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Matric. Number: 19/MHS01/443

Course code: PHY 303

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?

1. The human kidney is involved in the regulation of glucose homeostasis and in abnormalities found in diabetes mellitus via three different mechanisms:
2. release of glucose into the circulation via gluconeogenesis
3. uptake of glucose from the circulation to satisfy its energy needs

 (iii) reabsorption into the circulation of glucose from glomerular filtrate to conserve glucose carbon.

Plasma glucose concentrations are determined by the relative rates of glucose entry into, and removal from, the circulation. Normally, despite wide daily fluctuations in the rate of delivery of glucose into the circulation (e.g. meal ingestion) and in the demands of tissues for glucose (e.g. during exercise), plasma levels are maintained within a relatively narrow range throughout the day. Maximal plasma concentrations following meal ingestion are usually < 9.0 mmol/l [2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4232006/#b2)and minimal concentrations, after moderate fast or exercise, are usually > 3.0 mmol/l. This is in contrast to other substrates such as glycerol, lactate, free fatty acids (FFAs) and ketone bodies, for which daily fluctuation is much greater. Teleologically, this can be explained by the fact that, on the one hand, the body must defend itself from hyperglycaemia, which is associated with both chronic effects (including retinopathy, neuropathy, nephropathy and premature atherosclerosis) and acute effects (including diabetic ketoacidosis and hyperosmolar hyperglycaemic state, which have significant associated morbidity and mortality); on the other hand, the body must also defend itself against hypoglycaemia, which can cause cardiac arrhythmias, neurological dysfunction, coma, seizures and death. Brain function is particularly dependent on having adequate levels of plasma glucose because the brain is unable to either store or produce glucose and alternative sources of energy are either in short supply (e.g. ketone bodies) or are unable to pass the blood–brain barrier (e.g. FFAs).

The precise regulation of plasma glucose concentrations is mainly determined by hormonal and neural factors, which regulate endogenous production of glucose. Acute glucoregulatory mechanisms involve insulin, glucagon and catecholamines, which can effect changes in plasma glucose levels over a matter of minutes. Insulin suppresses glucose release in both the liver and kidney by direct enzyme activation/deactivation, as well as by reducing the availability of gluconeogenic substrates and actions on gluconeogenic activators. Glucagon has no effect on the kidney, but increases both gluconeogenesis and glycogenolysis in the liver. Catecholamines have multiple acute actions, including stimulation of renal glucose release, inhibition of insulin secretion, stimulation of glucagon secretion, and increases in gluconeogenic substrate supply, stimulation of lipolysis and reduced tissue glucose uptake.

Growth hormone, thyroid hormone and cortisol influence glucose levels over a period of hours by altering the sensitivity of the liver, kidney, adipose tissue and muscle to insulin, glucagon and catecholamines, and by altering the activity of key enzymes, which effect glycogen stores and availability of gluconeogenic precursors (lactate, glycogen and amino acids). In the post-absorptive state, glucose uptake by tissues is largely dependent on tissue needs and the mass-action effects of the ambient plasma glucose concentration and, to a lesser extent, on the permissive actions of insulin and counter-regulatory hormones (e.g. thyroid hormones, growth hormone, catecholamines and cortisol). In these circumstances, most uptake of glucose occurs in tissues that do not require insulin (e.g. brain, gastrointestinal tract, renal medulla). However, in the postprandial state, although insulin and other hormones exert greater influence on tissue uptake of glucose, changes in hepatic and renal glucose release into the circulation are still quite important.

