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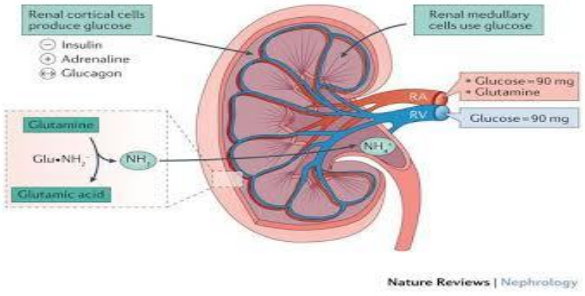
MATRIC NUMBER: 17/MHSO1/019

LEVEL: 300

DEPARTMENT: MEDICINE AND SURGERY

1. Discuss the role of kidney in glucose homeostasis.

Figure 1 Role of the kidney in glucose homeostasis



DeFronzo, R. A. *et al.* (2016) Renal, metabolic and cardiovascular considerations of SGLT2 inhibition *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2016.170

The plasma glucose concentration is determined by the amount of glucose synthesized, and the one removed from the circulation and metabolized. The regulation of endogenous production of glucose is determined by hormonal and neural factors. In the acute phase, gluco regulatory mechanisms involve insulin, glucagon and catecholamines and they can effect changes in plasma glucose levels in a matter of minutes. Insulin is able to suppress glucose release in both the kidney and liver by direct enzyme activation ⁄ deactivation and by reducing the availability of gluconeogenic substrates. Glucagon has no effect on the kidneys, but it stimulates glycogenolysis and gluconeogenesis in the liver. Catecholamines also have multiple acute actions. They can stimulate renal glucose release and glucagon secretion and inhibit insulin secretion.The kidneys are involved in maintaining glucose homeostasis through three different mechanisms: gluconeogenesis; glucose uptake from the blood for its own energy requests and reabsorption into the general circulation of glucose from glomerular filtrate in order to preserve energy.

- ***Renal gluconeogenesis***

The kidney is considered as 2 separate organs; the renal medulla is characterized mainly by glucose utilization and the renal cortex is responsible for glucose release. The separation of these activities represents the consequence of differences in the distribution of numerous enzymes along the nephron. The cells in the renal medulla can use only glucose for their needs (like the brain) and they have enzymes capable of glucosephosphorylation and glycolysis. 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-h overnight fast, approximately 10 µmol ⁄ (kg /min) of glucose is released into the circulation. Almost 50% of this is the result of glycogenolysis from the liver stocks and the other half is produced by liver and kidney gluconeogenesis. The renal cortex (like the liver) contains gluconeogenic enzymes and it can synthesize glucose-6-phosphate from precursors (lactate, glutamine, glycerol and alanine). Because it contains glucose-6-phosphatase, it is able to release glucose into the blood stream and the human liver and kidneys are the only organs that can perform gluconeogenesis. 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**.

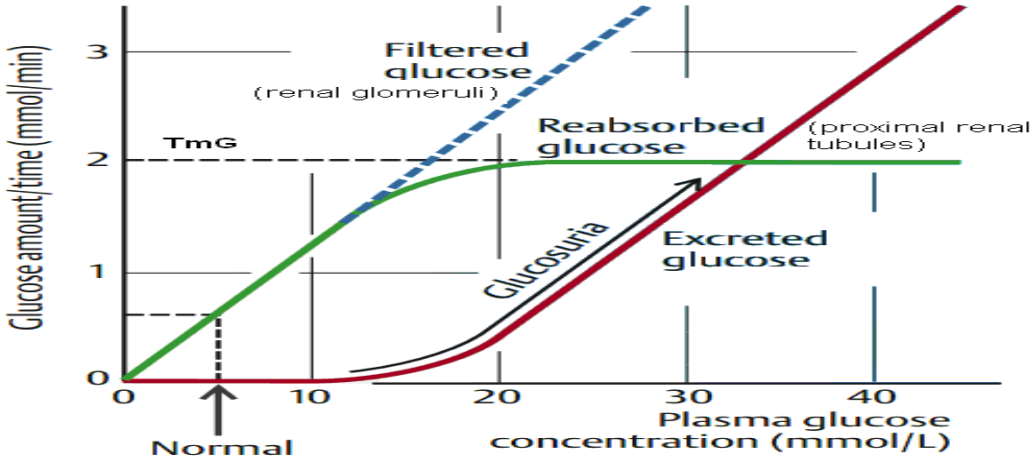
Hormones, such as growth hormone, cortisol and thyroid hormones can stimulate hepatic glucose release over a great period of time. Their effects on the kidneys regarding glucose release in humans are not completely deciphered.

