

CHAPTER 1

Structure and Function

ANATOMY OF THE KIDNEYS

The kidneys are a pair of bean-shaped organs located at the back of the body about the level of the waist. They receive their blood supply from the main artery of the body called the aorta. Each kidney measures 10–15 cm in length and weighs about 160 gm. Urine is conducted from the kidneys along two tubes known as the ureters which join the urinary bladder in the pelvis. The capacity of the bladder varies from 500 to 750 ml. Each kidney is made up of 1 million units called nephrons. Each nephron consists of two parts, the glomerulus which is a bunch of capillaries with thin walls serving as a filter, and the tubule which drains the glomerulus (Figs. 1.1 & 1.2).

The glomerular tuft is made up of a coil of capillaries which is fed by an afferent arteriole and drained by an efferent arteriole. The tuft lies in a space known as Bowman's capsule which is spherical and opens directly into the proximal tubule. The glomerular tuft and capsule is lined by epithelial cells. Ultrafiltration occurs across the capillary tuft and the fluid passes into the proximal tubule. Between the afferent and the efferent arterioles of the glomerulus lies the juxta-glomerular apparatus which lies in the area bounded by the two arterioles, the distal tubule of the same nephron and the lacis cells lying between the two arterioles.

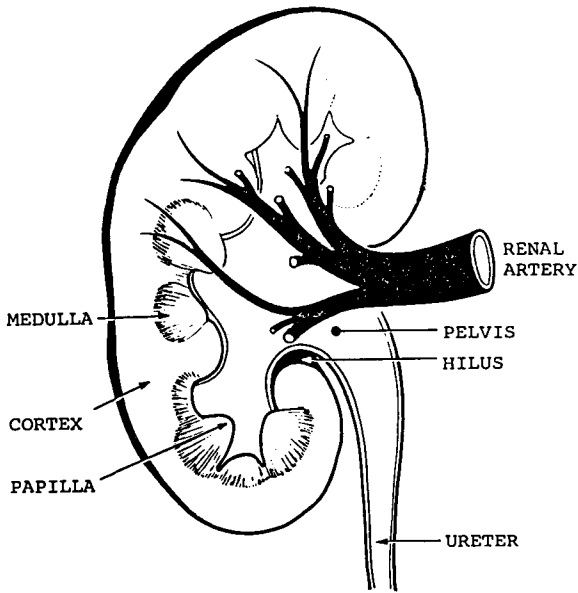


Fig. 1.1 The gross structure of the cut surface of the kidney

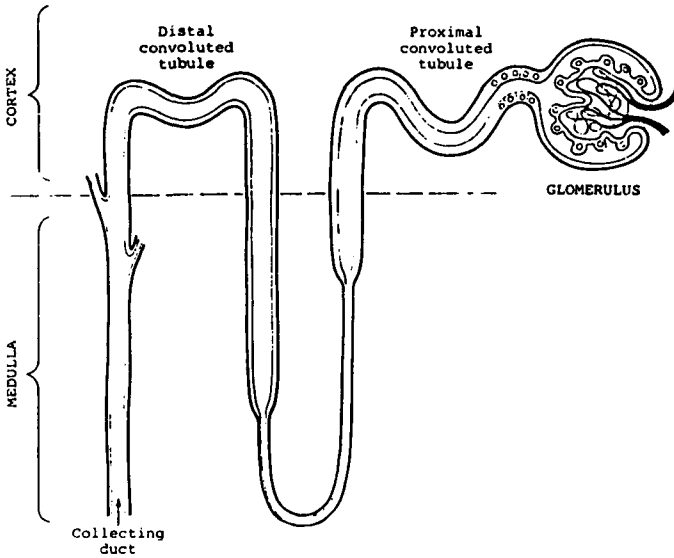


Fig. 1.2 Diagram of a nephron

Within the glomerular tuft are the mesangial cells and mesangial matrix. The mesangial cells have a supportive and phagocytic function and have been referred to as the third reticulo-endothelial system. They are capable of contraction and are involved in the pathogenesis of IgA nephritis and diabetic nephropathy. Factors or agents that cause increased mesangial cell contractility predispose to mesangial sclerosis and therefore glomerulosclerosis. The capillary loops abound around the core of mesangial cells and matrix. The wall of these capillary loops consists of three layers, the epithelial cells, the glomerular basement membrane and the endothelial cells (Fig. 1.3).