## **Renal gluconeogenesis**

### **The post-absorptive state**

After a 14- to 16-h overnight fast, glucose is released into the circulation at a rate of approximately 10 μmol/(kg min). Approximately 50% of this is the result of the breakdown of glycogen (glycogenolysis) stored in the liver and the other half is because of the production of new glucose molecules from precursors such as lactate, glycerol, alanine and other amino acids (gluconeogenesis) by liver and kidneys. The kidney is unable to release glucose through glycogenolysis because it contains very little glycogen and those renal cells that are able to synthesize glycogen lack the enzyme glucose-6-phosphatase and therefore cannot release glucose. In humans, only the liver and kidney contain significant amounts of the enzyme glucose-6-phosphatase and therefore are the only organs that are able to perform gluconeogenesis. Research over the last 15–20 years has established that the human liver and kidneys provide about equal amounts of glucose via gluconeogenesis in the post-absorptive state. Consequently, after an overnight fast, 75–80% of glucose released into the circulation derives from the liver and the remaining 20–25% derives from the kidneys. As the duration of fasting increases, glycogen stores in the liver become further depleted until, after 48 h, virtually all the glucose released into the circulation is derived from gluconeogenesis. Consequently, as the length of fast increases, the proportion of overall glucose release accounted for by renal gluconeogenesis increases.

It is important to note that kidney and liver differ in their use of gluconeogenic precursors and the effect of hormones on their release of glucose. Lactate is the predominant gluconeogenic precursor in both organs, but otherwise the kidney preferentially uses glutamine, whereas the liver preferentially uses alanine

With respect to hormonal influences, insulin suppresses glucose release by both organs with roughly comparable efficacy, whereas glucagon normally stimulates hepatic glucose release only, mainly via an early action on glycogenolysis. Catecholamines normally exert a direct effect on renal glucose release only although they may indirectly affect both hepatic and renal glucose release by increasing availability of gluconeogenic substrates and by suppressing insulin secretion. Cortisol, growth hormone and thyroid hormones have long-term stimulatory influences on hepatic glucose release (over a period of days). Their effects on renal glucose release in humans have yet to be determined.

### **The postprandial state**

Classically, metabolic studies have usually been undertaken in the post-absorptive state (i.e. 12–16 h after the last meal). However, most of the day people are in the postprandial state as this includes 4–6 h on three occasions during the day.

Postprandial plasma glucose levels are critically influenced by insulin and glucagon levels. Following ingestion of glucose, plasma glucose levels peak in 60–90 min and slowly return to post-absorptive levels after 3–4 h. This profile is mirrored by a fourfold increase in plasma insulin and a reciprocal suppression of plasma glucagon levels of ∼50%  Meyer et al. (2002) demonstrated that, after meal ingestion, overall endogenous glucose release decreases by ∼61%, with hepatic glycogenolysis virtually ceasing in the 4- to 6-h period. Teleologically, this is understandable because this period is responsible for replenishment of hepatic glycogen stores. Furthermore, suppression of endogenous glucose release limits postprandial hyperglycaemia. Hepatic gluconeogenesis also decreases by ∼82% and glucose molecules generated through this pathway are not generally released in the circulation, but are largely directed into hepatic glycogen. Perhaps surprisingly, renal gluconeogenesis actually increases by approximately twofold and accounts for ∼60% of endogenous glucose release in the postprandial period. This has been hypothesized to facilitate efficient repletion of glycogen stores in the liver.

These differences in regulation and reciprocal change in renal and hepatic glucose release have led to the concept of hepatorenal glucose reciprocity. This concept refers to the situations in which a physiological or pathological decrease in glucose release by kidney or liver is associated with a compensatory increase in glucose release by liver or kidney so as to prevent hypoglycaemia or to optimize homeostasis. Examples of this include the anhepatic phase after liver transplantation, prolonged fasting, acidosis, meal ingestion and insulin overdoses in diabetes mellitus.