- ***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, generated via glycolysis, is often absorbed by other organs and helps regenerating glucose .

- ***Glucose reabsorption***

Apart from the important role in gluconeogenesis and the role of renal cortex in glucose uptake, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. In normal conditions, the kidneys can reabsorb as much glucose as possible, the result being a virtually glucose free urine. Approximately 180 grams of glucose are filtered by the glomeruli from plasma, daily but all of this quantity is reabsorbed through glucose transporters that are present in cell membranes located in the proximal tubules. These glucose transporters have a limited capacity of reabsorption. If this capacity is exceeded, glucose usually appears in the urine. The tubular maximum for glucose (TmG), the term used for the maximum capacity, can vary from 260 to 350 mg/min/1.73 m2 in healthy subjects. It corresponds to blood glucose levels of 180-200 mg/dL. When the blood glucose is very high and the TmG is reached, the transporters cannot reabsorb all the glucose and glucosuria occurs



In a given day, the kidneys can produce, via gluconeogenesis, 15–55g glucose and it can metabolize 25–35g glucose. Regarding the glucose metabolic pathways, it is obvious that renal reabsorption represents the main mechanism by which the kidney is involved in glucose homeostasis. Therefore, the change in tubular glucose reabsorption may have a considerable impact on glucose homeostasis

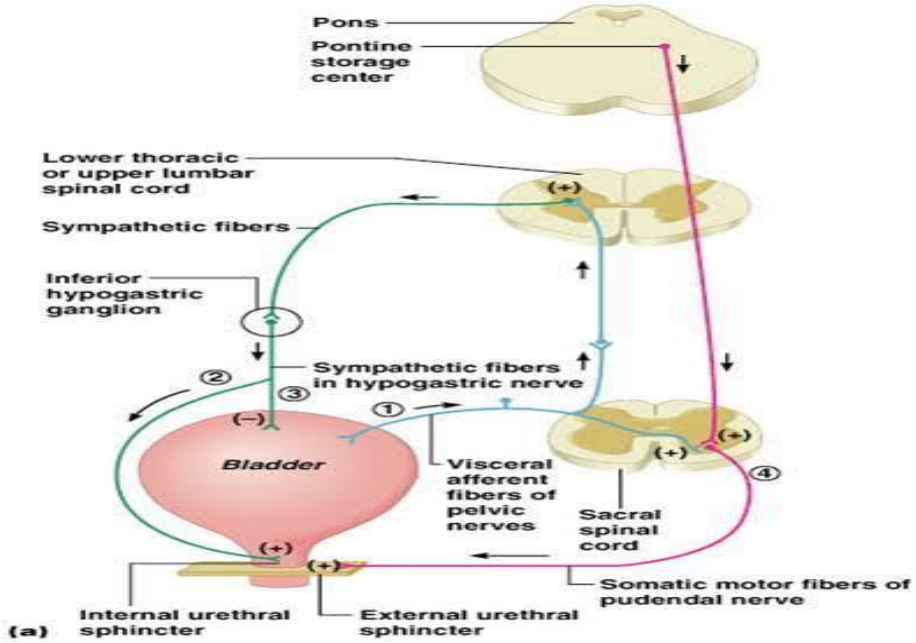
2. Discuss the process of micturition.

