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**Matric Number: 17/MHS01/333**

**Course Title:** Renal Physiology Body Fluid and Temperature Regulation
**Course Code:** PHS 303

**Department**: Medicine and Surgery

**Question**

1. Discuss the role of kidney in glucose homeostasis?
2. Discuss the process of micturition?
3. Explain juxtaglomerular apparatus?
4. Discuss the role of kidney in regulation of blood pressure?
5. Discuss the role of kidney in calcium homeostasis?

**Answers**

RENAL HANDLING OF GLUCOSE

 Glucose reabsorption

Mechanism of tubular reabsorption

 All the filtered glucose is completely reabsorbed into the proximal tubule by an active transport mechanism.

 Carrier mediated Na+−glucose co-transport. Carrier protein located at the apical membrane in the proximal tubule reabsorbs glucose from tubular fluid into the blood.

* The carrier protein for glucose in early and late proximal tubule is called SGLT-2 and SGLT-1, respectively (SGLT = sodium-dependent glucose transporter).
* The carrier is driven by the Na+ concentration gradient which exists between the high tubular (Na+) concentration and the low intracellular (Na+) gradient produced by the pumping out of Na+ through the basolateral surface.

 **Facilitated diffusion** moves the glucose out of the cell through the basolateral membrane. The carrier for facilitated diffusion across the basolateral membrane in early and late proximal tubule is called GLUT-2 and GLUT-1, respectively (GLUT = glucose transporter).

**Characteristics of glucose transport and glucose excretion**

Glucose is reabsorbed by a transport maximum process, i.e. there are limited number of Na+−glucose carriers. The characteristics of glucose transport and glucose excretion can be elicited from the glucose titration curve, which is constructed by plotting the following pairs of variables:

* The filtered load against plasma glucose concentration,
* The excretion rate against plasma glucose concentration and
* The difference between the filtered load and excretion rate (i.e. maximum tubular reabsorption capacity, Tr) against plasma concentration.

**Glucose titration curve depicts that**

Filtered load increases with the plasma glucose concentration (PG).

Renal threshold, i.e. the plasma glucose concentration at which glucose first appears in the urine (glycosuria) is about 180–200 mg/dL. At plasma levels below renal threshold, the reabsorption of glucose is complete (100%), i.e. all of the filtered glucose can be reabsorbed because plenty of carriers are available and hence no glucose is excreted in urine. In this region, the line of reabsorption is the same as that of filtration.

Transport maximum (Tm) refers to the plasma concentration at which carriers are fully saturated. Beyond plasma glucose concentration is 350 mg/dL (TmG) the reabsorption rate does not increase, i.e. becomes constant and is independent of PG. Therefore, as the TmG is reached, the urinary excretion rate increases linearly with increase in plasma glucose concentration.

Splay refers to the region of the glucose curve between threshold and TmG, i.e. between PG 180 and 350 mg/dL. It represents the excretion of glucose in urine before the TmG is fully achieved. Note in the region of splay, the reabsorption curve is rounded indicating that though the reabsorption rate is increasing with increase in PG, but reabsorption is less than filtration. Similarly, the excretion curve is also rounded in the region of splay, indicating that though the urinary excretion is increasing with increase in PG, but there is no linear relation. Causes of splay are:

* Heterogenicity in glomerular size, proximal tubular length and number of carrier proteins for glucose reabsorption.
* Variability in TmG of the nephron.

For example, there is variability in the number of glucose carrier, the transport rate of the carriers and the binding affinity of the Na+ glucose carriers.

