**Assignment**

**Question**

Q1. Discuss the role of kidney in glucose homeostasis?

Q2. Discuss the process of micturition?

Q3. Explain juxtaglomerular apparatus?

Q4 Discuss the role of kidney in regulation of blood pressure?

Q5. Discuss the role of Kidney in Calcium homeostasis?

**ANSWER.**

1. The kidneys are essentially designed to filter large quantities of plasma, reabsorb substances that the body must conserve, and secrete substances that must be eliminated. These basic functions are critical to regulation of fluid and electrolyte balance, body fluid osmolality, acid-based balance, excretion of metabolic waste and foreign chemicals, arterial pressure, hormone secretion, and, most relevant to this discussion, glucose balance. The 2 kidneys produce a total of approximately 120 mL/min of ultrafiltrate, yet only 1 mL/min of urine is produced. The basic urine-forming unit of the kidney is the nephron, which serves to filter water and small solutes from plasma and reabsorb electrolytes, amino acids, glucose, and protein. The nephron, of which there are approximately 1 million in each kidney, consists of a filtering apparatus (the glomerulus) that is connected to a long tubular portion that reabsorbs and conditions the glomerular ultrafiltrate. Fluid filtered from the glomerular capillaries flows into the tubular portion, which is made up of a proximal tubule, the Loop of Henle, and the distal tubule, all of which assist in reabsorbing essential substances and converting filtered fluid into urine.

Maintenance of glucose homeostasis is crucial in preventing pathological consequences that may result from hyperglycemia or hypoglycemia. Chronically uncontrolled hyperglycemia leads to a higher risk of macrovascular and microvascular complications, such as cardiovascular disease, nephropathy, neuropathy, and retinopathy. Hypoglycemia, on the other hand, may lead to a myriad of central nervous system complications (eg, confusion, behavioral changes, seizures, loss of consciousness, and even death), since the brain is the body’s largest consumer of glucose in the fasting or “postabsorptive” state. Maintenance of glucose homeostasis involves several complementary physiologic processes, including glucose absorption (in the gastrointestinal tract), glycogenolysis (in the liver), glucose reabsorption (in the kidneys), gluconeogenesis (in the liver and kidneys), and glucose excretion (in the kidneys).

With respect to renal involvement in glucose homeostasis, the primary mechanisms include release of glucose into the circulation via gluconeogenesis, uptake of glucose from the circulation to satisfy the kidneys’ energy needs, and reabsorption of glucose at the level of the proximal tubule.

**Glycogenolysis and Gluconeogenesis**  
  
Renal release of glucose into the circulation is the result of glycogenolysis and gluconeogenesis. Glycogenolysis involves the breakdown of glycogen to glucose-6-phosphate from precursors (eg, lactate, glycerol, amino acids) and its subsequent hydrolysis (via glucose-6-phosphatase) to free glucose. Conversely, gluconeogenesis involves formation of glucose-6-phosphate from those same precursors and subsequent conversion to free glucose. Interestingly, the liver and skeletal muscles contain most of the body’s glycogen stores, but only the liver contains glucose-6-phosphatase. As such, the breakdown of hepatic glycogen leads to release of glucose, whereas the breakdown of muscle glycogen leads to release of lactate. Lactate (generated via glycolysis of glucose by blood cells, the renal medulla, and other tissues) may be absorbed by organs and reformed into glucose.  
  
With regard to glucose utilization, the kidney may be perceived as 2 separate organs, with glucose utilization occurring predominantly in the renal medulla and glucose release limited to the renal cortex. These activities are separated as a result of differences in the distribution of various enzymes along the nephron. To this point, cells in the renal medulla (which, like the brain, are obligate users of glucose) have significant glucose-phosphorylating and glycolytic enzyme activity, and can therefore phosphorylate and accumulate glycogen. However, since these cells lack glucose-6-phosphatase and other gluconeogenic enzymes, they cannot release free glucose into the circulation. On the other hand, renal cortex cells do possess gluconeogenic enzymes (including glucose-6-phosphatase), and therefore can make and release glucose into the circulation. But because these cells have little phosphorylating capacity, they cannot synthesize glycogen.  
  
