1. **ROLE OF KIDNEY IN GLUCOSE HOMEOSTASIS**

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. While not traditionally discussed, the kidneys’ contributions to maintaining glucose homeostasis are significant and include such functions as release of glucose into the circulation via gluconeogenesis, uptake of glucose from the circulation to satisfy their energy needs, and reabsorption of glucose at the level of the proximal tubule. Renal release of glucose into the circulation is the result of glycogenolysis and gluconeogenesis, respectively involving the breaking down and formation of glucose-6-phosphate from precursors (eg, lactate, glycerol, amino acids). With regard to renal reabsorption of glucose, the kidneys normally 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. The process of renal glucose reabsorption is mediated by active (sodium-coupled glucose cotransporters) and passive (glucose transporters) transporters. In hyperglycemia, the kidneys may play an exacerbating role by reabsorbing excess glucose, ultimately contributing to chronic hyperglycemia, which in turn contributes to chronic glycemic burden and the risk of microvascular consequences. This article provides an extensive review of the kidneys’ role in normal human physiology, the mechanisms by which they contribute to glucose regulation, and the potential impact of glucose imbalance on the kidneys.

1. **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 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

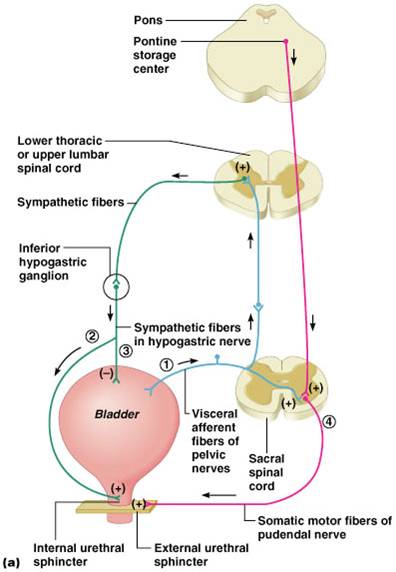
**Resting or Filling Stage**

In this phase 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.



The process of [micturition](https://www.toppr.com/guides/biology/excretory-products/micturition/) is governed by both the nervous and muscular systems. 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.

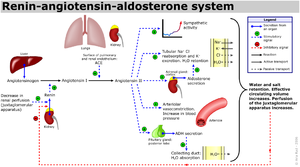
1. **EXPLAIN JUXTAGLOMERULAR APPARATUS**

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

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" \o "Renin)
3. [extraglomerular mesangial cells](https://en.wikipedia.org/wiki/Extraglomerular_mesangial_cells)

**Juxtaglomerular cells**

[](https://en.wikipedia.org/wiki/File:Renin-angiotensin-aldosterone_system.png)

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

*See also: [Renin–angiotensin system](https://en.wikipedia.org/wiki/Renin%E2%80%93angiotensin_system" \o "Renin–angiotensin system)*

[Renin](https://en.wikipedia.org/wiki/Renin) is produced by [juxtaglomerular cells](https://en.wikipedia.org/wiki/Juxtaglomerular_cells" \o "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" \o "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" \o "Renin) is also found in these cells. The specific function of extraglomerular mesangial cells is not well understood, although it has been associated with the secretion of [erythropoietin](https://en.wikipedia.org/wiki/Erythropoietin) and secretion of [renin](https://en.wikipedia.org/wiki/Renin" \o "Renin).

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

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

If a sudden change in [blood pressure](https://en.wikivet.net/Category:Blood_Pressure) occurs it is controlled in the short term by the sympathetic nervous system which alters three things:

* Total peripheral resistance
* Capacitance
* Cardiac output

It is only in the long term, in response to chronic changes in blood pressure that the kidney works to alter the balance between fluid intake and output in order to regulate blood pressure.

#### Three mechanisms of Renal Regulation

##### Pressure Diuresis

**Q = (PA - PE) ÷ R**

**Q** = Flow, **PA** = Pressure in afferent arteriole, **PE** = Pressure in efferent arteriole, **R** = Resistance

* As arteriolar blood pressure increases, so flow through the kidneys also increases - see above formula
* This increases filtration rate
* This increases urinary output

##### Pressure Natriuresis

* If renal perfusion pressure is increased then sodium excretion increases
* I.e. sodium excretion increases when blood pressure increases
* If more sodium is excreted less water is reabsorbed therefore the ECF volume decreases and blood pressure decreases.
* The actual mechanism is not clear but it is thought to involve a direct effect of the pressure on the renal interstitium.

##### [Renin-Angiotensin-Aldosterone System](https://en.wikivet.net/Renin_Angiotensin_Aldosterone_System)

* Specialized cells in the distal tubule called the macula densa sense the concentration of sodium and chloride.
* If blood pressure falls there is a reduction in concentration of sodium and chloride in the distal tubule which is sensed by the macula densa.
* The macula densa releases prostaglandins which act on the juxtaglomerular apparatus which releases renin into the bloodstream.
* The drop in blood pressure is also detected by baroreceptors in the aortic arch, carotid sinus and the afferent renal arteriole which stimulates renin release by the juxtaglomerular apparatus.
* Renin cleaves angiotensinogen into angiotensin 1 which in turn is cleaved by **[Angiotensin Converting Enzyme](https://en.wikivet.net/Angiotensin_Converting_Enzyme" \o "Angiotensin Converting Enzyme)**[(ACE)](https://en.wikivet.net/Angiotensin_Converting_Enzyme" \o "Angiotensin Converting Enzyme) into angiotensin 2.
* Angiotensin 2 is a potent vasoconstrictor and also stimulates the adrenal cortex to release [aldosterone](https://en.wikivet.net/Aldosterone" \o "Aldosterone).
* [Aldosterone](https://en.wikivet.net/Aldosterone) acts on the distal tubules and collecting ducts in the kidney causing retention of sodium and water.
* Blood pressure increases.
* 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.

