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MEDICINE AND HEALTH SCIENCE

MEDICINE AND SURGERY

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QUESTION 1:

Discuss the role of kidney in glucose homeostasis?

ANSWER

The plasma glucose concentration is determined by the amount of glucose synthesized, and the one removed from the circulation and metabolized. This concentration must be maintained within a relatively narrow range despite the wide daily fluctuations in glucose ingestion and glucose demands in various tissues. Other substrates such as free fatty acids (FFAs), glycerol, lactate and ketone bodies have greater daily fluctuations. This can be explained by the need of the body to protect himself against hyper- and hypoglycemia. Hyperglycemia is associated with both chronic effects (such as nephropathy, retinopathy, neuropathy and premature atherosclerosis) and also acute complications (including diabetic ketoacidosis and hyperosmolar hyperglycemic state that are associated with higher morbidity and mortality). Hypoglycemia is also harmful because it can cause neurological events (including coma, seizures), cardiac arrhythmias and death. The regulation of endogenous production of glucose is determined by hormonal and neural factors. In the acute phase, glucoregulatory mechanisms involve insulin, glucagon and catecholamines and they can effect changes in plasma glucose levels in a matter of minutes. Insulin is able to suppress glucose release in both the kidney and liver by direct enzyme activation ⁄ deactivation and by reducing the availability of gluconeogenic substrates. Glucagon has no effect on the kidneys, but it stimulates glycogenolysis and gluconeogenesis in the liver. Catecholamines also have multiple acute actions. They can stimulate renal glucose release and glucagon secretion and inhibit insulin secretion.

The kidneys are involved in maintaining glucose homeostasis through three different mechanisms: gluconeogenesis; glucose uptake from the blood for its own energy requests and reabsorption into the general circulation of glucose from glomerular filtrate in order to preserve energy.

Renal gluconeogenesis

From the point of view of glucose utilization, the kidney is considered as 2 separate organs; the renal medulla is characterized mainly by glucose utilization and the renal cortex is responsible for glucose release. The separation of these activities represents the consequence of differences in the distribution of numerous enzymes along the nephron. The cells in the renal medulla can use only glucose for their needs (like the brain) and they have enzymes capable of glucose-

phosphorylation and glycolysis. They can therefore phosphorylate important amounts of glucose and accumulate glycogen but, because these cells do not have glucose-6-phosphatase or any other gluconeogenic enzymes, they are unable to release glucose into the bloodstream. Moreover, the cells in the renal cortex have gluconeogenic enzymes and they can produce and release glucose into the circulation. However these cells cannot synthesize glycogen because they have little phosphorylating capacity. After a 16-h overnight fast, approximately 10 μmol／(kg /min) of glucose is released into the circulation. Almost 50% of this is the result of glycogenolysis from the liver stocks and the other half is produced by liver and kidney gluconeogenesis. The renal cortex (like the liver) contains gluconeogenic enzymes and it can synthesize glucose-6-phosphate from precursors (lactate, glutamine, glycerol and alanine). Because it contains glucose-6-phosphatase, it is able to release glucose into the blood stream and the human liver and kidneys are the only organs that can perform gluconeogenesis. Therefore, after an overnight fast, the liver produces 75–80% of glucose released into the circulation and the remaining 20–25% is derived from the kidneys.

Several studies have indicated that human kidneys and liver provide approximately the same amounts of glucose through gluconeogenesis in post absorptive period. If the duration of fasting is increased, the glycogen stores are depleted and gluconeogenesis produces all the glucose released into circulation. An important aspect is that kidney and liver use different gluconeogenic precursors and several hormones have different effects on their release of glucose. Lactate represents the predominant gluconeogenic precursor in both organs, but regarding the amino acids, the kidney prefers to use glutamine, whereas the liver preferentially uses alanine. Insulin can suppress glucose release in both organs with almost comparable efficacy, whereas glucagon stimulates hepatic glucose release only. Catecholamines normally have a direct effect only on renal glucose release, but their effect on both hepatic and renal glucose release may be indirect by increasing the quantity of gluconeogenic substrates available and by suppressing insulin secretion. Other hormones, such as growth hormone, cortisol and thyroid hormones can stimulate hepatic glucose release over a great period of time. Their effects on the kidneys regarding glucose release in humans are not completely deciphered. Renal gluconeogenesis can increase by approximately twofold and it can represent ~60% of endogenous glucose production in the postprandial state. This mechanism is believed to facilitate the repletion of glycogen stocks in the liver.