The magnitude of renal glucose release in humans is somewhat unclear, with inconclusive evidence regarding the contribution of the kidneys to total body gluconeogenesis.4 One analysis of 10 published studies concluded that the renal contribution to total body glucose release in the postabsorptive state is approximately 20%. Based on the assumption that gluconeogenesis accounts for approximately half of all circulatory glucose release during the fasting state, renal gluconeogenesis is projected, although not conclusively proven, to potentially be responsible for approximately 40% of all gluconeogenesis. Taking into consideration the potential contribution of renal gluconeogenesis, the kidneys appear to play a substantial role in overall glucose release in normal as well as pathophysiologic states (eg, hepatic insufficiency, counterregulation of hypoglycemia). To this point, evidence suggests that in patients with T2DM, renal glucose release is increased in both the postprandial and postabsorptive states, implicating the kidneys’ contribution to the hyperglycemia that characterizes this condition. In one study, a 3-fold increase in renal glucose release was observed in patients with diabetes versus those without. In contrast, hepatic glucose release increased by only 30% in the diabetic state. Potential mechanisms involved in excessive renal glucose release in T2DM include fasting gluconeogenesis, decreased postprandial insulin release, insulin resistance (known to suppress renal/hepatic insulin release), increased free fatty acid (FFA) concentrations (FFAs stimulate gluconeogenesis), greater availability of gluconeogenic precursors, and increased glycogenolysis. Again, it is clear that there is a renal contribution to glucose output in the body, but the actual contribution in individual patients with T2DM is still controversial.  
  
**Glucose Reabsorption**  
  
In addition to their important role in gluconeogenesis, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. Under normal conditions, the kidneys retrieve as much glucose as possible, rendering the urine virtually glucose free. The glomeruli filter from plasma approximately 180 grams of D-glucose per day, all of which is reabsorbed through glucose transporter proteins that are present in cell membranes within the proximal tubules. If the capacity of these transporters is exceeded, glucose appears in the urine. This maximum capacity, known as the tubular maximum for glucose (TmG), ranges from 260 to 350 mg/min/1.73 m2 in healthy adults and children, and corresponds to a plasma glucose level of approximately 200 mg/dL. Once the TmG (the threshold) is reached and transporters are unable to reabsorb all the glucose (as in T2DM), glucosuria ocurrs. The correlation between the degree of hyperglycemia and degree of glucosuria becomes linear when blood glucose concentrations have increased beyond a threshold. It should be noted that slight differences between individual nephrons and the imprecise nature of biological systems may alter this linear concentration/reabsorption curve, as indicated by a splay from the theoretical as the TmG is approached. As such, glucosuria may potentially develop before the expected TmG is reached. Glucosuria may also occur at lower plasma glucose concentrations in certain conditions of hyperfiltration (eg, pregnancy), but as a consequence of hyperfiltration rather than significant hyperglycemia.  
  
**Renal Glucose Transporters**

The transport of glucose (a polar compound with positive and negative charged areas, making it soluble in water) into and across cells is dependent on specialized carrier proteins in 2 gene families: the facilitated glucose transporters (GLUTs) and the sodium-coupled glucose cotransporters (SGLTs). These transporters control glucose transport and reabsorption in several tissue types, including the proximal renal tubule, small intestine, blood-brain barrier, and peripheral tissues.

GLUTs are involved in the passive transport of glucose across cell membranes, facilitating its downhill movement as it equilibrates across a membrane. SGLTs, on the other hand, mediate active transport of glucose against a concentration gradient by means of cotransport with sodium. Of the various SGLT proteins expressed in the kidneys, SGLT2 is considered most important; based on animal studies, it is responsible for reabsorbing 90% of the glucose filtered at the glomerulus. SGLT1 contributes to the other 10% of glucose reabsorbed in the proximal tubule. This predominant role of SGLT2 in renal reabsorption of glucose raises the prospect of therapeutically blocking this protein in patients with diabetes. Of the various GLUT proteins expressed in the kidneys, GLUT2 is the major transporter, releasing into circulation the glucose reabsorbed by SGLTs in the proximal tubular cells.