Micturition is a process by which urine is voided (expelled) from the urinary bladder. It is a reflex process. However, it can be controlled voluntarily to some extent in grown up children and adults. The organs in the body involved include 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 urinary bladder has two distinct stages or phases:

- 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 oblique placement of the ureters in the bladder wall prevents the urine from re-entering the ureters. .
- 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 process of micturition is regulated by both the nervous (autonomic and somatic) and muscular systems of the bladder and urethra. Micturition occurs by a reflex known as *micturition reflex*. This reflex is initiated by the stimulation of stretch receptors situated on the wall of urinary bladder and urethra. When about 300 to 400 mL of urine is collected in the bladder, intravesical pressure increases. This stretches the wall of bladder resulting in stimulation of stretch receptors and generation of sensory impulses.

<u>Pathway for Micturition Reflex</u>



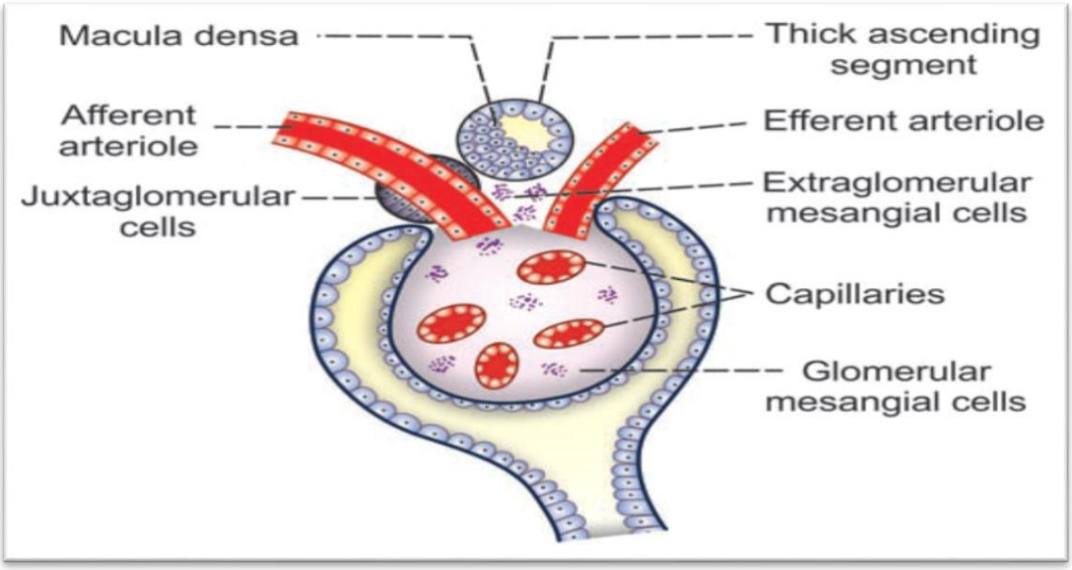
Sensory (afferent) impulses from the receptors reach the sacral segments of spinal cord via the sensory fibers of pelvic (parasympathetic) nerve. Motor (efferent) impulses produced in

spinal cord, travel through motor fibers of pelvic nerve towards bladder and internal sphincter. Motor impulses cause contraction of detrusor muscle and relaxation of internal sphincter so that, urine enters the urethra from the bladder. Once urine enters urethra, the stretch receptors in the urethra are stimulated and send afferent impulses to spinal cord via pelvic nerve fibers. Now the impulses generated from spinal centers inhibit pudendal nerve. So, the external sphincter relaxes and micturition occurs. Once a micturition reflex begins, it is *self-regenerative*, i.e. the initial contraction of bladder further activates the receptors to cause further increase in sensory impulses from the bladder and urethra. These impulses, in turn cause further increase in reflex contraction of bladder. The cycle continues repeatedly until the force of contraction of bladder reaches the maximum and the urine is voided out completely. During micturition, the flow of urine is facilitated by the increase in the abdominal pressure due to the voluntary contraction of abdominal muscles. 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.

Clinical correlate

- *Nocturnal micturition*: the involuntary voiding of urine at night. It is otherwise known as enuresis or bedwetting. This is due to absence of voluntary control of micturition.
- *Uninhibited neurogenic bladder*: the urinary bladder with frequent and uncontrollable micturition caused by lesion in midbrain. It is also called spastic neurogenic bladder or hyperactive neurogenic bladder.

