كلية المستقبل الجامعة قسم الصيدلة

المرحلة الثانية

# PHYSIOLOGY

## ENDOCRINE

## ADRENAL GLAND

**(L3)**

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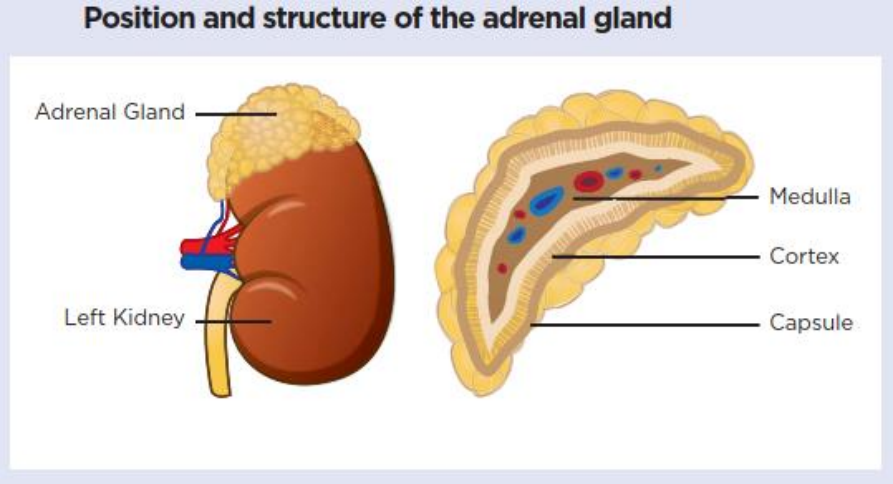
## Adrenal Glands

The adrenal glands, are paired endocrine glands also known as supra-renal glands, are found on top of the kidneys. They are **retroperitoneal** structures and composed of two major regions: the outer adrenal **cortex** and the inner adrenal **medulla**.




The adrenal medulla is the central part of the adrenal gland. The secretory cells of the medulla are known as chromaffin cells and they are responsible for producing adrenaline and noradrenaline.

The zona glomerulosa is the outermost layer of the adrenal cortex, and is responsible for secreting the mineralocorticoid hormones, such as aldosterone, which are important in regulating fluid and electrolyte balance.

The middle layer of the adrenal cortex is the zona fasciculata. It is the thickest of the three Zonas, measuring approximately 0.9mm and making up 50% of the mass of the Adrenal Gland. The cells of the zona fasciculata secrete the glucocorticoids cortisol and corticosterone, which regulate carbohydrate metabolism in the body.

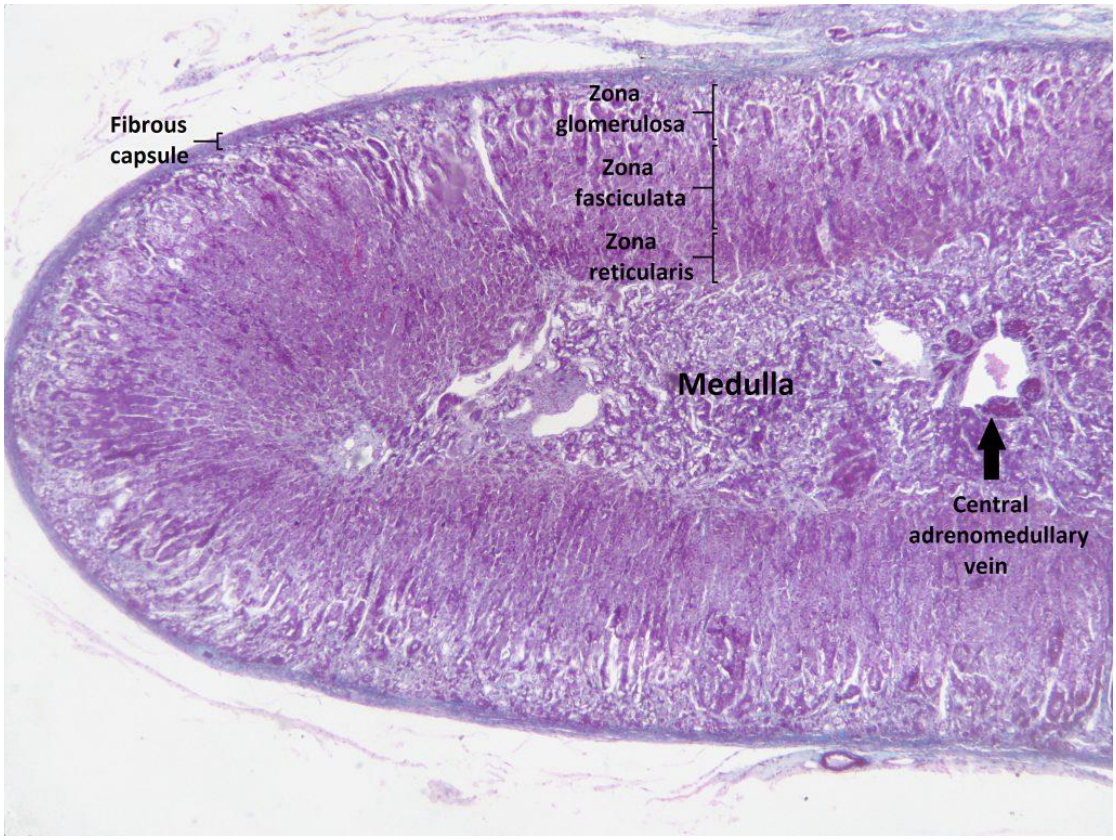
The zona reticularis is the innermost layer of the adrenal cortex. It is responsible for production and secretion of androgens – these are responsible for the normal development of sexual characteristics during puberty.

