NAME: AYENI, Adetola Olufoyeke

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**QUESTION 1: Discuss the role of kidney in glucose homeostasis?**

What is Homeostasis?

 Homeostasis which is a term described by ***American physiologist Walter B. Cannon***, is the maintenance of nearly constant conditions in the internal environment. The kidney as a functional organ is carrying out several homeostatic functions (Excretion of metabolic waste products and foreign chemicals, regulation of water and electrolyte balances, regulation of body fluid osmolality and electrolyte concentrations, etc.). Kidney functions in glucose balance by absorbing the entire quantity of the filtered glucose, especially in ensuring the energy needs during fasting.

 The kidneys are involved in maintaining glucose homeostasis through three different mechanisms, and they are:

1. Gluconeogenesis (taking place in liver and kidneys)
2. Glycogenolysis (which is the uptake of glucose from blood for its own energy requests) taking place in the liver.
3. Glucose reabsorption (The reabsorption into the general circulation of glucose from glomerular filtrate in order to preserve energy) taking place in the kidneys.
* GLUCONEOGENESIS:

 Gluconeogenesis is the metabolic process by which organisms produce glucose from non-carbohydrate precursors. *Glucose* is the only energy source used by the brain (with the exception of ketone bodies during times of fasting), testes, erythrocytes, and kidney (especially the renal medulla).

 The kidneys synthesize glucose from amino acids and other precursors during prolonged fasting and it is a process called **Gluconeogenesis**. The kidney's capacity to add glucose to the blood during prolonged periods of fasting rivals that of the liver. ***The kidney is considered into 2 parts, from the point of use****.* The separation of these activities represents the consequence of differences in the distribution of numerous enzymes along the nephron. The two parts are;

1. The **renal medulla**; which is characterized mainly by glucose utilization (i.e. use of glucose)
2. The **renal cortex**; which is responsible for glucose release.

 *Renal medulla* has cells which can only use glucose for their needs (like the brain) and they have enzymes capable of glucose-phosphorylation and glycolysis. They can therefore phosphorylate important amounts of glucose and accumulate glycogen but because these cells do not have glucose-6-phosphatase or any other gluconeogenic enzymes, they are unable to release glucose into the bloodstream. Moreover, the cells in the *renal cortex* have gluconeogenic enzymes and they can produce and release glucose into the circulation. However, these cells cannot synthesize glycogen because they have little phosphorylating capacity.

 After a 16 hour overnight fast, glucose of approximately 10 µmol (kg /min) is released into the circulation. Almost 50% of this release is as a result of glycogenolysis from the liver stocks and the other half is produced by gluconeogenesis (from both liver and kidney). The renal cortex (just like the liver) contains gluconeogenic enzymes which can synthesize glucose-6-phosphate from precursors (lactate, glutamine, glycerol and alanine) and because it contains glucose-6-phosphatase, it is able to release glucose into the blood stream. Therefore, after an overnight fast, the liver produces 75–80% of glucose released into the circulation and the remaining 20–25% is derived from the kidneys. *THE KIDNEY TOGETHER WITH THE HUMAN LIVER IS THE ONLY ONES THAT CAN PERFORM GLUCONEOGENESIS* (although, kidney and liver use different gluconeogenic precursors and several hormones have different effects on their release of glucose. Lactate represents the predominant gluconeogenic precursor in both organs, but regarding the amino-acids, the *kidney prefers to use glutamine*, whereas the *liver uses alanine*).

* GLYCOGENOLYSIS:

 Glycogenolysis is the breakdown of glycogen to glucose-6-phosphate and a hydrolysis reaction (using glucose-6-phosphatase) in order to free glucose. The liver is the only organ that contains glucose-6-phosphatase. So, the cleavage of hepatic glycogen releases glucose, while the cleavage of glycogen from other sources can release only lactate. Lactate, that is generated via glycolysis, is often absorbed by other organs and helps regenerating glucose

* 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 glucose per day, all of which is reabsorbed through **glucose transporter that are present in cell membranes within the proximal tubules**.