**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.

**Physiology of Micturition**

Neurophysiological Control of the Bladder Local Neural Pathways The spinal segments S2-S4 acting via efferent parasympathetic cholinergic neurons are responsible for the initiation and maintenance of detrusor contraction. Damage to these spinal segments results in abolition of the micturition reflex in man (Denny-Brown and Robertson, 1933b). After leaving the sacral foramina the pelvic splanchnic nerves, containing the parasympathetic innervation to the bladder and possibly some efferent somatic neurons to the intrinsic component of the urethral sphincter, pass lateral to the rectum to enter the inferior hypogastric or pelvic plexus. They are joined by the hypogastric nerve containing efferent sympathetic nerve fibres originating from the lower three thoracic and upper two lumbar segments of the spinal cord (Warwick and Williams, 1973). When combined they form a plexus lying at the base of the bladder. The limited knowledge available suggests that the pudendal nerve transmits urethral mucosal sensation (Nathan, 1956) and it has long been suggested that the afferent pathway of the micturition reflex is carried via the pelvic nerves (Learmonth, 1931). Additional afferent information is likely to be transmitted from the trigone via sympathetic neuronal pathways in the hypogastric nerves (Winter, 1971). From observation of patients undergoing anterolateral cordotomy Nathan and Smith (1951) concluded that some bladder and urethral sensation in the afferent limb of the micturition reflex passed proximally via the spinothalamic tracts. Reflexes Governing Micturition Barrington initially described five reflexes associated with micturition in the cat (1914), and added a further two on the basis of further study (1931, 1941). Two of these reflexes had their reflex centres in supraspinal sites (medulla and pons) and caused strong and sustained contractions. He considered these as essential for normal micturition, since bladder contraction and urethral relaxation were not coordinated after experimentally produced high spinal transection. The remaining five reflexes appeared confined to the spinal cord. Although it is tempting to relate these findings to man, Denny-Brown and Robertson, (1933a) failed to detect either initiation of micturition or vesical contraction resulting from distension of the posterior urethra in man and concluded that micturition was a reflex act resulting from bladder distension and mediated by a centre in the sacral cord (Denny-Brown and Robertson 1933b). More recently, Kuru (1965) has proposed that many interrelated reflexes act upon the sacral micturition centre, exerting both excitatory and inhibitory effects. Urine Storage During bladder filling, afferent activity from stretch receptors increases and passes via the posterior roots of the sacral cord and the lateral spinothalamic tracts to the brain, thereby mediating the desire to void. Activity within the striated component of the urethral sphincter is increased, and local spinal reflex activity in turn stimulates the pudendal motor neurons of the nucleus of Onufrowicz, which enhances the activity within striated muscles of the pelvic floor and sphincter. Local factors are important during bladder filling and these include not only receptive relaxation (Tang and Ruch, 1955), but also the passive viscoelastic properties of the bladder wall. Both abnormal bladder morphology resulting from collagenous infiltration, hypertrophy or altered muscle structure (e.g. obstructed bladder) and abnormal detrusor smooth muscle behaviour, either primary or secondary to neural dysfunction, could contribute to the genesis of poor bladder compliance and detrusor instability.

Initiation of Micturition

Once a threshold level of filling has been achieved, which will depend on circumstances and vary considerably between individuals, the increasing afferent activity impinges upon consciousness, and the subject becomes aware that the bladder is filling. Except during infancy, the normal human has complete volitional control over these reflex pathways.

1. **Juxtaglomerular apparatus**

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 the [glomerulus](https://en.wikipedia.org/wiki/Glomerulus_%28kidney%29).

The juxtaglomerular apparatus consists of three types of cells:

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

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_%28kidney%29). 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**

[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%22%20%5Co%20%22Tubuloglomerular%20feedback) (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%22%20%5Co%20%22Purinergic%20signaling). 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 kidney plays a central role in the regulation of arterial blood pressure. A large body of experimental

The kidney plays 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 system. As a result, many researchers argue that identifying any marked rise in blood pressure requires resetting of the relationship between arterial blood pressure and urinary sodium excretion, which can occur by an array of systemic or local mechanisms. Almost all of the monogenic forms of hypertension affect sites in the kidney associated with sodium handling and transport. Experimental models of spontaneous hypertension, such as the Dahl salt-sensitive rat, have been used to study the effects of kidney transplantation on blood pressure. Results from studies of kidney transplantation indicate that pressure sensitivity to sodium intake 'follows' the kidney, meaning that the recipient of a 'salt-resistant kidney' acquires sodium resistance, and that the recipient of a 'salt-sensitive kidney' acquires pressure sensitivity. The examples above and discussed in this Review demonstrate that it should come as no surprise that most disorders that affect the kidney or the renal vasculature commonly lead to secondary forms of hypertension.

The Kidneys And Their Influence On Blood Pressure

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.

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.

5.

Control of Renal Calcium Excretion and Extracellular Calcium Ion Concentration

The mechanisms for regulating calcium ion concentration are discussed in detail in Chapter 79, along with the endocrinology of the calcium-regulating hormones parathyroid hormone (PTH) and calcitonin. Therefore, calcium ion regulation is discussed only briefly in this chapter. 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 (hypocalcemia), 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, as discussed in Chapter 79. 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 reabsorption. The bones, however, do not have an inexhaustible supply of calcium. Therefore, over the long term, the intake of calcium must be balanced with calcium excretion by the gastrointestinal tract and the kidneys. The most important regulator of calcium reabsorption at both of these sites is PTH. Thus, PTH regulates plasma calcium concentration through three main effects: (1) by stimulating bone reabsorption; (2) by stimulating activation of vitamin D, which then increases intestinal reabsorption of calcium; and (3) by directly increasing renal tubular calcium reabsorption. The control of gastrointestinal calcium reabsorption and calcium exchange in the bones is discussed elsewhere, and the remainder of this section focuses on the mechanisms that control renal calcium excretion.

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