## The adrenal medulla

is the central part of the adrenal gland, surrounded by the cortex. The medulla plays a very important role in homeostasis: it serves to secrete **epinephrine (adrenaline**) and **norepinephrine (noradrenaline)**.

The main secreting cells of the adrenal medulla are called **chromaffin** cells, which are neuroendocrine cells that are modified sympathetic ganglia. The chromaffin cells are **neural**

**crest cell** derivatives. **Adrenaline** is released in response to activation of the **sympathetic nervous system**, fibres of which are carried to the adrenal medulla by the thoracic splanchnic nerves.




**Histology of the adrenal gland.**

## Function

The adrenal medulla is mainly responsible for the synthesis of the catecholamines, **adrenaline** and **noradrenaline**, but also has other secretory functions such as the production of **dopamine**. Both adrenaline and noradrenaline are produced from the amino acid **tyrosine,** through multiple reactions.

The synthesised adrenaline is stored in vesicles before being released into the blood stream. Adrenaline is mainly associated with the "**fight or flight response**", and noradrenaline also plays a role in the activation of the sympathetic nervous system as a neurotransmitter in post-ganglionic synapses.

It exhibits its actions through α and β adrenoreceptors (G protein coupled receptors), both in the central nervous system and in the periphery. The "fight or flight response" is a key survival mechanism, and causes a number of physiological changes, such as **increased cardiac output** and **increased glycogenolysis** in liver and muscle tissue.

**Phaeochromocytoma**

A **Phaeochromocytoma** is a **neuroendocrine** tumour of the adrenal medulla, specifically the chromaffin cells which secrete adrenaline as discussed previously. This leads to an excess of adrenaline, and leads to constant activation of the "flight or fight response". Hence, this can lead to symptoms such as: Tachycardia, Hypertension, Anxiety, Palpitations, Weight loss, Hyperglycaemia. In some situations it can lead to a **hypertensive crisis.** Whilst the above symptoms are all possible, the most typical presentation is intermittent attacks of headaches, excessive sweating and tachycardia.

## The adrenal cortex

## The Zona Glomerulosa, Structure :

The zona glomerulosa is the outermost layer of the adrenal cortex, lying just below the fibrous adrenal capsule. It accounts for around 15% of the thickness of the cortex. The secretory cells of the zona glomerulosa are arranged in oval-shaped clusters – its name comes from the Latin word *glomus*, meaning ball. These clusters are divided by connective tissue bands called trabeculae which extend down into the cortex from the adrenal capsule.

## Function

The primary function of the zona glomerulosa is the synthesis of **mineralocorticoid** hormones, which play an important role in the maintenance of electrolyte and water balance in the body. Mineralocorticoids are **steroid** hormones, and so are synthesized from **cholesterol**. The most important mineralocorticoid is **aldosterone**, which is responsible for controlling the uptake of $Na^+$ and secretion of $K^+$ in the collecting duct of the renal tubule.

