

Figure (1) Nephron

The normal glomerular filtration rate (GFR) is approximately 120 mL/min, equivalent to a volume of about 170 L/24 h. However, urine

production is only 1–2 L/24 h, depending on fluid intake; the bulk of the filtrate is reabsorbed further along the nephron.

Biochemistry of renal disorders

Different parts of the nephrons are in close anatomical association and are dependent on a common blood supply. Renal dysfunction of any kind affects all parts of the nephrons to some extent, although sometimes either glomerular or tubular dysfunction is predominant. The net effect of renal disease on plasma and urine depends on the proportion of glomeruli to tubules affected and on the number of nephrons involved.

Uraemia is the term used to describe a raised plasma urea concentration and is almost always accompanied by an elevated creatinine concentration.

Reduced glomerular filtration rate with normal tubular function

Plasma

- ✓ High urea (uraemia) and creatinine concentrations.
- ✓ Low bicarbonate concentration, with low pH (acidosis).
- ✓ Hyperkalaemia.
- ✓ Hyperuricaemia and hyperphosphataemia.

Urine

Reduced volume of urine (oliguria).

Reduced tubular function with normal glomerular filtration rate

Plasma

- ✓ Normal urea and creatinine concentrations (normal glomerular function).

- ✓ low bicarbonate concentration and low pH.
- ✓ hypokalaemia, hypophosphataemia, hypomagnesaemia and hypouricaemia.

Urine

- ✓ Increased volume.
- ✓ PH inappropriately high compared with that in plasma.
- ✓ Amino aciduria, phosphaturia and glycosuria.

Acute kidney injury (AKI)

This was previously known as acute renal failure. In adults, oliguria is defined as a urine output of less than 400 mL/day, or less than 15 mL/h; it usually indicates a low GFR and a rapid decline in renal function **over hours to weeks**, with retention of creatinine and nitrogenous waste products. Oliguria may be caused by the factors discussed below.

1. Acute oliguria with reduced GFR (pre-renal)

This is caused by factors that reduce the hydrostatic pressure gradient between the renal capillaries and the tubular lumen. A low intracapillary pressure is the most common cause. It is known as renal circulatory insufficiency (pre-renal uraemia) and may be due to:

A. Intravascular depletion of whole blood (haemorrhage) or plasma volume (usually due to gastrointestinal loss), or reduced intake.

B. Reduced pressure as a result of the vascular dilatation caused by 'shock', causes of which include myocardial infarction, cardiac failure and intravascular haemolysis, including mismatched blood transfusion.

The patient is usually hypotensive and clinically volume depleted. If renal blood flow is restored within a few hours, the condition is

reversible, but, the longer it persists, the greater the danger of intrinsic renal damage.

2. Acute oliguria due to intrinsic renal damage

This may be due to:

A. Prolonged renal circulatory insufficiency.

B. Acute glomerulonephritis.

C. Septicaemia.

D. Ingestion of a variety of poisons or drugs.

E. Myoglobulinuria, Bence Jones proteinuria.

3. Acute oliguria due to renal outflow obstruction (post-renal)

Oliguria or anuria (absence of urine) may occur in post-renal failure. The cause may be due to the following:

A. Intrarenal obstruction, with blockage of the tubular lumina by haemoglobin, myoglobin and, very rarely, urate or calcium. Obstruction caused by casts and oedema of tubular cells is usually the result of true renal damage.

B. Extrarenal obstruction, due to calculi, neoplasms, for example prostate or cervix, urethral or prostatic hypertrophy, any of which may cause sudden obstruction. The finding of a palpable bladder indicates urethral obstruction.

Abnormal findings in acute kidney injury

1. A careful clinical history, especially of taking nephrotoxic drugs, and examination may give clues to the cause of AKI. It is essential to exclude reversible causes of pre-renal failure, including hypovolaemia or hypotension, and also post-renal urinary tract obstruction (renal tract

imaging may be useful, such as abdominal radiograph if calculi are suspected, and renal tract ultrasound).

2. Increase plasma urea and creatinine, hyperkalaemia, hypermagnesaemia, hyperphosphataemia, hyperuricaemia and metabolic acidosis may occur in the oliguric phase of AKI.

Chronic kidney disease (CKD)

Chronic renal dysfunction defined as reduced GFR, proteinuria, haematuria and/or renal structural abnormalities of more than **90 days** duration, is usually the end result of conditions such as diabetes mellitus, hypertension, primary glomerulonephritis, autoimmune disease, obstructive uropathy, polycystic disease, renal artery stenosis, infections and tubular dysfunction and the use of nephrotoxic drugs. It is common, perhaps affecting about 13 per cent of the population.