## ****Formation of urine****

There are two kidneys which are bean-shaped and are approximately 10cm long, 5.5cm wide and 3cm thick. Each kidney weighs about 150g and has a marked indentation medially - the hilus - where the renal artery and renal nerves enter and the renal vein and ureter leave. Between them, the kidneys make approximately 30ml or more of urine every hour.

Approximately 25% of the cardiac output goes to the kidneys where organic waste products are removed in the million or so nephrons in each kidney. Normal urine production, therefore, depends on normal blood flow to the kidneys. The nephron is the functional unit of the kidney. Nephrons permit the passage of some substances out of the body but restrict the passage of others, for example, blood cells and large proteins.

### Filtration

As blood flows through the glomerulus (a capillary network that forms part of the nephron), much of the fluid and waste products in the blood are forced out through the walls of the capillaries, filtered, and then flow into the Bowman’s capsule .

The Bowman’s capsule is a double-walled endothelial cup that surrounds the glomerulus. This glomerular filtrate (about 125ml per minute) consists of water, glucose, waste salts such as sodium and potassium, and urea. [Urea is the most abundant waste product excreted by the kidneys](http://www.nursingtimes.net/clinical-archive/assessment-skills/why-do-we-test-for-urea-and-electrolytes-24-01-2014/) and is formed from ammonia, a highly toxic substance. Ammonia is formed in the liver from the breakdown of amino acids.

### Absorption

Much of the glomerular filtrate, including most of the water, is reabsorbed into the capillaries surrounding the proximal and distal convoluted tubules, the loop of Henle and the collecting tubules. All of the glucose will be reabsorbed unless blood glucose levels are high - more than 8.9 millimoles per litre (mmol/l) or 160 milligrams per decilitre (mg/dl) - in which case some glucose will be excreted in the urine.

Sodium is also reabsorbed but the amount varies, depending on how much the body requires to maintain a constant concentration of sodium ions in the blood.

### Secretion

This is the final stage of urine formation, and occurs at the distal and collecting tubules. Substances either diffuse or are actively transported out of the capillaries and into the collecting tubules to be excreted in the urine.

Hydrogen ions, potassium ions, ammonia and some drugs are all secreted at this stage and the kidneys play an important role in maintaining the acid-base balance within the body.

### Final composition of urine

The final composition of urine is the result of filtration, absorption and secretion by the nephrons. The kidneys produce, on average, one and a half litres of urine each day - this is mostly composed of water, is straw coloured and has a specific gravity of 1.005 to 1.030.

Urea, uric acid, creatinine, sodium chloride and potassium ions are all normal constituents of urine. Blood, ketones and glucose are not, and their presence may indicate disease.

## ****The ureters****

Urine passes from the kidneys to the bladder through the ureters where it is stored until it is eliminated via the urethra. Urine is moved along the ureters to the bladder by peristaltic contraction and gravity.

The ureters are muscular tubes about 30cm long. They are firmly attached to the posterior abdominal wall and are retroperitoneal; they do not enter the peritoneal cavity. The ureteral openings into the bladder are flattened (slit-shaped) rather than round. This is due to the oblique angle at which the ureters enter the bladder, which helps to prevent the back-flow of urine into the ureters when the bladder contracts.

## ****Storage of urine****

The bladder is a hollow, muscular sac which sits in the pelvis. In males, the base of the bladder lies between the rectum and pubic symphysis while in females the base is below the uterus and anterior to the vagina.

The bladder stores urine and can contain approximately one litre when full. It is held in position by the peritoneum surrounding it (though only its top surface lies within the peritoneum) and by strong umbilical ligaments.

The bladder is lined by mucosa. This is particularly thick in the area around the ureter openings and the junction with the urethra, where the mucosa acts as a funnel to channel urine into the urethra when the bladder contracts. During micturition, strong muscles in the bladder walls (the detrusor muscles) compress the bladder, pushing its contents into the urethra.