 These transporters have capacity and if the capacity of these transporters is exceeded, ***glucose appears in the urine***. This maximum capacity is called the ***TmG which stands for Tubular maximum for Glucose*** and 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*. Nevertheless, there can be slight differences between the nephrons and the inaccurate nature of biological systems may potentially lead to the development of glucosuria when blood glucose is below TmG.

 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 (eg, pregnancy), but as a consequence of hyperfiltration rather than significant hyperglycemia.

NOTE THAT:

* The process of renal glucose reabsorption is mediated by active (sodium-coupled glucose cotransporters) and passive (glucose transporters) transporters.
* Regarding the glucose metabolic pathways, it is obvious that **RENAL REABSORPTION represents the MAIN MECHANISM BY WHICH KIDNEY IS INVOLED IN GLUCOSE HOMEOSTASIS**. Therefore, the change in tubular glucose reabsorption may have a considerable impact on glucose homeostasis
* The kidneys have not been considered an important source of glucose (except during acidosis or after prolonged fasting). However, the full significance of the kidneys’ contribution to glucose homeostasis, under both physiologic and pathologic conditions, has become well recognized, and is thought to involve functions well beyond glucose uptake and release. Besides the liver, the kidney is the only organ capable of generating sufficient glucose (gluconeogenesis) to release into the circulation, and it is also responsible for filtration and subsequent reabsorption or excretion of glucose.
* RENAL GLUCOSE TRANSPORTERS

 Glucose is a polar compound with positive and negative charged areas; therefore it is *soluble in water*. It's transport into and across cells is dependent on two specialized carrier protein families and they are:

1. The GLUTs (facilitated glucose transporters) and the;
2. The SGLTs (sodium-coupled glucose cotransporters).

 These transporters are responsible for glucose passage and reabsorption in several tissue types, including the proximal renal tubule, blood-brain barrier, small intestine. ***GLUTs*** *are responsible for the passive transport of glucose across cell membranes, in order to equilibrate its concentrations across a membrane.* ***SGLTs****, on the other hand, are involved in active transport of glucose against a concentration gradient by means of sodium-glucose cotransport*

 There are 6 members of the SGLT family and they are seen below:

1. SGLT1, a cotranspoter with substrates (glucose, galactose) and they can be found in trachea, brain, testis, prostate, heart, intestine and kidney etc.
2. SGLT2, another cotransporter with glucose as substrate and can be found in kidney, brain, liver, muscle, heart etc.
3. SGLT4, another cotransporter with glucose and mannose as substrates and can be found in intestine, kidney, uterus, pancreas, liver, brain, lung, trachea etc.
4. SGLT5 is a cotransporter with unknown substrates and its found only in the kidney.
5. SGLT6 has glucose and myoinositol as substrates and is found in brain, kidney, intestine.
6. SMIT1, a cotransporter with glucose and myoinositol and located in brain, heart, lung, kidney etc.

NOTE THAT:

* SGLT2, based on studies, is said to be the most important because it is responsible for the reabsorption of 90% of the glucose filtered at the glomerulus. The other 10% of glucose reabsorbed in the proximal tubule is ensured by SGLT1.
* In GLUT proteins family expressed in the kidneys, GLUT2 is the major transporter and it releases into circulation the glucose reabsorbed by SGLTs in the proximal tubular cells.

**QUESTION 2: Discuss the process of Micturition?**

 Micturition is the process by which urinary bladder empties when it becomes filled. It can also be referred to as ***Urination***. Micturition or Urination is also known to be described as the voiding of the bladder which means to expel urine from the urinary bladder.

 The excretory system in humans includes a pair of kidneys (Left and Right kidneys), two ureters, a urinary bladder and a urethra. Basically, the kidney is filled with urine and it is transported to the urinary bladder via the ureters where it is stored till expulsion. The urinary bladder is the organ *which stores* the urine till expulsion; and it can store around *350-400ml* of urine before it expels out the urine.

STAGES OF MICTURITION

The micturition process involves two main steps or stages.