3. Explain juxtaglomerular apparatus.
   Juxtaglomerular apparatus is a specialized organ in the kidney situated near the glomerulus of each nephron. It is formed by three different structures
   - Macula densa: It is found between afferent and efferent arterioles of the same nephron and formed by tightly packed cuboidal epithelial cells. It is the end portion of thick ascending segment before it opens into distal convoluted tubule.
   - Extraglomerular mesangial cells: it is found in the triangular region bound by afferent arteriole, efferent arteriole and macula densa. These cells are also called agranular cells, lacis cells or Goormaghtigh cells. Apart from this mesangial cell there is another type found in between glomerular capillaries called *glomerular mesangial* or *intraglomerular mesangial cells*. Glomerular mesangial cells support the glomerular capillary loops by surrounding the capillaries in the form of a cellular network. These cells play an important role in regulating the glomerular filtration by their contractile property. They are phagocytic in nature. These cells also secrete glomerular interstitial matrix, prostaglandins and cytokines.
   - Juxtaglomerular cells: also called granular cells (due to presence of secretary granules in their cytoplasm), are specialized smooth muscle cells found in the wall of afferent arteriole just before if it enters the bowman capsule. These smooth muscle cells are mostly present in tunica media and tunica adventitia of the wall of the afferent arteriole.



Juxtaglomerular Apparatus

Functions of juxtaglomerular apparatus

i. Secretion of hormones: it is the main function of Juxtaglomerular apparatus. The hormones secreted are Renin and Prostaglandin.
   - *Renin:* is a peptide with 340 amino acids. Renin forms the renin-angiotensin system, which is a hormone system that plays an important role in the maintenance of blood pressure. Stimulants for renin secretion include: Fall in arterial blood pressure, Reduction in the ECF volume, Increased sympathetic activity, Decreased load of sodium and chloride in macula densa.
   - *Prostaglandins:* secreted by extraglomerular mesangial cells (EMC) of juxtaglomerular apparatus and interstitial cells of medulla.

ii. Secretion of cytokines like interleukin-2 and tumor necrosis factor by EMC and thromboxane A_2 by macula densa.

iii. Regulation of glomerular blood flow and glomerular filtration rate: macula densa of juxtaglomerular apparatus plays an important role in the feedback mechanism called tubuloglomerular feedback mechanism, which regulates the renal blood flow and glomerular filtration rate.

Clinical significance

- 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.

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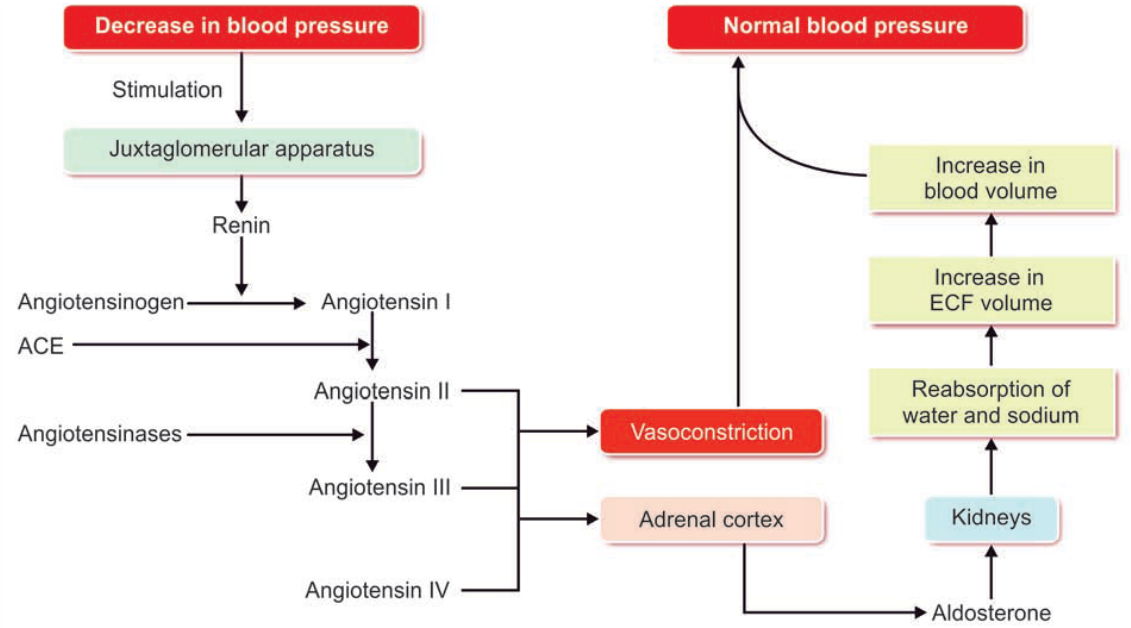
4. Discuss the role of kidney in regulation of blood pressure.

