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**COURSE TITLE: RENAL PHYSIOLOGY,BODY FLUID AND TEMPERATURE REGULATION**

**COURSE CODE: PHS303**

1. Discuss the role of kidney in glucose homeostasis

Kidney has an important role in ensuring the energy needs during fasting periods. This organ has a vital role in absorbing the entire quantity of the filtered glucose . Having a glomerular filtration rate of 180 liters per day, it filters approximately 180 grams of glucose per day, bringing its contribution in maintaining normal fasting plasma glucose (FPG) levels . The reabsorption of glucose is ensured by the sodium-glucose cotransporter (SGLT) 2, responsible for the reabsorption of 90% of glucose, and SGLT1, that reabsorbs the remaining glucose. In the fasting (postabsorptive) state in healthy individuals, the kidneys contribute about 20% to 25% of the glucose released into the circulation via [gluconeogenesis](https://www.sciencedirect.com/topics/medicine-and-dentistry/gluconeogenesis) (15–55 g per day), with the liver responsible for the remainder via both [glycogenolysis](https://www.sciencedirect.com/topics/medicine-and-dentistry/glycogenolysis) and gluconeogenesis. Renal gluconeogenesis occurs predominantly within proximal tubule cells in the renal cortex, and is chiefly regulated by insulin and [catecholamines](https://www.sciencedirect.com/topics/medicine-and-dentistry/catecholamine) (eg, adrenaline). Insulin reduces renal gluconeogenesis directly, and also reduces the availability of gluconeogenic substrates, such as lactate, [glutamine](https://www.sciencedirect.com/topics/medicine-and-dentistry/glutamine), and glycerol, thus reducing glucose release into the circulation. Adrenaline stimulates renal gluconeogenesis, stimulates renal glucose release, inhibits [insulin secretion](https://www.sciencedirect.com/topics/medicine-and-dentistry/insulin-release), increases the supply of gluconeogenic substrates, and reduces renal glucose uptake. In patients with type 2 diabetes mellitus, both renal and hepatic glucose release are increased as a result of increased gluconeogenesis. The human kidney is involved in the regulation of glucose homeostasis and in abnormalities found in diabetes mellitus via three different mechanisms: (i) release of glucose into the circulation via gluconeogenesis; (ii) uptake of glucose from the circulation to satisfy its energy needs; and (iii) reabsorption into the circulation of glucose from glomerular filtrate to conserve glucose carbon.

The relative increase in renal gluconeogenesis is thought to be substantially greater than in hepatic gluconeogenesis (300% vs 30%). Renal glycogenolysis is minimal in healthy individuals but may play a role in increased renal glucose release in patients with type 2 diabetes mellitus,due to accumulation of glycogen in diabetic kidneys. Renal gluconeogenesis and renal glucose uptake are increased in both the post-absorptive and postprandial states, and renal glucose reabsorption is increased. Specific SGLT2 inhibitors are being developed as a novel means of controlling hyperglycaemia in type 2 diabetes mellitus.

1. **DISCUSS THE PROCESS OF 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.

 Within the nervous system, the process is governed by the autonomous nervous system and the somatic system. Once the urinary bladder reaches its maximum capacity, the stretch receptors in the walls of the bladder send an impulse via the pelvic nerve to the brain via the spinal cord.

The micturition reflex is ultimately generated from the level of the spinal cord after it receives reflexes from the pontine region in the brain. Once the bladder and the urethra receive the signals to empty the bladder, the two sphincters relax and the detrusor muscle causes the contractions of the bladder.

Along with these muscles, the muscles of the abdomen also play a role by putting [pressure](https://www.toppr.com/guides/physics/force-and-pressure/introduction-to-pressure) on the bladder wall. This leads to complete emptying of the bladder. Micturition requires the coordinated activity of sympathetic, parasympathetic and somatic nerves. It also requires normal muscle tone and freedom from physical obstruction and psychological inhibition. Control from our higher brain centres allow us to determine the right time and place to allow this important physiological function to occur.

1. EXPLAIN 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 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_%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).

**Juxtaglomerular cells**

The [renin–angiotensin system](https://en.wikipedia.org/wiki/Renin%E2%80%93angiotensin_system) is activated when juxtaglomerular cells are poorly perfused.

[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) (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). 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.

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. DISCUSS THE ROLE OF KIDNEY IN REGULATION OF BLOOD PRESSURE

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 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. DISCUSS THE ROLE OF THE KIDNEY IN CALCIUM HOMEOSTASIS

The maintenance of calcium homeostasis is very important because calcium is the main component of bony skeleton and serves as the intracellular and extracellular messenger in numerous essential cellular events such as neuronal network, immune response, muscle contraction, and hormone secretion. Total body calcium in the adult human is about 1-2 kg and 99% of total calcium exists in bone. Even though only less than 1% of body calcium is in the extracellular space, maintaining the extracellular calcium concentration within a narrow range (8.5-10.5 mg/dL) is very important for calcium homeostasis. Approximately 40% of plasma calcium is protein-bound and 10% of calcium is in a complex with anions like phosphate, citrate, and sulfate etc. Only half of plasma calcium is in its free form (ionized form, iCa2+) and physiologically important. The ionized calcium is tightly regulated by hormones like parathyroid hormone (PTH), 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), calcitonin, and calcium itself. The kidney, intestine, and bone are the main target organs of these regulators, and the kidney plays a key role in the fine regulation of calcium excretion. The kidneys play a central role in the homeostasis of these ions. Gastrointestinal absorption is balanced by renal excretion. When body stores of these ions decline significantly, gastrointestinal absorption, bone resorption, and renal tubular reabsorption increase to normalize their levels. Renal regulation of these ions occurs through glomerular filtration and tubular reabsorption and/or secretion and is therefore an important determinant of plasma ion concentration. Under physiologic conditions, the whole body balance of calcium, phosphate, and magnesium is maintained by fine adjustments of urinary excretion to equal the net intake. Calcium balance is tightly regulated by the concerted action of calcium absorption in the intestine, reabsorption in the kidney, and exchange from bone, which are all under the control of the calciotropic hormones that are released upon a demand for calcium. In healthy adults, approximately 800–1000 mg of calcium should be ingested daily. This amount will vary depending on the amount of dairy product consumed. When 1 g of calcium is ingested in the diet, approximately 800 mg is excreted in the feces and 200 mg in the urine. Approximately 400 mg of the usual 1000 mg dietary calcium intake is absorbed by the intestine, and calcium loss by way of intestinal secretions is approximately 200 mg/d. Therefore, a net absorption of calcium is approximately 200 mg/d (20%). Although serum calcium levels can be maintained in the normal range by bone resorption, dietary intake is the only source by which the body can replenish stores of calcium in bone.