Glycogenolysis

Glycogenolysis is the breakdown of glycogen to glucose-6-phosphate and a hydrolysis reaction (using glucose-6-phosphatase) in order to free glucose. The liver is the only organ that contains glucose-6-phosphatase. So, the cleavage of hepatic glycogen releases glucose, while the cleavage of glycogen from other sources can release only lactate. Lactate that is generated via glycolysis is often absorbed by other organs and helps regenerating glucose.

Glucose reabsorption

Apart from the important role in gluconeogenesis and the role of renal cortex in glucose uptake, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. In normal conditions, the kidneys can reabsorb as much glucose as possible, the result being a virtually glucose free urine. Approximately 180 grams of glucose are filtered by the glomeruli from plasma, daily but all of this quantity is reabsorbed through glucose transporters that are present in cell membranes located in the proximal tubules. These glucose transporters have a limited capacity of reabsorption. If this capacity is exceeded, glucose usually appears in the urine. The tubular maximum for glucose (TmG), the term used for the maximum capacity, can vary from 260 to 350 mg/min/1.73 m2 in healthy subjects. It corresponds to blood glucose levels of 180-200 mg/dL. When the blood glucose is very high and the TmG is reached, the transporters cannot reabsorb all the glucose and glucosuria occurs. Nevertheless, there can be slight differences between the nephrons and the inaccurate nature of biological systems may potentially lead to the development of glucosuria when blood glucose is below TmG. Glucosuria may occur at lower plasma glucose levels in certain conditions of hyper filtration (eg. pregnancy), but as a consequence of hyper filtration and not of significant hyperglycemia.

The kidney in diabetes mellitus

All the metabolic pathways regarding the involvement of the kidney in glucose homeostasis are modified in subjects with diabetes mellitus. Subjects with type 2 diabetes mellitus (T2DM) have an increased renal release of glucose into the circulation in the fasting state. Although one can think that the liver determines increased glucose release into the circulation in diabetes, the liver and the kidneys have comparable increase in renal glucose release (2.60 and 2.21 μmol／(kg min). The kidney can increase its glucose production with 300% compared with the liver that can increase gluconeogenesis only by 30%. Gluconeogenesis, in the kidney, could explain this glucose increase, in the fasting state.

QUESTION 2

Discuss the process of micturition.

ANSWER

Micturition is the process by which urinary bladder empties when filled. The main physiological events in the process of micturition are:

- Filling of urinary bladder
- Emptying of urinary bladder.

FILLING OF URINARY BLADDER

1. **Transport of urine into urinary bladder through ureters:** As urine collects in the renal pelvis, the pressure in the pelvis increases and initiates a peristaltic contraction beginning in the pelvis and spreading along the ureter to force urine towards the bladder.
2. **Capacity of the bladder**: Physiological capacity of the bladder varies with age, being 20–50 mL at birth, about 200 mL at 1 year, and can be as high as 600 mL in young adult males. In all cases, the physiological capacity is about twice that at which the first desire to void is felt.
3. **Volume and pressure changes in bladder during filling:** The normal bladder is completely empty at the end of micturition and the intravesical pressure is equal to the intraabdominal pressure. As the bladder is filled up, it adjusts its tone and a fairly large volume of urine can be accommodated with minimal alterations in the intravesical pressure. This is possible because of the phenomenon of adaptation. The adaptation occurs because of the inherent property of plasticity, the smooth muscles of detrusor and because of law of Laplace

EMPTYING OF THE BLADDER

Emptying of the bladder is basically a reflex action called the micturition reflex, which is controlled by supraspinal centres and is assisted by contraction of perineal and abdominal muscles. Therefore, emptying of the urinary bladder focuses on:

- Micturition reflex
- Voluntary control of micturition
- Role of perineal and abdominal muscles in micturition.