**Control of aldosterone secretion:**

The release of aldosterone is under the influence of:

1- The level of K and Na in plasma:

The increased level of K (hyperkalemia) and the reduction in Na level (hyponatremia) will cause stimulation of aldosterone secretion (direct effect on the adrenal gland).

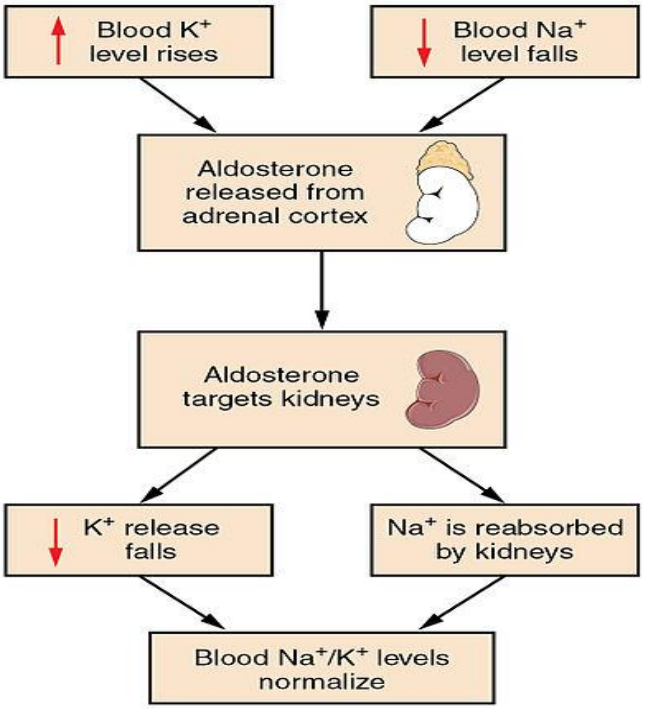



**Diagram showing an example of the regulation and action of aldosterone**

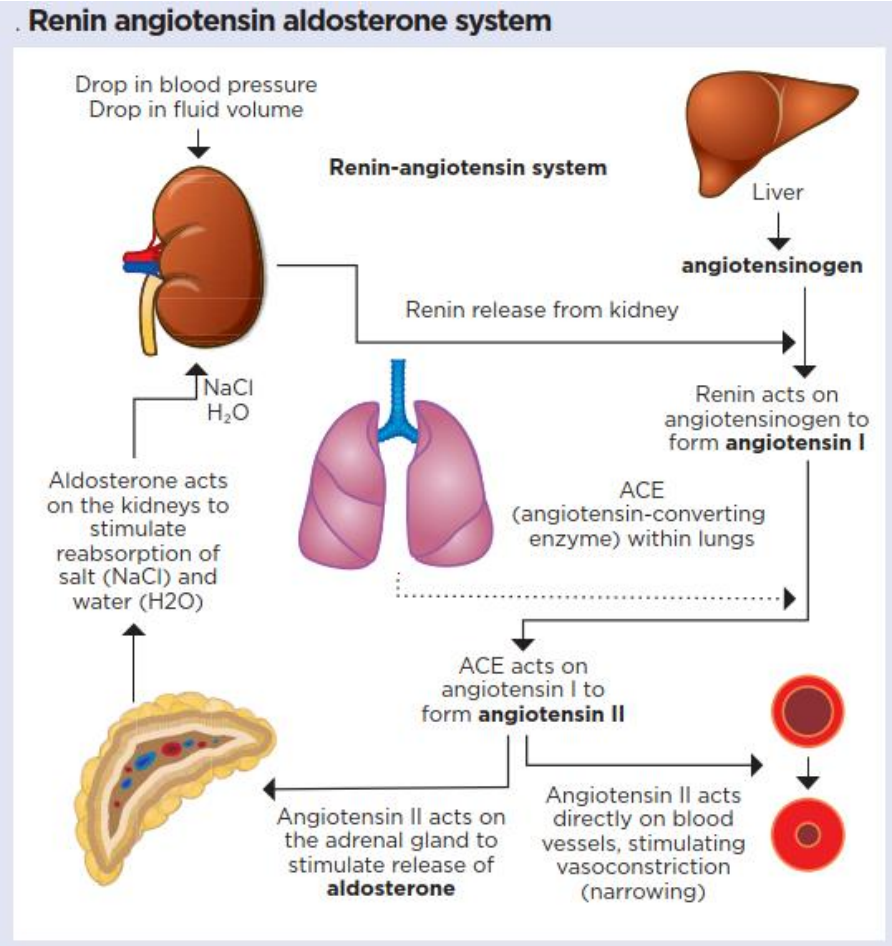
2. Heamorhage and hypovolemia:
This result in decrease in venous return decrease in cardiac output systolic blood pressure is reduced→ pressure in afferent arterioles in the kidney is reduced →stimulation of juxtaglomerular apparatus in the kidney → (the activation of the renin angiotensin aldosterone system (RAAS) i.e release of renin which acts on angiotensinogen (alpha 2 globulin synthesized by the liver), and convert it to angiotensin I (inactive protein ) which during its passage to the capillaries of the lung converted to angiotensin II (biologically active) by converting enzyme secreted by the endothelial lining of the blood vessel of the lung.