The kidney is plays an important role in long-term regulation of arterial blood pressure. Discuss the role of kidney in calcium homeostasis When blood pressure alters slowly in several days/months/years, the nervous mechanism adapts to the altered pressure and loses the sensitivity for the changes. It cannot regulate the pressure any more. In such conditions, the renal mechanism operates efficiently to regulate the blood pressure.



Regulation of blood pressure by reninangiotensin mechanism. ACE = Angiotensinconverting enzyme.

Kidneys regulate arterial blood pressure by two ways:

a. ***By regulation of ECF volume****:* When the blood pressure increases, kidneys excrete large amounts of water and salt, particularly sodium, by means of *pressure diuresis* and *pressure natriuresis*. Pressure diuresis is the excretion of large quantity of water in urine because of increased blood pressure. Even a slight increase in blood pressure doubles the water excretion. Pressure natriuresis is the excretion of large quantity of sodium in urine. Because of **diuresis** and **natriuresis,** there is a decrease in ECF volume and blood volume, which in turn brings the arterial blood pressure back to normal level. When blood pressure decreases, the reabsorption of water from renal tubules is increased. This in turn, increases ECF volume, blood volume and cardiac output, resulting in restoration of blood pressure.

b. ***Through renin-angiotensin mechanism:*** When renin is released into the blood, it acts on a specific plasma protein called *angiotensinogen* or *renin substrate***.** It is the α2-globulin. By the activity of renin, the angiotensinogen is converted into a decapeptide called *angiotensin I*. Angiotensin I is converted into *angiotensin II*, which is an octapeptide by the activity of angiotensin-converting enzyme (ACE) secreted from lungs. Most of the conversion of angiotensin I into angiotensin II takes place in lungs. Angiotensin II has a short half-life of about 1 to 2 minutes. Then it is rapidly degraded into a heptapeptide called *angiotensin III* by angiotensinases, which are present in RBCs and vascular beds in many tissues. Angiotensin III is converted into angiotensin IV, which is a hexapeptide.

   Actions of Angiotensin II: When blood pressure and ECF volume decrease, renin secretion from kidneys is increased. It converts angiotensinogen into angiotensin I. Angiotensin II acts in two ways to restore the blood pressure:

   - It causes constriction of arterioles in the body so that the peripheral resistance is increased and blood pressure rises. In addition, angiotensin II causes constriction of afferent arterioles in kidneys, so that glomerular filtration reduces. This results in retention of water and salts, increases ECF volume to normal level. This in turn increases the blood pressure to normal level.

- Simultaneously, angiotensin II stimulates the adrenal cortex to secrete aldosterone. This hormone increases reabsorption of sodium from renal tubules. Sodium reabsorption is followed by water reabsorption, resulting in increased ECF volume and blood volume. It increases the blood pressure to normal level.