Micturition reflex

Initiation: Micturition reflex is initiated by the stimulation of the stretch receptors located in the wall of urinary bladder.

Stimulus: Filling of bladder by 300–400 mL of urine in adults constitutes the adequate stimulus for the micturition reflex to occur.

Afferents: The afferents from the stretch receptors in the detrusor muscle and urethra travel along the pelvic splanchnic nerves and enter the spinal cord through dorsal roots to S2, S3 and S4 segments to reach the sacral micturition center. Sacral micturition center is formed by the sacral detrusor nucleus and sacral pudendal nucleus.

Efferent: Efferent arising from the sacral detrusor nucleus are the preganglionic parasympathetic fibers, which relay in the ganglia near or within bladder and urethra. The post-ganglionic parasympathetic fibers are excitatory to the detrusor muscle and inhibitory to the internal sphincter.

Response: Once micturition reflex is initiated, it is self-regenerative, i.e. initial contraction of the bladder wall further activates the receptors to increase the sensory impulses (afferents) from the

bladder and urethra which cause further increase in the reflex contraction of detrusor muscle of the bladder. The cycle thus keeps on repeating itself again and again until the bladder has reached a strong degree of contraction. Once the micturition reflex becomes powerful enough, this causes another reflex which passes through pudendal nerves to external sphincter to cause its inhibition. If this inhibition is more potent than the voluntary constrictor signals from brain, then urination will not occur. If not so, urination will not occur unless the bladder fills still more and micturition reflex becomes more powerful.

Voluntary control of micturition

Role of supraspinal centres

The micturition reflex is fundamentally a spinal reflex facilitated and inhibited by higher brain centres (supraspinal centres) and, like defecation, is subjected to voluntary facilitation and inhibition. In infants and young children, micturition is purely a reflex action. Voluntary control is gradually acquired as a learned ability of the toilet training. Once voluntary control is acquired, the supraspinal control centres exert final control of micturition by following means:

- The higher centres keep the micturition reflex partially inhibited all the time except when it is desired to micturate.
- When the convenient time to urinate present, the higher centres facilitate the sacral micturition center (SMC) to initiate a micturition reflex and inhibit the external urinary sphincter so that urination can occur.

Supraspinal control centres which control the micturition reflex (a completely automatic cord reflex) include the pontine micturition center (PMC) and suprapontine centres.

Pontine micturition center, corresponds to the locus ceruleus of the rostral pons. Neurons from PMC descend in the reticulospinal tract and exert control over the SMC and thoracolumbar sympathetics. Function of PMC is coordination of detrusor contraction and sphincter relaxation, which is important for proper micturition.

Suprapontine centres which relay their influence on the sacral micturition center through the PMC are:

- Cerebral cortex
- Basal ganglion
- Limbic system

Role of perineal and abdominal muscles in micturition

Certain muscular movements, which aid the emptying of bladder, but are not the essential component of micturition process are:

- At the onset of micturition, the levator ani and perineal muscles are relaxed, thereby shortening the post-urethra and decreasing the urethral resistance.

- The diaphragm descends and,
- The abdominal muscles contract, accelerating the flow of urine by raising intra-abdominal pressure which in turn secondarily increase the intravesical pressure thereby increasing the flow of urine.

Note. Certain important facts about micturition are:

- Avoiding contraction, once initiated, is normally maintained until all the urine has been discharged from the urinary bladder. This is a function of facilitating impulses from the higher centres. However, if required so, the micturition can be voluntarily stopped in between by inhibitory impulses from the higher centres.
- The bladder contracts in all directions like a toy balloon deflating from its neck.
- After urination, the female urethra empties by gravity, whereas the urine remaining in the urethra of male is expelled by several contractions of bulbospongiosus muscle.