1. Resting or filling stage
2. Voiding stage or emptying stage.

 The filling of the bladder occurs until the tension in its walls rises above a threshold. This tension elicits the second step, which a nervous reflex is called the *Micturition reflex* that empties the bladder or at least causes a conscious desire to urinate.

* RESTING OR FILLING STAGE:

 Here, the urinary bladder fills progressively with urine which is transported from the kidney via the *ureter* into the urinary bladder.

 In the Kidney, urine enters the renal calyces (and stretches it) from the collecting ducts and increasing their inherent pacemaker activity which in turn initiates peristaltic contractions that spread to the renal pelvis and then downward along the length and thereby forcing urine from the renal pelvis toward the bladder. In adults, *the ureters are normally 25-35 cm (10-14 inches) long*. The walls of ureters contain smooth muscle and are innervated by both sympathetic and parasympathetic nerves, as well as by intramural plexus of neurons and nerve fibers that extend the length of the ureters. *Peristaltic movements in the ureter is stimulated by parasympathetic stimulation and inhibited by sympathetic stimulation*.

 The ureter then enters the bladder and PASSES URINE INTO IT through a muscle called the ***Destrusor muscle*** in the trigone region of the bladder. Also, the destrusor muscle in the bladder wall tend to compress the bladder and thereby preventing- ***Reflux of urine*** (which is the backflow of urine from the bladder to the ureter) when the pressure builds up in the bladder during micturition or bladder compression.

Each peristaltic wave along the ureter increases the pressure within the ureter so that the region passing through the bladder wall opens and allows urine to flow into the bladder.

* VOIDING OR EMPTYING STAGE:

 This is the stage in which urine is expelled out of the bladder and this is caused by a nervous reflex called ***Micturition reflex***. Although the micturition reflex is an autonomic spinal cord reflex which can also be inhibited or facilitated by centers in the cerebral cortex or brain stem. The Micturition reflex leads to the bladder emptying or at least conscious desire to urinate. ***The contraction of the DESTRUSOR MUSCLE is the major step in emptying the bladder***.

 When the bladder is partially filled, these micturition contractions usually relax spontaneously after a fraction of a minute, the destrusor muscle stop contracting and pressure falls back to the baseline. The micturition reflexes become more frequent as the bladder continues to fill and even cause greater contractions of the destrusor muscle.

 The micturition reflex is '***self-regenerative***', and once it begins, the initial contraction of the bladder leads to the activation of the stretch receptors to cause a greater increase in sensory impulses from the bladder to the posterior urethra which also causes a further increase in reflex contraction of the bladder; and this cycle is repeated over and over until the bladder reaches a strong degree of contraction. Then after a few seconds, the self-regenerative reflex begins to fatigue and the regenerative cycle of micturition reflex ceases and permitting the bladder to relax. Thus, the micturition reflex is a single complete cycle of:

1. Progressive and rapid increase of pressure
2. The period of sustained pressure
3. The return of pressure to basal tone of the bladder.

NOTE THAT: Once the micturition reflex has occurred but has not succeeded in emptying the bladder, the nervous elements of this reflex usually remain in an inhibited state for a few minutes to 1 hour or more before another micturition reflex occurs. As the bladder becomes more filled, micturition reflexes occur more and more often and more and more powerfully.

 However, when the micturition reflex becomes powerful enough, it causes another reflex, which passes through the pudendal nerves to the external sphincter to inhibit it. If the inhibition becomes more potent in the brain than the voluntary constrictor signals to the external sphincter, **URINATION WILL OCCUR**. If not, urination will not occur until the bladder fills still further and the micturition reflex becomes more powerful.

**QUESTION 3: Explain the Juxtaglomerular apparatus?**

 The juxtaglomerular apparatus is a structure in the kidney that regulates the function of each nephron (which is the functional units of the kidney). It is also known as the **Juxtaglomerular complex**. 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.

