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1. Discuss the role of kidney in glucose homeostasis.

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).

As alluded to previously, the kidneys are capable of synthesizing and secreting many important hormones (eg, renin, prostaglandins, kinins, erythropoietin) and are involved in a wide variety of metabolic processes such as activation of vitamin D3, gluconeogenesis, and metabolism of numerous endogenous compounds (eg, insulin, steroids). 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.13

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.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 (e.g., hepatic insufficiency, counter regulation of hypoglycemia). To this point, evidence suggests that in patients with T2DM, renal glucose release is increased in both the postprandial and post absorptive 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 occurs.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 (e.g., 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.

2. Discuss the process of micturition.

What is Micturition?

Micturition is a process where urine is expelled from the body. Animals and humans have a specialized system of organs known as the excretory system to eliminate the waste products from the body. In other words, **the process of expelling urine from the body is called micturition.** It is brought about by reflex contraction of a special muscle called the detrusor muscle after voluntary relaxation of the sphincter muscle.

The [human excretory system](https://byjus.com/biology/human-excretory-system/) consists of a pair of kidneys and ureters, a urinary bladder, and a urethra. The kidneys play a major role in the process of urine formation and its excretion. The urine formed is stored in the urinary bladder. Micturition is also known as voiding phase of bladder control and lasts for a short time. As the bladder becomes full, the stretch receptors increase their firing rate. This increase the urge to urinate and causes micturition reflex. It sometimes even causes involuntary urination.

## Micturition Process

Micturition process consists of two phases:

* Storage phase
* Voiding phase

Storage Phase

The urinary bladder is a balloon-shaped, hollow, muscular, organ that acts as the storage organ for urine. The urinary bladder in a healthy urinary system can store up to 16 ounces of urine for 2 to 5 hours easily. The circular sphincter muscles prevent leakage of urine. They close tightly around the opening of the bladder into the tube (urethra) that allows the passage of urine outside the body.

Voiding Phase

When the bladder is filled with urine, the nerves in it are triggered, which in turn stimulates the need to urinate. The brain signals urinary bladder to contract. The receptors of the urinary bladder send a signal to the [central nervous system](https://byjus.com/biology/central-nervous-system/), in response to which the nervous system sends a signal that incites the contraction of the urinary bladder.  Through the urinary opening at the urethra, the urine is eliminated, and the process is called micturition. The neural mechanism involved is called the micturition reflex.

3. Explain juxtaglomerular apparatus

Juxtaglomerular apparatus

The [juxtaglomerular apparatus](https://www.sciencedirect.com/topics/medicine-and-dentistry/juxtaglomerular-apparatus) comprises afferent and efferent [arterioles](https://www.sciencedirect.com/topics/medicine-and-dentistry/arteriole), complemented by granular, renin-secreting cells, the [macula densa](https://www.sciencedirect.com/topics/medicine-and-dentistry/macula-densa), a specialized group of distal tubular cells and lacis cells (Goormaghtigh cells, polar cushion, extraglomerular mesangial cells). Lacis cells form a pyramid situated between the afferent and efferent arterioles and with its base on the macula densa and apex continuous with the glomerular [mesangium](https://www.sciencedirect.com/topics/medicine-and-dentistry/mesangium).41 The juxtaglomerular apparatus can be considered as an anatomical unit important in tubuloglomerular feedback control of renal blood flow, [glomerular filtration](https://www.sciencedirect.com/topics/medicine-and-dentistry/glomerulus-filtration) rate and possibly also tubular control of [renin](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/renin) secretion. Immunocytochemical study has confirmed that much of the renin in the kidney is located in the outer media of the afferent arterioles, normally to a greater extent in superficial cortex than in juxtamedullary regions. Renin release occurs outwards into the [extravascular space](https://www.sciencedirect.com/topics/medicine-and-dentistry/extravascular-space) and into renal capillaries.41 Renin-secreting cells are also found in more proximal segments of the afferent arterioles and in [interlobular arteries](https://www.sciencedirect.com/topics/medicine-and-dentistry/interlobular-arteries) as well as in efferent arterioles.42

Ultrastructure of the Juxtaglomerular Apparatus

The **juxtaglomerular apparatus** (JGA) is one component of an important feedback mechanism, the tubuloglomerular feedback mechanism that is described in Chapter 3. The following structures make up the JGA (see Figure 2-5):

1.

The **macula densa** of the thick ascending limb

2.

The [extraglomerular mesangial cells](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/extraglomerular-mesangial-cell)

3.

The renin- and angiotensin II–producing **granular cells** of the afferent arteriole

The cells of the macula densa represent a morphologically distinct region of the thick ascending limb. This region passes through the angle formed by the afferent and efferent arterioles of the same nephron. The cells of the macula densa are in contact with the extraglomerular [mesangial cells](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/mesangial-cell) and the granular cells of the afferent arterioles. Granular cells of the afferent arterioles are derived from metanephric mesenchymal cells. They contain smooth muscle myofilaments and they manufacture, store, and release **renin**. [Renin](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/renin) is involved in the formation of **angiotensin II** and ultimately in the secretion of [aldosterone](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/aldosterone) (see Chapters 4 and 6Chapter 4Chapter 6). The JGA is one component of the tubuloglomerular feedback mechanism that is involved in the auto regulation of [renal blood flow](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/kidney-blood-flow) and the GFR (see Chapter 3).