Note. In the urinary bladder dysfunction, bladder contractions are insufficient to completely empty the bladder, therefore, some urine is left in the urinary bladder called residual urine.

QUESTION 3

Explain the Juxtaglomerular apparatus

ANSWER

Juxtaglomerular apparatus

Juxtaglomerular (JG) apparatus as the name indicates (juxtanear) refers to the collection of specialized cells located very near to the glomerulus. It forms the major component of renin–angiotensin–aldosterone system. The JG apparatus comprises three types of cells:

- Juxtaglomerular cells
- Macula densa cells
- Mesangial cells.

1. **Juxtaglomerular cells:** JG cells are specialized myoepithelial (modified vascular smooth muscle) cells located in the media of the afferent arteriole in the region of JG apparatus.

Characteristic features of JG cells are:

- They have well-developed Golgi apparatus and endoplasmic reticulum, abundant mitochondria and ribosomes.
- They synthesize, store and release an enzyme called renin. Renin is stored in the secretory granules of JG cells and, therefore, these are also called granular cells.

- They act as baroreceptors (tension receptors) and respond to changes in the Trans mural pressure gradient between the afferent arterioles and the interstitium.
- They are densely innervated by the sympathetic nerve fibers and release their renin content in response to the sympathetic discharge.
- As these cells act as vascular volume receptors, they monitor renal perfusion pressure and are stimulated by hypovolemia or decreased renal perfusion pressure.

2. **Macula densa cells:** Macula densa cells refer to the specialized renal tubular epithelial cells of a short segment of the thick ascending limb of loop of Henle which passes between the afferent and efferent arterioles supplying its glomerulus of origin.

Characteristic features of macula densa cells are:

- They are not well adapted for reabsorption.
- They are not innervated.
- These cells are in direct contact with the mesangial cells and in close contact with the JG cells.
- They act as chemoreceptors and are stimulated by decreased NaCl concentration and thereby causing increased renin release.

3. **Mesangial cells**: Mesangial cells or lacis cells are the interstitial cells of the JG apparatus.

Characteristic features of these cells are:

- They are in contact with both the macula densa cells (on one side) and JG cells (on the other side).
- Functionally, these cells possibly relay the signals from macula densa to the granular cells after modulating the signals. In this way, a decreased intraluminal Na+ load, Cl– load, or both in the region of macula densa stimulates the JG cells to secrete renin.
- They also show granulation to secrete renin in conditions of extreme hyperactivity.
- They also secrete various substances and take up immune complexes

QUESTION 4

Discuss the role of kidney in regulation of blood pressure

ANSWER

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. 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.

Regulatory mechanisms of renal blood flow include:

- Auto regulation
- Hormonal regulation
- Nervous regulation

AUTOREGULATION OF RENAL BLOOD FLOW

The RBF and thus the GFR remain constant over a wide range of renal arterial pressures (80–200 mm Hg). This occurs due to an intrarenal mechanism known as auto regulation.

Mechanisms of auto regulation

Two mechanisms are considered responsible for the autoregulation of RBF and GFR: one mechanism that responds to changes in the arterial pressure and another that responds to changes in NaCl concentration of tubular fluid.

1. **Myogenic mechanism:** It is related to an intrinsic property of vascular smooth muscle: the tendency to contract when it is stretched. Thus, when renal arterial pressure is raised, the afferent arterioles are stretched, which contract and increase the vascular resistance. The increased vascular resistance offsets the effect of increased arterial pressure and thereby maintains a constant RBF and GFR.

2. **Tubuloglomerular feedback mechanism**: Tubuloglomerular feedback (TGF) mechanism is based on the NaCl concentration of tubular fluid. It involves a feedback loop which operates as:

- Changes in the GFR cause changes in the NaCl concentration of fluid in the loop of Henle.
- Changes in the NaCl concentration are sensed by the macula densa cells and converted into a signal.
- The signal from the macula densa cells changes the vascular resistance in the afferent arterioles.
- Signals obtained due to an increased concentration of NaCl produce vasoconstriction; conversely, signals obtained due to decreased NaCl cause vasodilatation of afferent arterioles.
- The effector mechanism responsible for vasoconstriction and vasodilatation is not exactly known. Perhaps, adenosine triphosphate (ATP), which selectively constricts the afferent arterioles and metabolites of arachidonic acid, may contribute to TGF mechanism.