 The juxtaglomerular apparatus consists of three types of cells with their respective functions, and they are:

1. Macula densa, a part of the distal convoluted tubule of the same nephron
2. Juxtaglomerular cells, (also known as *granular cells*) which secrete renin
3. Extraglomerular mesangial cells.
* Macula Densa:

 The macula densa is a specialized group of epithelial cells in the distal convoluted tubule that comes in close contact with the afferent and efferent arterioles. These cells contain Golgi apparatus which are intracellular secretory organelles directed towards the arterioles suggesting that these cells may be secreting a substance towards the arterioles. Cells in the macula densa respond to changes in the sodium chloride levels in the distal tubule of the nephron via the tubuloglomerular feedback (TGF) loop.

 It is thought that the macula densa cells are sensory cells that respond to the sodium concentration in the fluid within the distal tubule and, perhaps, to the rate of fluid flow past them. An increase in sodium concentration in the tubular fluid leads to a reduction in the production of renin by extraglomerular mesangial cells and juxtaglomerular cells.

* Juxtaglomerular cells:

 The juxtaglomerular cells (**JG cells or granular cells**) are cells in the kidney that synthesize, store, and secrete the ***enzyme renin***. The juxtaglomerular cells secrete renin, and as specialized smooth muscle cells surrounding the afferent arteriole also have the capacity to affect the perfusion of the glomerulus.

 These juxtaglomerular cells are similar to 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*:

1. Stimulation of the beta-1 adrenergic receptor
2. Decrease in renal perfusion pressure (detected directly by the granular cells)
3. Decrease in NaCl concentration at the macula densa, often due to a decrease in glomerular filtration rate

NOTE THAT:

* The juxtaglomerular cells of the afferent arteriole act as *high-pressure baroreceptors* and are able to detect changes in blood pressure. An increase in renal arterial pressure inhibits renin release.
* Although these cells are activated by prostaglandins released from the macula densa cells, they can also release renin independently of the macula densa. Baroreceptors found in the arterioles trigger renin secretion if there is a fall in blood pressure in the arterioles. Activation of the sympathetic nervous system can also stimulate renin release through activation of beta-1 receptors. Renin is a protease enzyme that catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is converted into the active vasoconstrictor angiotensin II by Angiotensin Converting Enzyme (ACE) found in the kidney and largely in the lung.
* Excess secretion of renin by the juxtaglomerular cells can lead to excess activity of the renin–angiotensin system, hypertension and an increase in blood volume. One cause of this can be increased renin production due to narrowing of the renal artery, or a tumor of juxtaglomerular cells that produces renin. These will lead to secondary hyperaldosteronism, which will cause hypertension, high blood sodium, low blood potassium, and metabolic alkalosis.
* Extraglomerular mesangial cells:

 They are flat and elongated cells located near the macula densa. Extraglomerular mesangial cells (also known as ***Lacis cells, Polkissen cells, or Goormaghtigh cells***) are pale/light-staining pericytes in the kidney found outside the glomerulus, near the vascular pole. They are located in the junction between the afferent and efferent arterioles and glomerular capillaries. 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 is also found in these cells.

 They are a type of smooth muscle cell, and although their function is yet to be fully clarified, they play a role in auto regulation of blood flow to the kidney and regulation of systemic blood pressure through the renin-angiotensin system; they are also associated with secretion of erythropoetin. They are distinguished from intraglomerular mesangial cells, which are situated between the basement membrane and the epithelial cells within the glomerulus.

**QUESTION 4: Discuss the role of kidney in regulation of blood pressure?**

 The kidney has the capability to control and regulate arterial pressure through:

1. Regulating Extracellular fluid volume.
2. Renin-Angiotensin system.
* REGULATION OF EXTRACELLULAR FLUID VOLUME

 Extracellular fluid volume is determined mainly by the balance between the intake and output of water and salt. In many instances the salt and water intakes are dictated by a person's habit rather than by physiological control mechanism. Therefore, the burden of the ECF volume regulation is often placed on the kidneys which must adapt their excretion of salt and water to match the intake of salt and water under steady conditions.

 Increased fluid volume can elevate arterial pressure by increasing cardiac output or total peripheral resistance. The overall mechanism by which increased ECF volume may elevate arterial pressure, if vascular capacity is not simultaneously increased.