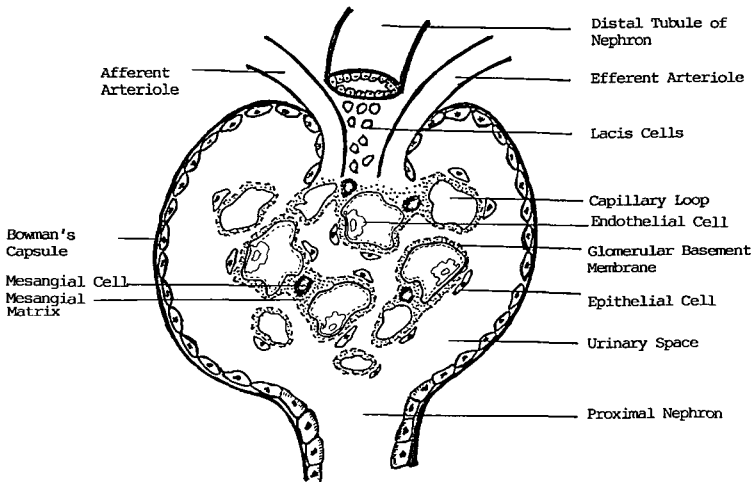


Fig. 1.3 Diagram of a glomerulus

The term “proliferative glomerulonephritis” refers to a proliferation of one of the three types of cells within the glomerulus: mesangial cells, endothelial cells or epithelial cells; and hence the different types of proliferative glomerulonephritis (GN): Mesangial Proliferative GN,

Endocapillary Proliferative GN and Crescentic GN. In Crescentic GN, there is now evidence to show that macrophages from the circulation as well as those in situ within the glomeruli gain entry into the glomerular tuft and transform themselves into epithelial cells and it is the proliferation of these transformed epithelial cells which forms the crescents in Crescentic GN.

The glomerular basement membrane (GBM) is composed of three layers (notice that many things occur in “threes”): a central dense zone, known as the lamina densa, an inner and outer lucent zone, known respectively as the lamina rara interna and externa. The GBM is 80 nm thick.

Ultrastructural studies reveal that the “filtration barrier” is composed of an inner fenestrated endothelium, the GBM as the middle layer and the outer layer of interdigital epithelial foot processes.

Pores have never been visualised on the GBM which is biochemically a hydrated gel composed of collagen-like and non-collagenous glycoproteins. The non-collagenase glycoprotein is rich in hydroxyproline, galactose, mannose and sialic acid. The epithelial foot processes are covered by glycoproteins which are rich in sialic acid. The negative (anionic) charges of sialic acid help to keep the foot processes apart. The negative charges on the basement membrane (due to the presence of glycosaminoglycans, such as heparan sulphate) and around the epithelial slits (due to sialic acid), constitute a filtration barrier. This explains why the fractional clearance of negatively charged particles is less than that of neutral particles of similar molecular dimensions as negatively charged particles are repelled at the GBM. Positive (cationic) charges are attracted to the GBM. They interfere with the integrity of glomerular permselectivity (maintained by the negative charges) and induce proteinuria. Hence, positively

charged particles have a higher fractional clearance than negatively charged particles.

Antibodies to the non-collagenous glycoproteins (which carry negative charges), but not antibodies to the collagenous glycoproteins, are nephrotoxic in experimentally induced anti-GBM nephritis.

Therefore it is not only the molecular size but also the electrostatic charge which determines a particle's exclusion from glomerular filtration. Loss of the charge barrier results in the loss of glomerular permselectivity and causes proteinuria.

FUNCTIONS OF THE KIDNEYS

Each day the two kidneys excrete about 1.5 to 2.5 litres of urine. One of the most important functions of the kidney is to regulate the amount of water and salt excreted. About 99% of the filtered salt is reabsorbed by the tubules. The output of salt is regulated to maintain a normal and constant salt level in the body. The renal tubules also reabsorb dissolved substances like glucose and amino acids, the building blocks of proteins. The kidney has the important task of ridding the body of excess acid and potassium.

There is a minimum amount of soluble waste we must excrete through our kidneys each day. They are mainly nitrogenous waste products, principally urea. These products are poisonous and they are the substances retained in the body when the kidney fails.

The kidney is also a producer of certain hormones. Renin is one of them. Renin by itself is inactive but it acts on angiotensin I to produce angiotensin II which causes blood vessels to constrict thereby raising the blood pressure. Another

hormone produced by the kidney is the active form of vitamin D which is necessary for strong and healthy bones as it promotes the absorption of calcium from the bowels. Without it we suffer from rickets. Erythropoietin, the third hormone produced by the kidney is necessary for the formation of red blood cells in the bone marrow. Patients with diseased kidneys are anaemic because they lack erythropoietin. Prostaglandins, another hormone, regulates the blood flow and blood pressure.