**MICTURITION.**

Micturition or urination is the process of expelling urine from the bladder. This act is also known as voiding of the bladder. The [excretory system](https://www.toppr.com/guides/biology/excretory-products/human-excretory-system/) in humans includes a pair of kidneys, two ureters, a urinary bladder and a urethra. The kidneys filter the urine and it is transported to the urinary bladder via the ureters where it is stored till its expulsion. The process of micturition is regulated by the [nervous system](https://www.toppr.com/guides/biology/control-and-coordination/nervous-system/) and the [muscles](https://www.toppr.com/guides/biology/locomotion-and-movement/muscle/) of the bladder and urethra. The urinary bladder can store around 350-400ml of urine before it expels it out.

**Stages of Micturition**

The urinary bladder has two distinct stages or phases:

1. Resting or filling stage
2. Voiding stage

Resting or Filling Stage

It is in this phase of the bladder that the urine is transported from the kidneys via the ureters into the bladder. The ureters are thin muscular tubes that arise from each of the kidneys and extend downwards where they enter the bladder obliquely.

The oblique placement of the ureters in the bladder wall serves a very important [function](https://www.toppr.com/guides/maths/relations-and-functions/functions/). The opening of the ureter into the urinary bladder is not guarded by any sphincter or muscle. Therefore, this oblique [nature](https://www.toppr.com/guides/business-studies/business-services/nature-and-types-of-services/) of opening prevents the urine from re-entering the ureters. At the same time, the main muscle of the urinary bladder, the detrusor muscle, is relaxing allowing the bladder to distend and accommodate more urine.

Voiding Stage

During this stage, both the urinary bladder and the urethra come into play together. The detrusor muscle of the urinary bladder which was relaxing so far starts to contract once the bladder’s storage capacity is reached.

The urethra is controlled by two sets of muscles: The internal and external urethral sphincters. The internal sphincter is a smooth muscle whereas the external one is [skeletal](https://www.toppr.com/guides/biology/locomotion-and-movement/skeletal-system/). Both these sphincters are in a contracted state during the filling stage.

### Control of micturition

Children and adults have considerable control over when and where they pass urine. They can also increase or decrease the rate of flow and even stop and start again, so micturition is clearly more than just a simple reflex. This control is learnt in infancy and involves other sensory fibres in the bladder wall. These fibres convey information on the degree of bladder fullness via the spine to the higher centres of the brain, the thalamus and cerebral cortex. This causes us to become aware that we need to pass urine and of the urgency of the situation.

These links between the spine and cerebral cortex are not established until about two years of age and it is suggested that toilet-training is therefore not physiologically possible until that time.

1. The **juxtaglomerular apparatus** (also known as the **juxtaglomerular complex**) is a structure in the [kidney](https://en.wikipedia.org/wiki/Kidney) that regulates the function of each [nephron](https://en.wikipedia.org/wiki/Nephron), the functional units of the kidney. The juxtaglomerular apparatus is named because it is next to (juxta-) the [glomerulus](https://en.wikipedia.org/wiki/Glomerulus_(kidney)).

The juxtaglomerular apparatus consists of three types of cells:

* the [macula densa](https://en.wikipedia.org/wiki/Macula_densa), a part of the distal convoluted tubule of the same nephron
* [juxtaglomerular cells](https://en.wikipedia.org/wiki/Juxtaglomerular_cell), (also known as granular cells) which secrete [renin](https://en.wikipedia.org/wiki/Renin)
* [extraglomerular mesangial cells](https://en.wikipedia.org/wiki/Extraglomerular_mesangial_cells).

The juxtaglomerular apparatus is part of the kidney [nephron](https://en.wikipedia.org/wiki/Nephron), next to the [glomerulus](https://en.wikipedia.org/wiki/Glomerulus_(kidney)). It is found between [afferent arteriole](https://en.wikipedia.org/wiki/Afferent_arteriole) and the [distal convoluted tubule](https://en.wikipedia.org/wiki/Distal_convoluted_tubule) of the same nephron. This location is critical to its function in regulating renal blood flow and [glomerular filtration rate](https://en.wikipedia.org/wiki/Glomerular_filtration_rate).

