Renal Disease

By

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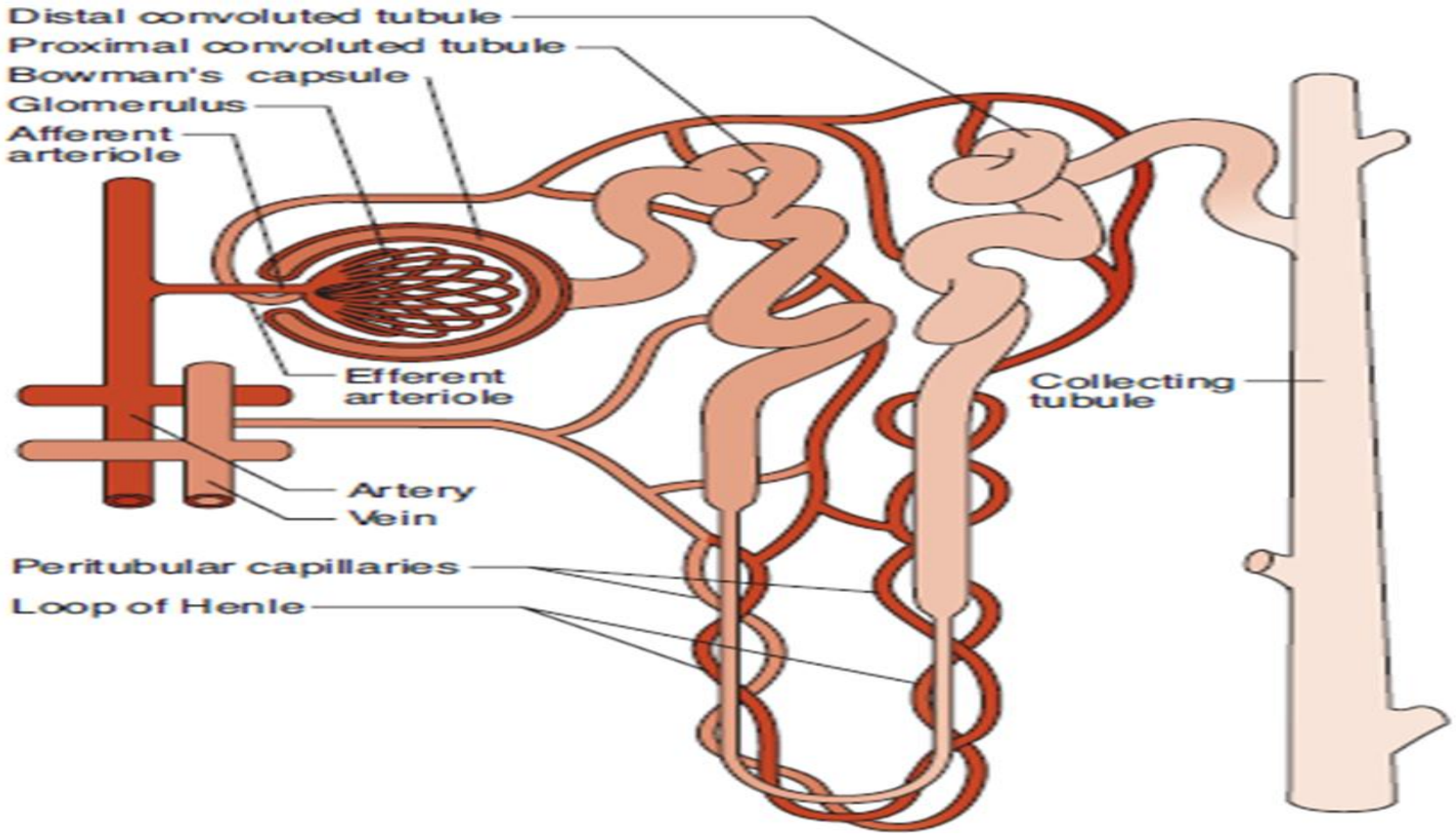
Kidney

- The kidneys are paired retroperitoneal organs each comprising about 1 million nephrons, which act as independent functional units. They have multiple physiological functions, which can be broadly categorized as the excretion of waste products, the homeostatic regulation of the ECF volume and composition, and endocrine. In order to achieve these functions, they receive a rich blood supply, accounting to about 25% of the cardiac output.
- The excretory and homeostatic functions are achieved through filtration at the glomerulus and tubular reabsorption. The glomeruli act as filters which are permeable to water and low molecular weight substances, but impermeable to macro-molecules. This impermeability is determined by both size and charge, with proteins smaller than albumin (68 kDa) being filtered, and positively charged molecules being filtered more readily than those with a negative charge.

- The filtration rate is determined by the differences in hydrostatic and oncotic pressures between the glomerular capillaries and the lumen of the nephron, by the nature of the glomerular basement membrane and by the total glomerular area available for filtration. The total glomerular area available reflects the total number of functioning nephrons.
- The total volume of the glomerular filtrate amounts to about 170 L/day (12 times the typical ECF volume), and has a composition similar to plasma except that it is almost free of protein.

Figure 1 Representation of a nephron and its blood supply.



- The renal tubules are presented with this volume of water, most of which needs to be reabsorbed, containing a complex mixture of ions and small molecules some of which have to be retained, some of them in a regulated manner; small amounts of small proteins which are reabsorbed and catabolized ; and metabolic waste products such as urea, creatinine and sulphate ions, which are excreted. The proximal convoluted tubule is responsible for the obligatory reabsorption of much of the glomerular filtrate, with further reabsorption in the distal convoluted tubule being subject to homeostatic control mechanisms.