**Angiotensin II : 1**-increases the peripheral resistance and **2**- it has direct stimulation to the adrenal cortex to release aldosteron→Na retention and K elimination as a result we have increase in the blood pressure

**So suprarenal gland is essential for life removal of it will lead to hypotension and death within short period of time.**

*Blood pressure regulation*

The primary stimulus for aldosterone release is the activation of the renin angiotensin aldosterone system (RAAS). The RAAS is the most important physiological mechanism for medium to long-term control of blood pressure and is centered around a plasma protein called angiotensinogen, produced by the liver. When the kidneys detect a drop in blood pressure, they produce the enzyme renin and the activation of the renin angiotensin aldosterone system (RAAS).




The following factors **increase** the rate of aldosterone production within the zona glomerulosa:

Increase in plasma K+ concentration, Decrease in plasma pH (acidosis)

Decreased blood pressure, as detected by atrial stretch receptors

Increase in plasma concentration of Angiotensin-II

It is also worth noting that aldosterone secretion follows a **diurnal rhythm,** with higher levels typically being released during sleep.

***Primary aldosteronism***

PA, also known as Conn's syndrome is a condition that is most often caused by benign enlargement (hyperplasia) of the adrenal glands or by tumours in the adrenal cortex. It leads to excess secretion of aldosterone, causing hypernatraemia, which increases blood volume and blood pressure. Patients with PA also usually show hypokalaemia as increased aldosterone promotes the rapid secretion of potassium in the urine. Other signs and symptoms include water retention and neurological/ psychological symptoms, including anxiety, stress, depression and nervousness. Most importantly, the increased reabsorption of sodium and water by the kidneys

leads to **hypertension**, which increases the patient's risk of diseases such as **strokes** and **ischaemic heart disease**.

**The Zona Fasciculata**

is the middle zone of the **Adrenal Cortex**, deep to the **Zona Glomerulosa** and superficial to the **Zona Reticularis**. It is the thickest of the three adrenal layers, measuring approximately 0.9mm and making up 50% of the mass of the Adrenal Gland.

**Structure** : The Zona Fasciculata is made up of **parenchymal** cells known as spongiocytes, arranged into columns (sometimes called fascicles) with venous sinuses in between.

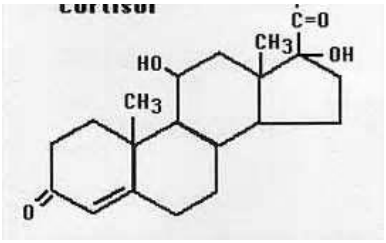
**Function :** The cells of the Zona Fasciculata secrete the glucocorticoids **Cortisol** and **Corticosterone**.

**The Glucocorticoids** have gained their name because they exhibit important effects that increase blood glucose concentration. Approximately 90 to 95 percent of the cortisol in the plasma binds to plasma proteins, especially a globulin called *cortisol-binding globulin* or *transcortin* and, to a lesser extent, to albumin.About 2% is in the free form which is the active form. **This high degree of binding to plasma proteins slows the elimination of cortisol from the plasma; therefore, cortisol has a relatively long half life** (the bound cortisol act as a reservoir for the hormone)

Two are of exceptional importance to the normal endocrine function of the human body: *aldosterone*, which is the principal mineralocorticoid, and *cortisol*, which is the principal glucocorticoid.

**Functions of the Glucocorticoids:**

At least 95 per cent of the glucocorticoid activity of the adrenocortical secretionsresults from the secretion of *cortisol*,




# Cortisol:

**The physiological action of cortisol:**

**1-Effects of Cortisol on Carbohydrate Metabolism:**

It increases blood glucose concentration (antihypoglycemic effect) .When hypoglycemia →stimulation of CRH (corticotrophin releasing hormone) secretion→ release of ACTH → cortisol release and increase in blood glucose level. How?