FUNCTION

### Juxtaglomerular cells

[Renin](https://en.wikipedia.org/wiki/Renin) is produced by [juxtaglomerular cells](https://en.wikipedia.org/wiki/Juxtaglomerular_cells). These cells are similar to [epithelium](https://en.wikipedia.org/wiki/Epithelium) and are located in the tunica media of the afferent arterioles as they enter the glomeruli. The juxtaglomerular cells secrete renin in response to:

* Stimulation of the [beta-1 adrenergic receptor](https://en.wikipedia.org/wiki/Beta-1_adrenergic_receptor)
* Decrease in renal perfusion pressure (detected directly by the granular cells)
* Decrease in NaCl concentration at the macula densa, often due to a decrease in [glomerular filtration rate](https://en.wikipedia.org/wiki/Glomerular_filtration_rate)

**Extraglomerular mesangial cells**

[Extraglomerular mesangial cells](https://en.wikipedia.org/wiki/Extraglomerular_mesangial_cells) are located in the junction between the afferent and efferent arterioles. These cells have a contractile property similar to vascular smooth muscles and thus play a role in “regulating GFR” by altering the vessel diameter. [Renin](https://en.wikipedia.org/wiki/Renin) is also found in these cells.

**Macula densa**

At the point where the afferent arterioles enter the glomerulus and the efferent arteriole leaves it, the tubule of the [nephron](https://en.wikipedia.org/wiki/Nephron) touches the arterioles of the [glomerulus](https://en.wikipedia.org/wiki/Glomerulus) from which it rose. At this location, in the wall of the distal convoluted tubule, there is a modified region of tubular epithelium called the [macula densa](https://en.wikipedia.org/wiki/Macula_densa). Cells in the macula densa respond to changes in the [sodium chloride](https://en.wikipedia.org/wiki/Sodium_chloride) levels in the distal tubule of the nephron via the [tubuloglomerular feedback](https://en.wikipedia.org/wiki/Tubuloglomerular_feedback" \o "Tubuloglomerular feedback) (TGF) loop.

The macula densa's detection of elevated sodium chloride, which leads to an increase in GFR, is based on the concept of [purinergic signaling](https://en.wikipedia.org/wiki/Purinergic_signaling" \o "Purinergic signaling). An increase in the [salt](https://en.wikipedia.org/wiki/Sodium_chloride) concentration causes several [cell signals](https://en.wikipedia.org/wiki/Signal_transduction) to eventually cause the adjacent afferent arteriole to [constrict](https://en.wikipedia.org/wiki/Vasoconstriction). This decreases the amount of blood coming from the afferent arterioles to the glomerular capillaries, and therefore decreases the amount of fluid that goes from the glomerular capillaries into the Bowman's space (the [glomerular filtration rate (GFR)](https://en.wikipedia.org/wiki/Glomerular_filtration_rate)).

When there is a decrease in the sodium concentration, less sodium is reabsorbed in the macular densa cells. The cells increase the production of [nitric oxide](https://en.wikipedia.org/wiki/Nitric_oxide) and [Prostaglandins](https://en.wikipedia.org/wiki/Prostaglandins) to vasodilate the afferent arterioles and increase renin release.

CLINICAL SIGNIFICANCE

Excess secretion of renin by the [juxtaglomerular cells](https://en.wikipedia.org/wiki/Juxtaglomerular_cells) can lead to excess activity of the renin–angiotensin system, [hypertension](https://en.wikipedia.org/wiki/Hypertension) and an increase in [blood volume](https://en.wikipedia.org/wiki/Blood_volume). This is not responsive to the usual treatment for [essential hypertension](https://en.wikipedia.org/wiki/Essential_hypertension), namely medications and lifestyle modification.

One cause of this can be increased renin production due to [narrowing of the renal artery](https://en.wikipedia.org/wiki/Renal_artery_stenosis), or a tumour of juxtaglomerular cells that produces renin. These will lead to [secondary hyperaldosteronism](https://en.wikipedia.org/wiki/Secondary_hyperaldosteronism), which will cause hypertension, [high blood sodium](https://en.wikipedia.org/wiki/Hypernatremia), [low blood potassium](https://en.wikipedia.org/wiki/Hypokalemia), and metabolic alkalosis.