## **Renal glucose utilization**

In the post-absorptive setting after an overnight fast, the kidneys utilize approximately 10% of all glucose utilized by the body. After meal ingestion their glucose utilization increases in an absolute sense. In terms of whole-body glucose economy, normally approximately 45% of ingested glucose is thought to be converted to glycogen in the liver, ∼30% is taken up by skeletal muscle and later converted to glycogen, ∼15% is taken up by the brain, ∼5% is taken up by the adipose tissue and ∼10% is taken up by the kidneys. The metabolic fate of glucose is different in different regions of the kidney. Because of its low oxygen tension, and low levels of oxidative enzymes, the renal medulla is an obligate user of glucose for its energy requirement and does so anaerobically. Consequently, lactate is the main metabolic end product of glucose taken up in the renal medulla, not carbon dioxide (CO2) and water. In contrast, the renal cortex has little glucose phosphorylating capacity but a high level of oxidative enzymes. Consequently, this part of the kidney does not take up and use very much glucose, with oxidation of FFAs acting as the main source of energy. A major energy-requiring process in the kidney is the reabsorption of glucose from glomerular filtrate in the proximal convoluted tubule.

## **Renal glucose reabsorption**

In addition to releasing glucose into the circulation by synthesizing new glucose molecules via gluconeogenesis and its utilization of glucose, the kidney can also influence glucose homeostasis by returning glucose to the circulation via the reabsorption of glucose from glomerular filtrate. Normally, approximately 180 l of plasma are filtered by the kidneys each day. As the average plasma glucose concentration throughout a 24-h period is ∼5.5 mmol/l (100 mg/dl), ∼180 g of glucose is filtered by the kidneys each day. In healthy individuals, virtually all of this is reabsorbed into the circulation and the urine is essentially free from glucose. To put this into perspective, in a given day, the kidneys produce 15–55 g glucose via gluconeogenesis and metabolize 25–35 g glucose. Therefore, in terms of glucose economy, it is clear that renal reabsorption is the primary mechanism by which the kidney influences glucose homeostasis. Alterations in renal tubular glucose reabsorption may therefore be expected to have a considerable impact on glucose homeostasis.

Reabsorption of glucose from glomerular filtrate occurs by means of sodium–glucose co-transporters (SGLTs) in the proximal convoluted tubulae. There are six members of this family. approximately 90% of glucose is reabsorbed by SGLT2, a high-capacity low-affinity glucose transporter (Km ∼10 mmol/l; Vmax ∼10 nmol/(min mg) protein. SGLT2 is thought to be located exclusively on the luminal surface of the epithelial cells lining the S1 and S2 segments of the proximal tubule.

Transport of sodium and glucose by SGLT2 occurs in a 1:1 ratio. The remaining ∼10% of glucose reabsorption is mediated by SGLT1, a high-affinity, low-capacity glucose/galactose transporter (Km ∼0.2 mmol/l; Vmax ∼10 nmol/(min mg) protein; sodium:glucose coupling ratio = 2:1) located on the luminal surface of epithelial cells lining the S3 segment of the proximal tubule. SGLT1 is also extensively expressed in the small intestine and in other tissues. Glucose reabsorbed from the proximal tubules by SGLTs is then released into the circulation through the action of facilitative glucose transporters (GLUTs) at the basolateral membrane of the epithelial cells lining the proximal tubules (GLUT2 in the S1/2 segments and GLUT1 in the S3 segment). SGLT-mediated glucose transport is an active process, moving glucose against a concentration gradient, utilizing energy derived from the sodium electrochemical potential gradient across the brush border membrane and maintained by the transport of intracellular sodium into the blood via sodium:potassium adenosine triphosphatase (ATPase) pumps at the basolateral membrane. In contrast, GLUTs facilitate passive transport (equilibration) of glucose Glucose is freely filtered in the glomerulus, so that, as plasma glucose levels increase, the amount of glucose in the glomerular filtrate increases linearly. Reabsorption of filtered glucose also increases linearly until the maximal reabsorptive capacity is exceeded. This is often referred to as the renal threshold and equates to a filtration rate of 260–350 mg/min per 1.73 m which occurs at plasma glucose concentrations of 11.0 mmol/l in healthy adults. Above this plasma glucose concentration, the percentage of filtered glucose that is reabsorbed decreases and the percentage of the filtered load of glucose that is excreted in the urine increases, resulting in glucosuria. The ‘rounding’ of the titration curve seen around the transition from complete reabsorption to urinary excretion of excess glucose can be accounted for by heterogeneity in the glomerular filtration rate and glucose reabsorptive capacity of different individual neurons.