- The endocrine functions of the kidney include the ability to synthesis hormones (e.g. renin, erythropoietin, calcitriol), to respond to them (e.g. aldosterone, parathyroid hormone (PTH)) and to inactivate or excrete them (e.g. insulin, glucagon). All of these functions may be affected by renal disease, with local or systemic consequences.
- Many diseases affect renal function. In some, several functions are affected; in others, there is selective impairment of glomerular function or of one or more tubular functions.

Impaired renal function

- It is convenient to subdivide the causes of impaired renal function into pre-renal, renal and post-renal.
- 1. Pre-renal causes may develop whenever there is reduced renal perfusion, and are essentially the result of a physiological response to hypovolaemia or a drop in blood pressure. This causes renal vasoconstriction and a redistribution of blood such that there is a decrease in GFR, but preservation of tubular function. Stimulation of vasopressin secretion and of the renin-angiotensin-aldosterone system causes the excretion of small volumes of concentrated urine with a low Na content. Renal blood flow also falls in congestive cardiac failure, and may be further reduced if such patients are treated with potent diuretics. If pre-renal causes are not treated adequately and promptly by restoring renal perfusion, there can be a progression to intrinsic renal failure.

- 2. Renal causes may be due to acute kidney injury or chronic kidney disease, with reduction in glomerular filtration.
- 3. Post-renal causes occur due to outflow obstruction, which may occur at different levels (i.e. in the ureter, bladder or urethra), due to various causes (e.g. renal stones, prostatism, genitourinary cancer). As with prerenal causes, this may in turn cause damage to the kidney.

Renal tubular acidosis

- At least two distinct tubular abnormalities may give rise to conditions in which there is acidosis of renal origin but little or no change in plasma [creatinine], or other measure of the GFR. The impaired ability to excrete H+ means that when Na+ is reabsorbed in the distal tubule, there is an increased loss of K+, resulting in K+ depletion and hypokalaemia. This combination of metabolic acidosis and hypokalaemia is an unusual one, since hyperkalaemia is more commonly seen in acidosis.

- *Distal renal tubular acidosis (type I) is the more common type. It is due to an inability to maintain a gradient of [H+] across the distal tubule and collecting ducts. It is usually caused by an inherited abnormality, but may occur in certain forms of acquired renal disease. Bone disease, commonly osteomalacia , results from the buffering of H+ by bone, and there is often hypercalciuria and nephrocalcinosis . Loss of Na+ and K+ in the urine and hypokalaemia are common. Urinary pH rarely falls below 6.0 and never below 5.3 in the ammonium chloride test of urinary acidification.
- * Proximal renal tubular acidosis (type II) is much less common. It is due to proximal tubular loss of HCO- 3 caused by a low renal threshold for HCO- 3. This means that if the [HCO- 3] is low, HCO- 3 may be completely reabsorbed, resulting in the excretion of normal amounts of acid, but at the expense of a continuing systemic acidosis. [HCO- 3] rarely falls below about 15 mmol/L. Occasionally, this is an isolated abnormality.
- More often, it occurs as one of the features in some patients with Fanconi syndrome . If these patients are given enough NH4Cl to reduce plasma [total CO2] below the renal threshold for HCO-3, urinary pH may fall below 5.3. Diagnosis requires assessment of the renal threshold for HCO-3.

- **Glycosuria**
- Glucose is most commonly found in the urine in patients with diabetes, when the plasma [glucose] exceeds the renal threshold.
- Glycosuria in the presence of a normal plasma [glucose] occurs in proximal tubular malfunction causing a reduced renal threshold. This can be a benign isolated abnormality, may occur during pregnancy or may be part of a more generalized disorder (the Fanconi syndrome).
- **The amino acidurias**
- Amino acids can be categorized into four groups - the neutral, acidic and basic amino acids, and the amino acids proline and hydroxyproline . Each has its own specific mechanism for transport across the proximal tubular cell.
- Normally, the renal tubules reabsorb all the filtered amino acids except for small amounts of glycine, serine, alanine and glutamine. Amino aciduria may be due to disease of the renal tubule (renal or low threshold type), or to raised plasma [amino acids] (generalized or overflow type).

- Renal amino aciduria may be due to impairment of one of the specific transport mechanisms. For example, in cystinuria there is a hereditary defect in the epithelial transport of cystine and the basic amino acids lysine, ornithine and arginine; it is a rare cause of renal (cystine) stones. Renal amino aciduria may also occur as a nonspecific abnormality due to generalized tubular damage, together with reabsorption defects affecting glucose or phosphate, or both.
- The overflow types of amino aciduria result when the renal threshold for amino acids is exceeded, due to overproduction or to accumulation of amino acids in the body (e.g. PKU (Phenylketonuria); acute hepatic necrosis).
- **Fanconi syndrome**
- Fanconi syndrome may be inherited (e.g. in cystinosis) or secondary to a number of other disorders (e.g. heavy metal poisoning, multiple myeloma). The syndrome comprises multiple defects of proximal tubular function.
- There are excessive urinary losses of amino acids (generalized amino aciduria), phosphate, glucose and sometimes HCO-3, which gives rise to a proximal renal tubular acidosis. Distal tubular functions may also be affected. Sometimes globulins of low molecular mass may be detectable in urine, in addition to the amino aciduria.