The sequential events are:

1. Increased extracellular fluid volume, which
2. Increases the blood volume, which
3. Increases the mean circulatory filling pressure, which
4. Increases venous return of blood to the heart, which
5. Increases cardiac output, which
6. Increases arterial pressure.

The increased arterial pressure, in turn, increases renal excretion of salt and water and may return Extracellular fluid volume to nearly normal if kidney function is normal.

* RENIN-ANGIOTENSIN SYSTEM IN ARTERIAL PRESSURE CONTROL

 The kidney also has the capability to control pressure using a mechanism called **Renin-Angiotensin system**. *Renin* involved in this, is a protein enzyme released by the kidneys when the arterial blood pressure falls too low and in turn it raises the arterial pressure in several ways and thus helping to correct initial fall in pressure. Renin is synthesized and stored in an inactive form called ***prorenin in the juxtaglomerular cells (JG cells)***of the kidney. These cells are the modified smooth muscle cells located mainly in the walls of afferent arterioles immediately proximal to the glomeruli.

 When the arterial pressure falls, intrinsic reactions in the kidneys cause many of the prorenin molecules in the JG cells to split and release renin; and most of the renin enters the renal blood and then passes out of the kidney to circulate throughout the entire body. However, small amount of renin remains in the local fluids of the kidney and initiate several intrarenal functions.

RENIN itself *is an enzyme* and not some vasoactive substance. It acts enzymatically on another plasma protein which a globulin called **Renin substrate or Angiotensinogen**, to release a 10-amino acid peptide called **Angiotensin I**; which has the mild vasoconstrictor properties but it is not enough to cause significant change in circulatory function. The circulatory renin persists in the blood for 30 mins-1hour and continues to cause the formation of more angiotensin I during this entire time.

 However, two additional amino acids split from the angiotensin I, within few seconds to minutes after angiotensin I formation, to form the 8-amino acid peptide called **Angiotensin II**; This conversion occurs to a great extent in the lungs while the blood flows through a small vessels of the lungs catalyzed by an enzyme called **ACE-Angiotensin Converting Enzyme**, that is present in the endothelium of the lung vessels. There are other tissues such as kidneys and blood vessels also contain converting enzymes and therefore form angiotensin II locally.

 Angiotensin II has two principal effects that **elevate blood pressure**.

**FIRST**, Vasoconstriction in many areas of the body.

 Vasoconstriction occurs rapidly and intensely in the arterioles and much less so in the veins. The constriction of the arterioles increases peripheral resistance and thereby increasing the arterial pressure. Also a mild constriction of the veins promotes increased venous return of blood to the heart and thereby helping the heart pump against the increasing pressure.

**SECOND**, Decreased excretion of both salt and water by the kidneys.

 This action increases the ECF (Extracellular Fluid) volume and then increases arterial pressure during subsequent hours and days. This long term effect, acting through the ECF volume mechanism, is even more powerful than the acute vasoconstrictor mechanism in eventually raising arterial pressure.

NOTE THAT:

* **Angiotensin I**; has the mild vasoconstrictor properties but it is not enough to cause significant change in circulatory function. The renin persists in the blood for 30 mins-1hour and continues to cause the formation of more angiotensin I during this entire time.
* **Angiotensin II**; is an extremely powerful vasoconstrictor and it affect circulatory functions as well. Angiotensin II persists in the blood for only 1/2 minutes because it is rapidly inactivated by multiple blood and tissue enzymes collectively called **Angiotensinas**.
* 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.
* Angiotensin II causes renal retention of salt and water which is an important means for long-term control of arterial pressure. It is in two major ways
1. Angiotensin II acting directly on the kidneys to cause salt and water retention
2. Angiotensin II causes adrenal glands to secrete aldosterone and this aldosterone in-turn increases salt and water reabsorption by the kidney tubules.

 Thus, whenever excess amounts of angiotensin II circulate in the blood, the entire long-term renal-body fluids mechanism for arterial pressure control automatically becomes set to a higher arterial pressure level than normal.