1. The kidneys play a central role in the regulation of arterial blood pressure. A large body of experimental and physiological evidence indicates that renal control of extracellular volume and renal perfusion pressure are closely involved in maintaining the arterial circulation and blood pressure. Renal artery perfusion pressure directly regulates sodium excretion; a process known as pressure natriuresis, and influences the activity of various vasoactive systems such as the renin–angiotensin–aldosterone (RAS) system [9]. Along with vessel morphology, blood viscosity is one of the key factors influencing resistance and hence blood pressure. A key modulator of blood viscosity is the renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS), a hormone system that regulates blood pressure and water balance.

The blood pressure in the body depends upon:

• The force by which the heart pumps out blood from the ventricles of the heart - and this is dependent on how much the heart muscle gets stretched by the inflowing blood into the ventricles.

• The degree to which the arteries and arterioles constrict-- increases the resistance to blood flow, thus requiring a higher blood pressure.

• The volume of blood circulating round the body; if the volume is high, the ventricles get more filled, and the heart muscle gets more stretched.

The kidney influences blood pressure by:

• Causing the arteries and veins to constrict

• Increasing the circulating blood volume

Specialized cells called macula densa are located in a portion of the distal tubule located near and in the wall of the afferent arteriole. These cells sense the Na in the filtrate, while the arterial cells (juxtaglomerular cells) sense the blood pressure. When the blood pressure drops, the amount of filtered Na also drops. The arterial cells sense the drop in blood pressure, and the decrease in Na concentration is relayed to them by the macula densa cells. The juxtaglomerular cells then release an enzyme called renin.

Renin converts angiotensinogen (a peptide, or amino acid derivative) into angiotensin-1. Angiotensin-1 is thereafter converted to angiotensin-2 by an angiotensin-converting enzyme (ACE), found in the lungs. Angiotensin-2 causes blood vessels to contract -- the increased blood vessel constrictions elevate the blood pressure. When the volume of blood is low, arterial cells in the kidneys secrete renin directly into circulation. Plasma renin then carries out the conversion of angiotensinogen released by the liver to angiotensin-1. Angiotensin-1 is subsequently converted to angiotensin-2 by the enzyme angiotensin converting enzyme found in the lungs. Angiotensin-2m a potent vasoactive peptide causes blood vessels to constrict, resulting in increased blood pressure. Angiotensin-2 also stimulates the secretion of the hormone aldosterone from the adrenal cortex.

Aldosterone causes the tubules of the kidneys to increase the reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also increases blood pressure. If the renin-angiotensin-aldosterone system is too active, blood pressure will be too high. Many drugs interrupt different steps in this system to lower blood pressure. These drugs are one of the main ways to control high blood pressure (hypertension), heart failure, kidney failure, and harmful effects of diabetes. It is believed that angiotensin-1 may have some minor activity, but angiotensin-2 is the major bioactive product. Angiotensin-2 has a variety of effects on the body: throughout the body, it is a potent vasoconstrictor of arterioles.

1. The total amount of calcium in the human body ranges from 1000 to 1200 g. Approximately 99% of body calcium resides in the skeleton; the other 1% is present in the extracellular and intracellular spaces. Although >99% of the total body calcium is located in bone, calcium is a critical cation in both the extracellular and intracellular spaces. Approximately 1% of the calcium in the skeleton is freely exchangeable with calcium in the extracellular fluid compartment. Serum calcium concentration is held in a very narrow range in both spaces. Calcium serves a vital role in nerve impulse transmission, muscular contraction, blood coagulation, hormone secretion, and intercellular adhesion.