Physiological significance and certain important facts about autoregulation

Physiological significance: A small change in GFR has great effect on urinary output and therefore on loss of solutes and water. If RBF and GFR were to change suddenly in proportion to change in blood pressure, urinary excretion of fluid and solute would also change suddenly. Such changes in water and solute excretion, without comparable alterations in intake, would prove disastrous due to alterations in fluid and electrolyte balance. Thus, autoregulation of RBF and GFR is an effective mechanism for uncoupling renal function from fluctuations in the arterial pressure and maintain fluid and electrolyte balance.

Certain important facts about autoregulation is to be noted are:

- Autoregulation of RBF and GFR is virtually absent at the mean arterial blood pressure below 80 mm Hg,
- Autoregulation is not a perfect mechanism, i.e. RBF and GFR do change slightly with variation in the arterial blood pressure.
- Several hormones and other factors can change RBF and GFR, despite autoregulation mechanisms.

HORMONAL REGULATION

As mentioned above, despite autoregulation, several hormones and other factors have a major effect on RBF and GFR by affecting afferent and/or efferent arteriolar resistance.

1. **Hormones that cause vasoconstriction, and thereby decrease RBF and GFR include:**

- Norepinephrine causes an intense vasoconstriction of both afferent and efferent arterioles.
- Angiotensin II, in low concentrations, causes a predominant constriction of the efferent arterioles. However, at higher concentrations, it causes constriction of both afferent as well as efferent arterioles.
- Endothelin causes profound vasoconstriction of the afferent and efferent arterioles. It is secreted by the endothelial cells of renal vessels, mesangial cells and distal tubular cells.

2. Hormones that cause vasodilatation and thereby increase RBF and GFR include:

- Prostaglandins,
- Nitric oxide (NO)
- Bradykinin
- Atrial natriuretic peptide (ANP),
- Glucocorticoids,
- Dopamine
- Histamine.

NERVOUS REGULATION

Under normal circulatory conditions, sympathetic tone is minimum. Mild-to-moderate stimulation of sympathetic nerves usually has mild effects on RBF because of autoregulation mechanism.

Strong acute stimulation of sympathetic nerves may produce marked fall in RBF (even to 10–30% of normal) temporarily due to constriction of both afferent and efferent arterioles. This effect is mediated mainly by α1-adrenergic receptors and to a lesser extent by post-synaptic α2-adrenergic receptors.

Note. This system works to preserve arterial pressure at the expense of maintaining normal RBF in conditions of acute hypotension due to severe hemorrhage. Further, an increase in sympathetic activity also increases the release of epinephrine and angiotensin-II, enhancing vasoconstriction (vide infra).

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.

QUESTION 5

Discuss the role of kidney in calcium homeostasis.

ANSWER

Extracellular fluid calcium ion concentration normally remains tightly controlled within a few percentage points of its normal level, 2.4 mEq/L. When calcium ion concentration falls to low levels (hypocalcaemia), the excitability of nerve and muscle cells increases markedly and can in extreme cases result in hypocalcemic tetany. This is characterized by spastic skeletal muscle contractions. Hypercalcemia (increased calcium concentration) depresses neuromuscular excitability and can lead to cardiac arrhythmias. About 50 per cent of the total calcium in the plasma (5 mEq/L) exists in the ionized form, which is the form that has biological activity at cell membranes. The remainder is either bound to the plasma proteins (about 40 per cent) or complexed in the non-ionized form with anions such as phosphate and citrate (about 10 per cent). Changes in plasma hydrogen ion concentration can influence the degree of calcium binding to plasma proteins. With acidosis, less calcium is bound to the plasma proteins. Conversely, in alkalosis, a greater amount of calcium is bound to the plasma proteins. Therefore, patients with alkalosis are more susceptible to hypocalcemic tetany. As with other substances in the body, the intake of calcium must be balanced with the net loss of calcium over the long term. Unlike ions such as sodium and chloride, however, a large share of calcium excretion occurs in the feces. The usual rate of dietary calcium intake is about 1000 mg/day, with about 900 mg/day of calcium excreted in the feces. Under certain conditions, fecal calcium excretion can exceed calcium ingestion because calcium can also be secreted into the intestinal lumen. Therefore, the gastrointestinal tract and the regulatory mechanisms that influence intestinal calcium absorption and secretion play a major role in calcium homeostasis. Almost all the calcium in the body (99 per cent) is stored in the bone, with only about 1 per cent in the extracellular fluid and 0.1 per