**QUESTION 5: Discuss the role of kidney in Calcium homeostasis?**

 The maintenance of calcium homeostasis is very important. Calcium is the **main component** of bony skeleton. It plays a key role in many physiologic processes such as contraction of skeletal, cardiac and smooth muscles, blood clotting and transmission of nerve impulses. Extracellular calcium ion concentration is determined by the interplay of calcium absorption from kidney and renal excretion of calcium etc. Kidney is involved in the *absorption, reabsorption and excretion of calcium*. Calcium homeostasis occurs with the control of **Parathyroid Hormone**.

* ABSORPTION OF CALCIUM

 The usual rates of intake are about 1000 mg/day for calcium, about the amounts in 1 liter of milk. Normally, divalent cations such as calcium ions are poorly absorbed from the intestines however, **vitamin D promotes calcium absorption** by the intestines and about 35% (350mg/day) of the ingested calcium is usually absorbed; the remaining calcium present in the intestine is excreted in the feces. An additional 250mg/day of calcium enters the intestines via secreted gastrointestinal juices and sloughed mucosal cells. Thus about 90% (900mg/day) of the daily intake of calcium is excreted in the feces.

**Calcium is absorbed** from the intestinal tract and the *Vitamin D has a potent effect* to increase such absorption. However, vitamin D itself is not the active substance that actually causes these effects, but rather it is first converted through a succession of reactions in the liver and in the kidney to have the final active product called ***1,25-dihydroxycholecalciferol*** also called **1,25(OH)2D3**. After cholecalciferol is formed in the skin, it undergoes processes to be converted to 25-Hydroxycholecalciferol in the liver and also undergoes several processes to be form 1,25-Dihydroxycholecalciferol in the kidney.

* KIDNEY IS INVOLVED in the formation of 1,25-Dihydroxycholecalciferol and Its control by Parathyroid Hormone (PTH)

 The conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol occurs in the *proximal tubules of the kidneys*. 1,25-dihydroxycholecalciferol is by far the most active form of Vitamin D because the previous products have less than 1/1000 of the vitamin D effect. Therefore, in the absence of the kidneys, Vitamin D loses almost all its effectiveness. This conversion requires PTH and in its absence, none of the 1,25-dihydroxycholecalciferol is formed.

* RENAL EXCRETION OF CALCIUM

 The kidney is critically important in calcium homeostasis. Renal **excretion of Calcium** is that approximately 10% (100mg/day) of ingested calcium is excreted in the urine and also about 41% of plasma calcium is bound to plasma proteins and is therefore not filtered by the glomerular capillaries. Normally, the renal tubules reabsorb 99% of filtered calcium and about 100mg/day are excreted in the urine and approximately 90% of the calcium in the glomerular filtrate is reabsorbed in the *proximal tubules, loops of Henle and early distal tubules*.

In the late distal tubules and early collecting ducts, reabsorption of the remaining 10% is more variable depending on the calcium ion concentration in the blood. When calcium concentration is low, the reabsorption is great and thus almost no calcium is lost in urine. Conversely, even a minute increase in blood calcium ion concentration above normal increases calcium excretion markedly.

 THE MOST IMPORTANT FACTOR OF CONTROLLING THIS REABSORPTION OF CALCIUM IN THE DISTAL PORTIONS OF THE NEPHRON AND THEREFORE CONTROLLING THE RATE OF CALCIUM EXCRETION IS **PARATHYROID HORMONE**. **Parathyroid hormone** is one of the important calcium-regulating hormones in the body. Its principal action in the kidneys is to increase tubular reabsorption of calcium mainly in the *late distal tubules, the collecting tubules and the early collecting ducts and perhaps also in the ascending loop of Henle.* It increases intestinal absorption of calcium by increasing the formation in the kidneys of 1,25-dihydroxycholecalciferol from vitamin D.

1. PTH increases reabsorption of calcium by the renal tubules leading to decreased excretion of calcium
2. PTH is necessary for conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol which in-turn increases calcium absorption by the intestines.

All these together provide a powerful means of regulating extracellular calcium concentration.