Total serum calcium consists of ionized, protein bound, and complexed fractions (approximately 48%, 46%, and 7%, respectively). The complexed calcium is bound to molecules such as phosphate and citrate. The ultrafilterable calcium equals the total of the ionized and complexed fractions. Normal total serum calcium is approximately 8.9–10.1 mg/dl (about 2.2–2.5 mmol/l). Calcium can be bound to albumin and globulins. For each 1.0-g/dl decrease in serum albumin, total serum calcium decreases by 0.8 mg/dl. For each 1.0-g/dl decrease in serum globulin fraction, total serum calcium decreases by 0.12 mg/dl. Acute alkalosis decreases the ionized calcium. Because both hydrogen ions and calcium are bound to serum albumin, in the presence of metabolic alkalosis, bound hydrogen ions dissociate from albumin, freeing up the albumin to bind with more calcium and thereby decreasing the freely ionized portion of the total serum calcium. For every 0.1 change in pH, ionized calcium changes by 0.12 mg/dl.

In humans who have a GFR of 170 liters per 24 hours, roughly 10 g of calcium is filtered per day. The amount of calcium excreted in the urine usually ranges from 100 to 200 mg per 24 hours; hence, 98%–99% of the filtered load of calcium is reabsorbed by the renal tubules. Approximately 60%–70% of the filtered calcium is reabsorbed in the proximal convoluted tubule, 20% in the loop of Henle, 10% by the distal convoluted tubule, and 5% by the collecting duct. The terminal nephron, although responsible for the reabsorption of only 5%–10% of the filtered calcium load, is the major site for regulation of calcium excretion.

The reabsorption of calcium in the proximal convoluted tubule parallels that of sodium and water. Proximal tubular calcium reabsorption is thought to occur mainly by passive diffusion and solvent drag. This is based on the observation that the ratio of calcium in the proximal tubule fluid to that in the glomerular filtrate is 1:1.2. The passive paracellular pathways account for approximately 80% of calcium reabsorption in this segment of the nephron. A small but significant component of active calcium transport is observed in the proximal tubules. The active transport of calcium proceeds in a two-step process, with calcium entry from the tubular fluid across the apical membrane and exit though the basolateral membrane. This active transport is generally considered to constitute 10%–15% of total proximal tubule calcium reabsorption and it is mainly regulated by parathyroid hormone (PTH) and calcitonin.

No reabsorption of calcium occurs within the thin segment of the loop of Henle. In the thick ascending limb of the loop of Henle, 20% of the filtered calcium is reabsorbed largely by the cortical thick ascending limb, through both transcellular and paracellular routes. In the thick ascending limb, the bulk of calcium reabsorption proceeds through the paracellular pathway and is proportional to the transtubular electrochemical driving force. The apical Na+-K+-2Cl− cotransporter NKCC2 and the renal outer medullary potassium K+ (ROMK) channel generate the “driving force” for paracellular cation transport. Whereas NaCl reabsorption through NKCC2 is electroneutral (NKCC2 translocates one Na+, one K+, and two Cl− ions from the lumen into the cell), apical potassium represents the rate-limiting step of this process and potassium ions back-diffuse into the lumen through the ROMK channels. Na+ and Cl− accumulated inside the cell are then transported into the bloodstream through basolateral Na+-K+-ATPase and Cl− channels, respectively. Overall, these processes yield a net cellular reabsorption of NaCl and the generation of a lumen-positive transepithelial potential difference, which drives nonselective calcium reabsorption through the paracellular route. Calcium transport in the thick ascending limb of the loop of Henle is also influenced by the calcium-sensing receptor (CaSR), which is localized in the basolateral membrane. How CaSR controls the calcium reabsorption in the thick ascending limb is now better understood. Using microdissected, in vitro microperfused rat cortical thick ascending limb, an acute inhibition of the CaSR does not alter NaCl reabsorption or the transepithelial potential difference but increased the permeability to calcium of the paracellular pathway. The tight junction in the thick ascending limb expresses several claudins, including claudin-14, claudin-16, and claudin-19. A normal expression of claudin-16 and claudin-19 is required for a normal absorption of divalent cations in this tubular segment. The disruption of CaSR decreases the abundance of the claudin-14 mRNA and increases that of the claudin-16 mRNA. A treatment by cinacalcet increases the abundance of claudin-14 mRNA, and in cell culture models overexpression of claudin-14, decreases the paracellular permeability to calcium. Calciotropic hormones, such as PTH and calcitonin, stimulate active cellular calcium absorption in the cortical thick ascending limb.