Histological examination shows that not all nephrons are equally affected: some may be completely destroyed and others almost normal. Also, some segments of the nephrons may be more affected than others. The effects of chronic renal disease can be explained by this patchy distribution of damage. The loss of 75 per cent of renal tissue produces a fall in GFR of 50 per cent. The CKD may pass through two main phases:

A. Polyuric phase: At first, glomerular function may be adequate to maintain plasma urea and creatinine concentrations within the reference range. As more glomeruli are involved, the rate of urea excretion falls and the plasma concentration rises. This causes an osmotic diuresis in functioning nephrons; in other nephrons the tubules may be damaged out of proportion to the glomeruli. Both tubular dysfunction in nephrons with functioning glomeruli and the osmotic diuresis through intact nephrons contribute to the polyuria.

B. Oliguric phase: If nephron destruction continues, the findings become more like those of pure glomerular dysfunction. Glomerular filtration decreases significantly and urine output falls; oliguria precipitates a steep rise in plasma urea, creatinine and potassium concentrations; and the metabolic acidosis becomes more severe.

Abnormal findings in chronic kidney disease

1. Increase plasma **urea** and **creatinine**.

2. Hyperkalaemia and **metabolic acidosis** may occur in the CKD.

3. Hyperphosphataemia and **hypocalcaemia**. Plasma phosphate concentrations rise and plasma total calcium concentrations fall. Impaired renal tubular function and the raised phosphate concentration inhibit the conversion of vitamin D to the active metabolite and this contributes to the fall in plasma calcium concentration. Usually, hypocalcaemia should be treated only after correction of hyperphosphataemia. After several years of CKD, secondary hyperparathyroidism may cause decalcification of bone. Some of these features of CKD can also evoke renal osteodystrophy.

4. Plasma urate concentrations rise (**hyperuricaemia**) in parallel with plasma urea. **Hypermagnesaemia** can also occur.

5. Normochromic, normocytic anemia due to erythropoietin deficiency is common and, because haemopoiesis is impaired, does not respond to iron therapy; this can be treated with recombinant erythropoietin.

6. One of the commonest causes of death in patients with CKD is **cardiovascular disease**, in part explained by hypertension and a dyslipidaemia of hypertriglyceridaemia and low HDL.

7. The presence of increasing **proteinuria** may be the best single predictor of disease progression.

Nephrotic syndrome

The nephrotic syndrome is caused by increased glomerular basement membrane permeability, resulting in protein loss, usually more than 3 gram a day, with consequent hypoproteinaemia, hypoalbuminaemia and peripheral oedema. All but the highest molecular weight plasma proteins can pass through the glomerular basement membrane. The main effects are on plasma proteins and are associated with hyperlipidaemia and hyperfibrinoginaemia. Uraemia occurs only in late stages of the disorder, when many glomeruli have ceased to function. It is usually associated with systemic disease such as post-infectious glomerulonephritis, e.g. post-streptococcal.

Glomerular function tests

1. Measurement of plasma concentrations of urea and creatinine

Urea is derived in the liver from amino acids and therefore from protein, whether originating from the diet or from tissues. The normal kidney can excrete large amounts of urea. If the rate of production exceeds the rate of clearance, plasma concentrations rise.

The rate of urea production is accelerated by:

1. A high-protein diet.
2. Absorption of amino acids and peptides from digested blood after haemorrhage into the gastrointestinal lumen or soft tissues.
3. Increased catabolism due to starvation, tissue damage or steroid treatment.

Conversely, the plasma urea concentration may be lower than 1.0 mmol/L:

1. Those due to increased GFR or haemo dilution (common):

A. Pregnancy.

B. Intravenous infusion (hospitalized patients).

C. Inappropriate ADH secretion (syndrome of inappropriate ADH secretion, SIADH).

2. Those due to decreased synthesis:

A. Use of amino acids for protein anabolism during growth, especially in children.

B. Low protein intake.

C. Very severe liver disease.

Creatinine is largely derived from **endogenous** sources by muscle creatine breakdown. Plasma creatinine usually correlates with muscle mass, with 95 per cent of creatine occurring in skeletal muscle. The high-protein diets and catabolic states probably affect the plasma concentration of creatinine **less than that of urea**. The normal kidney can excrete large amounts of creatinine. If the rate of production exceeds the rate of clearance, plasma concentrations rise.

Serum urea and creatinine levels do not begin to increase until the GFR has fallen by 50% or more.