## **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 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 and the muscles 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. The opening of the ureter into the urinary bladder is not guarded by any sphincter or muscle. Therefore, this oblique nature 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. Both these sphincters are in a contracted state during the filling stage.

##  The process of 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 on the bladder wall. This leads to complete emptying of the bladder.

1. The juxtaglomerular apparatus (also known as the juxtaglomerular complex) is a structure in the kidney that regulates the function of each nephron, the functional units of the kidney. The juxtaglomerular apparatus is named because it is next to the glomerulus.

The juxtaglomerular apparatus consists of three types of cells:

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

## Structure

The juxtaglomerular apparatus is part of the kidney nephron, next to the glomerulus. It is found between afferent arteriole and the distal convoluted tubule of the same nephron. This location is critical to its function in regulating renal blood flow and glomerular filtration rate.

## Functions

### Juxtaglomerular cells

[Renin](https://en.m.wikipedia.org/wiki/Renin) is produced by [juxtaglomerular cells](https://en.m.wikipedia.org/wiki/Juxtaglomerular_cells). These cells are similar to [epithelium](https://en.m.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.m.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.m.wikipedia.org/wiki/Glomerular_filtration_rate).

### Extraglomerular mesangial cells

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.m.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.m.wikipedia.org/wiki/Nephron) touches the arterioles of the [glomerulus](https://en.m.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.m.wikipedia.org/wiki/Macula_densa). Cells in the macula densa respond to changes in the [sodium chloride](https://en.m.wikipedia.org/wiki/Sodium_chloride) levels in the distal tubule of the nephron via the [tubuloglomerular feedback](https://en.m.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.m.wikipedia.org/wiki/Purinergic_signaling). An increase in the salt concentration causes several [cell signals](https://en.m.wikipedia.org/wiki/Signal_transduction) to eventually cause the adjacent afferent arteriole to [constrict](https://en.m.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.m.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.m.wikipedia.org/wiki/Nitric_oxide) and [Prostaglandins](https://en.m.wikipedia.org/wiki/Prostaglandins) to vasodilate the afferent arterioles and increase renin release.

Significance

Excess secretion of renin by the [juxtaglomerular cells](https://en.m.wikipedia.org/wiki/Juxtaglomerular_cells) can lead to excess activity of the renin–angiotensin system, [hypertension](https://en.m.wikipedia.org/wiki/Hypertension) and an increase in [blood volume](https://en.m.wikipedia.org/wiki/Blood_volume). This is not responsive to the usual treatment for [essential hypertension](https://en.m.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.m.wikipedia.org/wiki/Renal_artery_stenosis), or a tumour of juxtaglomerular cells that produces renin. These will lead to [secondary hyperaldosteronism](https://en.m.wikipedia.org/wiki/Secondary_hyperaldosteronism), which will cause hypertension, [high blood sodium](https://en.m.wikipedia.org/wiki/Hypernatremia), [low blood potassium](https://en.m.wikipedia.org/wiki/Hypokalemia), and metabolic alkalosis.

## Control of Blood Pressure

If a sudden change in [blood pressure](https://en.wikivet.net/Category%3ABlood_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. It is this response which will be covered here.

## Renal Regulation

* Increased pressure has a direct effect on the kidney.

#### Three mechanisms of Renal Regulation

##### Pressure Diuresis

##### 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

* 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 (ACE)](https://en.wikivet.net/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).
* [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.

##  Regulation of Renal Blood Flow

It is essential that renal blood flow is maintained to ensure that adequate filtration of toxins from the blood takes place. Changes in pressure affect renal blood flow. Important auto-regulatory processes are responsible for this .