1. **ROLE OF 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 important1). The ionized calcium is tightly regulated by hormones like parathyroid hormone (PTH), 1,25-dihy

droxyvitamin 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 excretion1). This review will focus on how the kidney works for calcium homeostasis on a molecular basis and discuss new players in the regulation of calcium excretion which were identified recently.

**Overview of renal Ca2+ handling**

About 50% of plasma calcium (ionized and complexed form; ultrafilterable fraction, excluding the protein bound form) is freely filtered through the renal glomerulus, and 99% of the filtered calcium is actually reabsorbed along renal tubules. The excreted calcium in the final urine is about 200 mg per day in an adult person with an average diet. Several factors are involved in th regulation of calcium in renal tubules. PTH and activated vitamin D enhance calcium reabsorption in the thick ascending limb (TAL), distal convoluted tubule (DCT) and/or connecting tubule (CNT), and estrogen promotes calcium absorption in the DCT/CNT1, 2). Acidosis contributes to hypercalciuria by reducing calcium reabsorption in the proximal tubule (PT) and DCT, and alkalosis vice versa3). Diuretics like thiazide and furosemide also alter calcium absorption in the renal tubules; thiazide promotes calcium reabsorption and furosemide inhibits it4, 5). Plasma calcium itself also controls renal calcium absorption through altered PTH secretion as well as via binding to the calcium sensing receptor (CaSR) in the TAL. To facilitate Ca2+ reabsorption along renal tubules; (i) voltage difference between the lumen and blood compartment should be favorable for Ca2+ passage, i.e., a positive voltage in the lumen; (ii) concentration difference should be favorable for Ca2+ passage with a higher Ca2+ concentration in the lumen; (iii) an active transporter should exist if the voltage or concentration difference is not favorable for Ca2+ reabsorption. Each renal tubular segment has a different Ca2+ concentration difference or voltage environment for its unique mechanism for calcium reabsorption.

**Renal Ca2+ handling along the tubules**

Fifty to sixty percent of filtered calcium is absorbed in parallel with sodium and water in the PT, suggesting that the passive pathway is the main route of Ca2+ absorption in this segment. Claudin-2 is especially concentrated in the tight junction and also expressed in the basolateral membrane of the PT as the candidate for paracellular Ca2+ channel in the PT6). There is no evidence that Ca2+ reabsorption occurs in the thin descending and ascending limb. In the TAL, 15% of filtered calcium is absorbed, and the passive absorption through paracellular space is known as the main mechanism (Fig. 1). Paracellin-1 (claudin-16) is exclusively expressed in the tight junction of TAL and has been known as the important magnesium channel in the TAL6). Paracellin-1 mutation caused hypercalciuria and nephrocalcinosis in addition to hypomagnesemia2). This finding supports that paracellin-1 is not only the main Mg2+ channel, but also works as the paracellular Ca2+ channel in the TAL. There are some evidences that active transport occurs in the TAL, but no specific channel has yet been identified1). The CaSR is a member of G protein-coupled receptors and suppresses PTH secretion by sensing high plasma Ca2+ level in the parathyroid glands7). In the kidney, the CaSR is most highly expressed in the TAL. Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant disease due to the mutation of CaSR gene, and is manifested as hypercalcemia, hypophosphatemia, parathyroid hyperplasia, and unusually low renal clearance of calcium. Hypocalciuria, despite of hyperactivity of PTH in FHH, suggests that CaSR plays a direct role in Ca2+ absorption, especially in the TAL independent to PTH action8). Although only 10-15% of filtered Ca2+ is absorbed in the DCT and CNT, these are the main sites in which the fine regulation of Ca2+ excretion and the major action of PTH and activated vitamin D occur. In the DCT and CNT, the luminal voltage is negative and Ca2+ concentration in the lumen is lower than that of plasma. Thus, active transport mechanism against voltage and concentration gradient should exist in these segments. Several Ca2+ transporting proteins are involved in this active transmembrane transport of Ca2+ in the DCT and CNT. Transcellular Ca2+ reabsorption can occur by three steps; (i) entry of Ca2+ through the calcium channels (TRPV5, TRPV6) in the apical membrane, (ii) binding of Ca2+ with calcium binding protein (calbindin) and diffusion in the cytoplasm (which enables no significant change in the intracellular i[Ca2+], and (iii) Ca2+ extrusion via an ATP-dependent plasma membrane Ca2+-ATPase (PMCA1b) and an Na2+/Ca2 exchanger (NCX1) in the basolateral membrane. In the collecting duct (CD), there is no evidence that Ca2+ reabsorption occurs even though calcium channel

(TRPV6) was documented to be expressed in CD cells. Each renal tubule has a unique environment and plays a different role in Ca2+ reabsorption. The coordinated play of different renal tubules could maintain harmony of renal Ca2+ handling.