Angiotensin III *and* ***Angiotensin IV*** like angiotensin II also increase the blood pressure and stimulate adrenal cortex to secrete aldosterone

Clinical correlate

- Kidney failure

5. Discuss the role of kidney in calcium homeostasis.

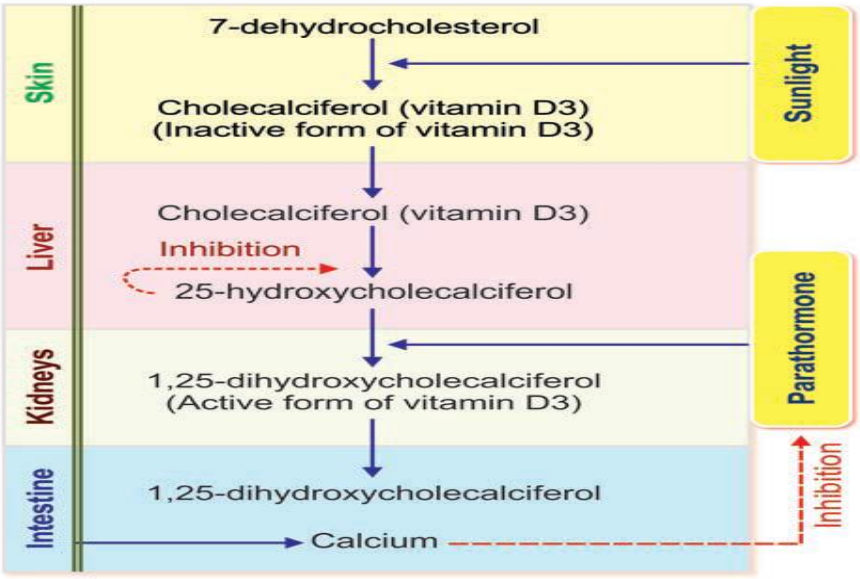
Calcium is a micronutrient needed by all living organisms. It is the most abundant mineral in the body and it is vital for bone health. It is necessary for maintaining healthy communication between the brain and other parts of the body. It plays a role in muscle movement and cardiovascular function. Food rich in calcium include yogurt, milk, sardines and salmon, cheese, tofu, legumes and grains, fortified fruit juices and so on. Calcium cannot be absorbed in the body without the active form of vitamin D3 (1,25-dihydroxycholecalciferol) which aids in its absorption in the small intestine. Vitamin D comes from fish oil, fortified dairy products and exposure to sunlight. The role of kidney in calcium homeostasis will be shown in the steps of activation of calcium.

Vitamin D is very essential for calcium absorption from the GI tract (specifically small intestine). But vitamin D itself is not an active substance. Instead, vitamin D has to be converted into 1,25-dihydroxycholecalciferol in the liver and kidney in the presence of Parathyroid hormone. The 1,25-dihydroxycholecalciferol is the active product. There are various forms of vitamin D. But, the most important one is vitamin D3 (*cholecalciferol*). Vitamin D3 is synthesized in the **skin** from 7-dehydrocholesterol, by the action of **ultraviolet rays** from the **sunlight.** It is also obtained from dietary sources. The activation of vitamin D3 occurs in two steps:

First step: Cholecalciferol (vitamin D3) is converted into 25-hydroxycholecalciferol in the **liver**. This process is limited and is inhibited by 25-hydroxycholecalciferol itself by feedback mechanism. This inhibition is essential for two reasons*: Regulation of the amount of active vitamin D* and *Storage of vitamin D for months together*.

If vitamin D3 is converted into 25-hydroxycholecalciferol, it remains in the body only for 2 to 5 days. But vitamin D3 is stored in liver for several months.

Second step: 25-hydroxycholecalciferol is converted into 1,25-dihydroxycholecalciferol **(calcitriol)** in **kidney**. It is the active form of vitamin D3. This step needs the presence of Parathyroid hormone (PTH). PTH also increases the reabsorption of calcium from the renal tubules along with magnesium ions and hydrogen ions. It increases calcium reabsorption mainly from distal convoluted tubule and proximal part of collecting duct.



Schematic diagram showing activation of vitamin D

Clinical correlate

- *Kidney failure*: damage of the kidney for greater or equal 3months as defined by structural and functional abnormalities of the kidney with or without decreased glomerular filtration rate.
- *Kidney stone*: development of solid piece of material in the urinary tract.