The main function of the kidneys is to make urine which contains the waste products of our metabolic processes. By regulating the rate at which these substances are excreted the kidneys are able to maintain the internal environment or the “milieu interieur”. The production of urine depends on the renal plasma flow and the glomerular filtration. Hence the measurement of the glomerular filtration rate (GFR) is an index of renal function.

In addition to various substances which are cleared by the kidneys, there are others which are filtered and reabsorbed like glucose and sodium, and some which are secreted or excreted by the renal tubules.

Renal Handling of Sodium

Sodium is filtered at the glomeruli and actively reabsorbed by the tubules. About 80% of filtered sodium chloride and water are reabsorbed by the proximal tubules. The sodium which reaches the distal tubule is reabsorbed by an ion exchange mechanism. Potassium and hydrogen ions are passed into the tubular lumen and sodium ions are removed actively from the lumen. This exchange mechanism is enhanced by aldosterone. Therefore, altogether about 99% of filtered sodium is reabsorbed. The volume of the extracellular fluid is

determined by the sodium content of the body which is regulated by the kidneys.

Renal Handling of Potassium

The majority of potassium is reabsorbed in the proximal tubules and that which is found in the urine is derived from potassium exchanged for sodium which is reabsorbed in the distal tubules and the collecting ducts.

Kidney Regulation of Acid-Base Balance

Extracellular fluid is maintained at a pH between 7.35 to 7.45. Two forms of acid which are continuously produced by the body require buffering and subsequent excretion.

- i. Carbon dioxide which is formed as a result of cellular metabolism combines with water to form carbonic acid. In the lungs, carbonic acid dissociates and CO_2 is eliminated in the expired air.
- ii. Fixed acids are acids which cannot be excreted via the lungs. They are also produced by the body's metabolic processes. The hydrogen ions produced by these fixed acids are buffered by bicarbonate ions in the body. The role of kidneys is to "regenerate" the bicarbonate which has been used up in the buffering of fixed acids.

Acidification of the Urine and Excretion of H^+

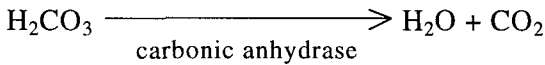
In normal persons, renal acidification maintains the plasma bicarbonate at physiologic concentrations by reclaiming all the filtered bicarbonate and excreting endogenously produced non-volatile or fixed acids.

This mechanism takes place at 3 sites.

i. At the Proximal Tubules:

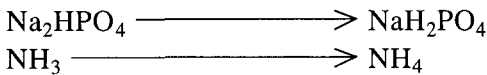
85% to 90% of filtered bicarbonate is reclaimed. For each mole of Na^+ reabsorbed, one mole of H^+ is excreted and one mole of bicarbonate is generated and returned to the blood.

Secreted H^+ titrates HCO_3^- to H_2CO_3 in the tubular lumen.



ii. At the Distal Tubule:

10% to 15% of filtered bicarbonate is titrated with secreted H^+ . The urine pH is now about 6.2. Also titrated are the urinary buffers:



Titrateable Acid = Measure of H^+ excreted as NaH_2PO_4

iii. At the Collecting Duct:

5% of bicarbonate is reabsorbed. The secretory capacity for H^+ is small but the large gradient generated for H^+ secretion enables the kidney to reduce the urinary pH to values of 5 or less and excrete NH_4 and titrateable acid at a rate equal to the endogenous production of the fixed acids.

Therefore

Net Acid Excretion = Titrateable Acid + NH_4 – Bicarbonate excreted

In Metabolic Acidosis:

Bicarbonate is titrated to extinction in the proximal tubule. The secretion of H^+ at the distal tubule is not buffered by

delivered bicarbonate as the gradient of H^+ at the lumen-peritubule is decreased. Urine pH is less than 5, net H^+ excretion is increased, but total H^+ secretion is decreased.

In Metabolic Alkalosis:

The amount of bicarbonate delivered to the distal tubule exceeds the H^+ secretory capacity. Urine pH is 8. Bicarbonaturia swamps H^+ excretion, though the total H^+ secretion is increased.

Adequacy of Gradient-Generating and Acid-Excreting Ability

The adequacy of gradient-generating and acid-excreting ability is evaluated by measurements of urinary pH, titratable acid and ammonium during metabolic acidosis, either spontaneous or induced by means of the ammonium chloride loading test (short or long test).