The [juxtaglomerular apparatus](https://www.sciencedirect.com/topics/medicine-and-dentistry/juxtaglomerular-apparatus) is involved in maintaining blood pressure and volume by the production of the hormone [renin](https://www.sciencedirect.com/topics/medicine-and-dentistry/renin). It is a specialized adaptation of vascular and tubular tissues that allows blood flow to affect renin output. The juxtaglomerular apparatus comprises:

1. Renin-producing cells located in the walls of the afferent and efferent [arterioles](https://www.sciencedirect.com/topics/medicine-and-dentistry/arteriole) at the vascular hilum of the [glomerulus](https://www.sciencedirect.com/topics/medicine-and-dentistry/glomerulus)
2. Lacis cells
3. The [macula densa](https://www.sciencedirect.com/topics/medicine-and-dentistry/macula-densa) area of distal tubule (Fig. 15.28).

**Renin-secreting cells contain neuroendocrine granules**

In man, renin-producing cells are concentrated mainly in the walls of the afferent [arteriole](https://www.sciencedirect.com/topics/medicine-and-dentistry/arteriole), although small numbers are present in the efferent arteriole.

Renin-producing cells have the ultra-structural features of highly specialized myoepithelial cells, with some contractile filaments. They also contain neuroendocrine granules of many shapes and sizes, although two distinct types can be recognized.

Type I granules are irregular in shape and contain rhomboidal crystalline bodies (protogranules), which are believed to be the precursors of the other types of granules.

Type II granules are larger, spherical, uniformly electron dense, and have an ill-defined membrane; they are thought to represent the mature renin-secreting granules.

The lacis cells resemble [mesangial cells](https://www.sciencedirect.com/topics/medicine-and-dentistry/mesangial-cell)

Lacis cells have a network (lacis) of thin interwoven processes, which are separated by an acellular matrix of basement membrane-like material. Lacis cells occupy the triangular region bordered by the macula densa at the base and the afferent and efferent arterioles at the sides; the apex is formed by the base of the glomerular [mesangium](https://www.sciencedirect.com/topics/medicine-and-dentistry/mesangium).

Because of their apparent continuity with the glomerular mesangium at the vascular pole of the glomerulus, these cells have also been called ‘extraglomerular mesangial cells’. Their function is not definitively known but they have numerous processes containing [gap junctions](https://www.sciencedirect.com/topics/medicine-and-dentistry/gap-junction) and are thought to provide electrical coupling among themselves and to the mesangium and glomerular arterioles.

**The macula densa is a specialized adaptation of distal tubular epithelium**

The macula densa is a specialized zone of the distal tubule where it is in close contact with the vascular hilum of the glomerulus.

In this region, the epithelial cells of the distal tubule are taller and more tightly packed than elsewhere in the tubule and the nuclei lie closer to the luminal surface; the Golgi is located between the nucleus and the [basement membrane](https://www.sciencedirect.com/topics/medicine-and-dentistry/basement-membrane).

The precise function of this specialized zone of distal tubule is not known but it may act as a sensor, regulating juxtaglomerular function by monitoring sodium and chloride levels in the distal tubule lumen.

[Renin](https://www.sciencedirect.com/topics/medicine-and-dentistry/renin) converts [angiotensinogen](https://www.sciencedirect.com/topics/medicine-and-dentistry/angiotensinogen) to active [angiotensin](https://www.sciencedirect.com/topics/medicine-and-dentistry/angiotensin) which then causes the adrenals to secrete [aldosterone](https://www.sciencedirect.com/topics/medicine-and-dentistry/aldosterone)

Renin produced in the juxtaglomerular apparatus catalyzes the conversion of inactive angiotensinogen. Angiotensinogen is an α2-globulin produced in the liver, converted by renin to the decapeptide [angiotensin I](https://www.sciencedirect.com/topics/medicine-and-dentistry/angiotensin-i). Angiotensin I is then converted to [angiotensin II](https://www.sciencedirect.com/topics/medicine-and-dentistry/angiotensin-ii), which stimulates the secretion of aldosterone by the [zona glomerulosa](https://www.sciencedirect.com/topics/medicine-and-dentistry/zona-glomerulosa) of the [adrenal cortex](https://www.sciencedirect.com/topics/medicine-and-dentistry/adrenal-cortex) (see p. 275).

Aldosterone is a [mineralocorticoid](https://www.sciencedirect.com/topics/medicine-and-dentistry/mineralocorticoid) hormone that regulates body [sodium and potassium ion](https://www.sciencedirect.com/topics/medicine-and-dentistry/sodium-ion) levels through its effect on the [sodium pump](https://www.sciencedirect.com/topics/medicine-and-dentistry/adenosine-triphosphatase-potassium-sodium) mechanism at cell membranes.

In the distal tubule of the kidney, aldosterone promotes the reabsorption of sodium [ions](https://www.sciencedirect.com/topics/medicine-and-dentistry/inorganic-ions) and water from the glomerular filtrate (Fig. 15.29), and thereby contributes to the maintenance of plasma volume and blood pressure.

4. Discuss the role of kidney in blood pressure regulation

The renin-angiotensin system or RAS regulates blood pressure and fluid balance in the body. When blood volume or sodium levels in the body are low, or blood potassium is high, cells in the kidney release the enzyme, renin. Renin converts angiotensinogen, which is produced in the liver, to the hormone angiotensin I. An enzyme known as ACE or angiotensin-converting enzyme found in the lungs metabolizes angiotensin I into angiotensin II. Angiotensin II causes blood vessels to constrict and blood pressure to increase. Angiotensin II stimulates the release of the hormone aldosterone in the adrenal glands, which causes the renal tubules to retain sodium and water and excrete potassium. Together, angiotensin II and aldosterone work to raise blood volume, blood pressure and sodium levels in the blood to restore the balance of sodium, potassium, and fluids. If the renin-angiotensin system becomes overactive, consistently high blood pressure results.

5. Discuss the role of kidney in calcium homeostasis

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.