cent in the intracellular fluid. The bone, therefore, acts as a large reservoir for storing calcium and as a source of calcium when extracellular fluid calcium concentration tends to decrease. One of the most important regulators of bone uptake and release of calcium is PTH. When extracellular fluid calcium concentration falls below normal, the parathyroid glands are directly stimulated by the low calcium levels to promote increased secretion of PTH. This hormone then acts directly on the bones to increase the resorption of bone salts (release of salts from the bones) and, therefore, to release large amounts of calcium into the extracellular fluid, thereby returning calcium levels back toward normal. When calcium ion concentration is elevated, PTH secretion decreases, so that almost no bone resorption now occurs; instead, excess calcium is deposited in the bones because of new bone formation. Thus, the day-to-day regulation of calcium ion concentration is mediated in large part by the effect of PTH on bone resorption.

CONTROL OF CALCIUM EXCRETION BY THE KIDNEYS

Because calcium is both filtered and reabsorbed in the kidneys but not secreted, the rate of renal calcium excretion is calculated as;

Renal calcium excretion = Calcium filtered - Calcium reabsorbed

Only about 50 per cent of the plasma calcium is ionized, with the remainder being bound to the plasma proteins or complexed with anions such as phosphate. Therefore, only about 50 per cent of the plasma calcium can be filtered at the glomerulus. Normally, about 99 per cent of the filtered calcium is reabsorbed by the tubules, with only about 1 per cent of the filtered calcium being excreted. About 65 per cent of the filtered calcium is reabsorbed in the proximal tubule, 25 to 30 per cent is reabsorbed in the loop of Henle, and 4 to 9 per cent is reabsorbed in the distal and collecting tubules. This pattern of reabsorption is similar to that for sodium. As is true with the other ions, calcium excretion is adjusted to meet the body's needs. With an increase in calcium intake, there is also increased renal calcium excretion, although much of the increase of calcium intake is eliminated in the feces. With calcium depletion, calcium excretion by the kidneys decreases as a result of enhanced tubular reabsorption.

One of the primary controllers of renal tubular calcium reabsorption is PTH. With increased levels of PTH, there is increased calcium reabsorption in the thick ascending loops of Henle and distal tubules, which reduces urinary excretion of calcium. Conversely, reduction of PTH promotes calcium excretion by decreasing reabsorption in the loops of Henle and distal tubules. In the proximal tubule, calcium reabsorption usually parallels sodium and water reabsorption. Therefore, in instances of extracellular volume expansion or increased arterial pressure—both of which decrease proximal sodium and water reabsorption—there is also reduction in calcium reabsorption and, consequently, increased urinary excretion of calcium. Conversely, with extracellular volume contraction or decreased blood pressure, calcium excretion decreases primarily because of increased proximal tubular reabsorption. Another factor that influences calcium reabsorption is the plasma concentration of phosphate. An increase in plasma phosphate stimulates PTH, which increases calcium reabsorption by the renal tubules, thereby reducing

calcium excretion. The opposite occurs with reduction in plasma phosphate concentration. Calcium reabsorption is also stimulated by metabolic acidosis and inhibited by metabolic alkalosis. Most of the effect of hydrogen ion concentration on calcium excretion results from changes in calcium reabsorption in the distal tubule.