2. Clearance as an assessment of glomerular filtration rate

Clearance: is the volume of plasma that could be completely cleared from substance in 1 minute.

$$\textbf{Clearance} = U_x \times V/P_x$$

- U_x = urine concentration of x (mg/dL)
- P_x = plasma concentration of x (mg/dL)
- V = urine output (mL/min)

✓ If X is neither reabsorbed nor secreted, clearance = GFR (Inulin clearance)

✓ If X is reabsorbed, clearance < GFR (Urea clearance)

✓ If X is secreted, clearance > GFR
(Creatinine clearance)

Creatinine and urea are produced endogenously but inulin is an **exogenous** compound (polymer of fructose). Creatinine clearance, urea clearance, inulin clearance can be used to estimate GFR.
- Creatinine clearance > GFR because it secreted by the renal tubules.
- Urea clearance < GFR because it reabsorbed by the renal tubules.
- Inulin meets all of the criteria for the **ideal** substance to measure GFR.
Inulin clearance = GFR because it is not secreted and not reabsorbed by the renal tubules. Inulin clearance is the "**gold standard**" for GFR determination.

3. Cystatin C (CysC)

- An endogenous substance that can be used as a marker of GFR. Cystatin C is a 13-kDa protein that is a member of the family of cystine proteinase inhibitors.
- Unlike other endogenous compounds, **CysC** is not secreted and reabsorbed by the renal tubules. It has been suggested that plasma **CysC** may approximate to the '**ideal**' endogenous marker for GFR, as blood concentrations are independent of patient age and sex.

Renal tubular disorders

Renal tubular disorders can be **congenital** or **acquired**; they can involve single or multiple aspects of tubular function. The congenital conditions are inherited and all are rare: their clinical sequelae relate to the consequences of loss of substances that are normally completely or partially reabsorbed by the tubules.

1) Fanconi syndrome. This is a generalized disorder of tubular function characterized by glycosuria, amino aciduria, phosphaturia and acidosis.

2) Renal tubular acidosis (RTA). There may be defect in hydrogen ion excretion or impairment of bicarbonate reabsorption, or hypoaldosteronism (secondary to adrenal disease, or to renal disease).

3) Defects of urinary concentration. Impairment of urinary concentration is a feature of nephrogenic diabetes insipidus, a group of primary tubular disorders.

4) Glycosuria, amino aciduria

5) Hypophosphataemic rickets (vitamin-D-resistant rickets). A defect in tubular phosphate reabsorption leads to severe rickets and growth retardation. This does not respond to treatment with vitamin D alone, even if administered in massive doses, but can be treated effectively with a combination of oral phosphate supplements and vitamin D, usually given as a 1α- hydroxylated derivative.

Tests of renal tubular function

Many rely on the **detection of increased quantities of substances in the urine that are normally reabsorbed by the tubules**. The presence of glycosuria in a subject with a normal blood glucose concentration implies proximal tubular malfunction that may be either isolated (renal glycosuria) or part of a generalized tubular defect (Fanconi syndrome). Aminoaciduria can occur with tubular defects and can be investigated by amino acid chromatography. The small amount of (principally low molecular weight) protein that is filtered by the glomeruli is normally absorbed by and catabolized in the proximal renal tubular cells. **The presence of low molecular weight proteins in urine can indicate renal tubular damage.** The measurement of retinol-binding protein (RBP) or α1-microglobulin is more reliable but, in practice, specific evidence of tubular damage is rarely required clinically. Albumin is also normally filtered to a small extent, and

proximal tubular damage may result in increased urinary excretion in the microalbuminuria range. The only tests of **distal tubular function** in widespread use are the **fluid deprivation test**, to assess renal concentrating ability, and tests of **urinary acidification**, to diagnose distal renal tubular acidosis.

Renal calculi

Renal calculi are usually composed of products of metabolism present in normal glomerular filtrate, often at concentrations near their maximum solubility.

Conditions favoring renal calculus formation

1. A high urinary concentration of one or more constituents of the glomerular filtrate, due to:

A. Low urinary volume with normal renal function, because of restricted fluid intake or excessive fluid loss over a long period of time.

B. High rate of excretion of the metabolic product forming the stone.

2. Changes in pH of the urine, often due to bacterial infection, which favour precipitation of different salts at different hydrogen ion concentrations.

3. Urinary stagnation due to obstruction to urinary outflow or renal tract structural abnormality.

4. Lack of normal inhibitors: urine normally contains inhibitors, such as citrate, pyrophosphate and glycoproteins, which inhibit the growth of calcium phosphate and calcium oxalate crystals respectively.

Constituents of urinary calculi

Renal calculi may consist of the following: **calcium-containing salts** (80 % of all renal stones) as calcium oxalate and calcium phosphate, **struvite** (magnesium ammonium phosphate) (10 % of all renal stones), **urate** (8 % of all renal stones), **cystine** (rare) and **xanthine** (rare).