##

## The Role of Salt

Increasing the salt intake of an animal increases blood pressure in the short term. It increases the osmolarity of the blood which therefore increases water movement from tissues to the blood causing an increased circulating volume. As a result of this increased osmolarity more ADH is released as the osmoreceptors in the hypothalamus are triggered. This results in increased water retention in the kidneys further increasing the circulating volume. Secondary to the increase in salt the thirst centre is stimulated to increase fluid intake to try and counter act the increased osmolarity. This would increase blood volume and therefore pressure temporarily until this was corrected by the compensatory mechanisms .

1. It would be very difficult to name a physiologic process that does not depend, in one way or another, on calcium. It is critical to maintain blood calcium concentrations within a tight normal range. Deviations above or below the normal range frequently lead to serious disease.
* Hypocalcemia refers to low blood calcium concentration. Clinical signs of this disorder reflect increased neuromuscular excitability and include muscle spasms, tetany and cardiac dysfunction.
* Hypercalcemia indicates a concentration of blood calcium higher than normal. The normal concentration of calcium and phosphate in blood and extracellular fluid is near the saturation point; elevations can lead to diffuse precipitation of calcium phosphate in tissues, leading to widespread organ dysfunction and damage.

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 the 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/CNT. Acidosis contributes to hypercalciuria by reducing calcium reabsorption in the proximal tubule (PT) and DCT, and alkalosis vice versa.. Diuretics like thiazide and furosemide also alter calcium absorption in the renal tubules; thiazide promotes calcium reabsorption and furosemide inhibits it. 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 PT. 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. Paracellin-1 (claudin-16) is exclusively expressed in the tight junction of TAL and has been known as the important magnesium channel in the TAL.Paracellin-1 mutation caused hypercalciuria and nephrocalcinosis in addition to hypomagnesemia. 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 identified. The CaSR is a member of G protein-coupled receptors and suppresses PTH secretion by sensing high plasma Ca2+ level in the parathyroid glands. 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 action.

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 calciumbinding 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.

Plasma calcium concentration is maintained within a narrow range (8.5-10.5 mg/dL) by the coordinated action of parathyroid hormone (PTH), 1,25(OH)2D3, calcitonin, and ionized calcium (iCa2+) itself. The kidney plays a key role in this process by the fine regulation of calcium excretion. More than 95% of filtered calcium is reabsorbed along the renal tubules. In the proximal tubules, 60% of filtered calcium is reabsorbed by passive mechanisms. In the thick ascending limb, 15% of calcium is reabsorbed by paracellular diffusion through paracellin-1 (claudin-16). The calcium sensing receptor (CaSR) in the basolateral membrane of the thick ascending limb senses the change in iCa2+ and inhibits calcium reabsorption independent to PTH and 1,25(OH)2D3. The fine regulation of calcium excretion occurs in the distal convoluted tubules and connecting tubules despite the fact that only 10-15% of filtered calcium is reabsorbed there. Transient receptor potential vanilloid 5 (TRPV5) and 6 (TRPV6) in the apical membrane act as the main portal of entry, calbindin-D28K delivers Ca2+ in the cytoplasm, and then Na2+/Ca2+exchanger (NCX1) and plasma membrane Ca2+-ATPase in the basolateral membrane serve as an exit. In the cortical collecting duct, TRPV6 is expressed, but the role might be negligible. In addition to PTH(parathyroid hormone) and 1,25(OH)2D3, acid-base disturbance, diuretics, and estrogen affect on these calcium channels. Recently, klotho and fibroblast growth factor 23 (FGF23) are suggested as new players in the calcium metabolism. Klotho is exclusively expressed in the kidney and co-localized with TRPV5, NCX1, and calbindin-D28K. Klotho increases calcium reabsorption through trafficking of TRPV5 to the plasma membrane, and also converts FGF receptor to the specific FGF23 receptor. FGF23:klotho complex bound to FGF receptor inhibits 1α-hydroxylase of vitamin D, and contributes to calcium reabsorption and phosphate excretion in the kidney.