With small reduction in plasma bicarbonate concentration, eg. 3 to 4 mEq/l, normal subjects decrease urinary pH to less than 5.3, titratable acid increased to more than 25 and ammonium to more than 39 mEq per minute. Urine pH of 5.3 and below denotes ability to acidify the urine and urine pH above 5.3 denotes inability to acidify the urine.

In non-azotemic renal acidification defect, the urinary pH is high during acidosis and excretion rates of titratable acid and ammonium is reduced. The serum chloride increases as bicarbonate decreases. This defect is termed "Renal Tubular Acidosis" by Pines and Mudge.

Concentration of Urine

There is a progressive increase in tissue osmolarity from cortex to papillary tip. In the kidney the loops of Henle

function as countercurrent multipliers. Fluid in the descending limb becomes progressively more concentrated during its passage from the cortico-medullary junction to the tip of the loop. In the ascending limb, sodium is reabsorbed more rapidly than water and the fluid passing to the distal convoluted tubule is more dilute than that which enters the descending limb. A gradient between the limbs is created by the transport of sodium unaccompanied by equivalent amounts of water out of the ascending limb into the interstitial fluid. Water then diffuses out of the descending limb so concentrating the contents of the limb until an equilibrium is reached in which the concentration of the fluid at any point in the descending limb is the same as that of the interstitial fluid at the same level and slightly higher than that at the corresponding point of the ascending limb.

The collecting ducts pass through the medulla. In the presence of antidiuretic hormone (ADH), water diffuses from the collecting ducts into the hypertonic medullary interstitium. This makes the urine progressively concentrated.

Also under the influence of ADH the collecting ducts, normally not permeable to urea, become highly permeable to urea. Urea diffuses from the collecting ducts into the medullary interstitial fluid. The urea trapped in the medullary interstitium extracts water from the descending limb of the loop of Henle and amplifies the effect of the counter-current multiplier. This permits the production of a more highly concentrated urine.

Hormones and the Kidneys

Many hormones influence various aspects of renal function. These are antidiuretic hormone, cortisol, aldosterone,

parathyroid hormone, growth hormone, sex hormones, erythropoietin, prostaglandins and angiotensin II.

The autoregulation of renal blood flow maintains and regulates the GFR. Changes in the mean arterial pressure can induce changes in the opposite directions of afferent and efferent arteriolar resistances, resulting in near constancy of the GFR. For example, a reduction in systemic arterial pressure produces dilatation of afferent arterioles thus increasing the blood flow to the glomeruli and maintaining the perfusion pressure. However, if the efferent arterioles also dilate, the pressure will be transmitted to the post-glomerular capillary bed and GFR will decrease.

Vasoconstriction of the efferent arteriole is achieved by intrarenal generation of angiotensin II. The juxta-glomerular apparatus senses the perfusion pressure by means of stretch receptors in the afferent arteriole. A decrease in systemic arterial pressure releases renin from afferent arterioles.

In glomerular hyperfiltration, there is afferent arteriolar dilatation with increase of blood flow to the glomerulus. At the efferent arteriole, angiotensin II receptors induce vasoconstriction. The end result is increase in intraglomerular blood pressure (intraglomerular hypertension). This causes increase in single nephron GFR with increase in creatinine clearance and proteinuria. With time, however, the intraglomerular hypertension induces glomerulosclerosis. Hyperfiltration occurs in any condition where some glomeruli are sclerosed. Hyperfiltration or hyperperfusion then occurs in the remnant glomeruli. This condition occurs in diabetic nephropathy and IgA nephritis.

Prostaglandins play an essential role in normal renal function, especially PGE₂. Prostaglandins are located in the renal medulla. They modify the adenylcyclase cyclic AMP system

and also have a role in regulation of renal blood flow and of ADH secretion and actions. Prostaglandins have also been implicated in hypertension. This is based on observations that a reduction in the renal production of certain types of prostaglandins is associated with reduced natriuresis and hypertension in experimental animals.

Other hormones like antidiuretic hormone (vasopressin) regulates water excretion. Cortisol promotes sodium retention and potassium and hydrogen loss by the kidneys. Aldosterone enhances the reabsorption of sodium from the distal tubular fluid in exchange for potassium and hydrogen ions which have increased excretion.

Parathyroid hormone diminishes the urinary output of calcium and hydrogen ions and increases that of phosphate and potassium ions. Growth hormone has some sodium retaining properties. Oestrogens may lead to salt and water retention and to a rise in GFR and renal blood flow in pregnancy. Progesterone induces sodium and water loss.