**a-It stimulates gluconeogenesis** (formation of carbohydrate from proteins and some other substances) by the liver, this effect is part of the effect on protein, because it *increases the enzymes required to convert amino acids into glucose in the liver cells. And it causes mobilization of amino acids from the extrahepatic tissues mainly from muscle.* As a result, more amino acids become available in the plasma to enter into the gluconeogenesis process of the

liver and thereby to promote the formation of glucose.
The increase in glucose level will stimulate insulin secretion; **also it reduces the sensitivity of many tissues, especially skeletal muscle and adipose tissue, to the stimulatory effects of insulin on glucose uptake and utilization**. If this persists for long time it will cause Betta cell exhaustion →diabetes mellitus.

**b-Decreased Glucose Utilization by Cells**:
Cortisol causes a moderate decrease in the rate of glucose utilization by most cells in the body (skeleton, muscles and adipose tissue), by inhibiting glucose entry to the cells→ increase blood glucose concentration to be available for normal brain function ,so it protect the brain from hypoglycemia.

**2-Effect on protein metabolism:**
It exerts **catabolic** effect on proteins. It will reduce the protein stores in essentially all body cells except those of the liver. This is caused by both decreased protein synthesis and increased catabolism of protein already in the cells. Also it depresses the formation of RNA and subsequent protein synthesis in many extrahepatic tissues, especially in muscle and lymphoid tissue. It diverts amino acids from the muscles and the liver for the process of deamination and gluconeogenesis, so it facilitates the breakdown of proteins.

**3-Effects of Cortisol on Fat Metabolism:**
It promotes mobilization of fatty acids from adipose tissue. This increases the concentration of free fatty acids in the plasma, which also increases their utilization for energy.

**4-Effect on minerals:**
It has a similar effect to aldosterone, although it is weaker than it (1/10 the power of Aldosterone). It promotes sodium retention and potassium elimination, excessive secretion will lead to more sodium retention → water retention, but no edema because there is increase in the glomerular filtration rate (GFR).

**1-Effect on respiration:**
It is important for the synthesis of surfactant during intrauterine life (to prevent respiratory distress syndrome). In females who are about to deliver preterm babies we usually give them cortisol to promote the formation of surfactant.

**2-Effect on water balance:**
It causes sodium retention which leads to water retention .It also causes increase in GFR (glomerular filtration rate), which counteract the water retention and the person does not develop edema.

**3-Effect on cardiovascular system:**
Cortisol restores vascular reactivity. It helps in maintaining arterial response to sympathetic tone. Deficiency of the hormone leads to hypotensive subject due to failure to maintain the peripheral resistance. While patients with hyper function of the adrenal cortex are hypertensive (because of the increase in peripheral resistance).

**4-Effect on GIT:**
Cortisol reduces the resistance of gastric mucosa to HCL so increase secretion of it leads to ulcer (so before giving the patient steroid tablets ask him if he has gastric pain or ulcer otherwise it may cause perforation to the stomach). Also it has an antivitamin D effect .It prevent the absorption of the vitamin from the intestine.

**5-Effect on lymphoid tissue and heamopoiesis:**
Cortisol suppresses the **production of antibodies** (used in chronic inflammatory diseases) in which inappropriate antibodies are produced in the subject against his own tissues (The

administration of large doses of cortisol causes decreases the output of both T cells and antibodies from the lymphoid tissue. **As a result, the level of immunity for almost all foreign invaders of the body is decreased**. Conversely, this ability of cortisol and other glucocorticoids to suppress immunity makes them useful drugs in preventing immunological rejection of transplanted hearts, kidneys, and other tissues.

**6- Effect on bones:**

Excessive secretion leads to osteoporosis due to destruction of the matrix of the bone (catabolic effect of cortisol on protein found in the matrix).This effect of cortisol in mobilizing proteins could make amino acids available to needs of the cells to synthesize substances essential to life.

**7- Anti- inflammatory effect of cortisol:**

It has the following effects to prevent inflammation:

*1-**Cortisol stabilizes the lysosomal membranes**, so decreases the proteolytic enzymes that are released by the lysosomes**.***

2. ***Cortisol decreases the permeability of the capillaries***. This prevents loss of plasma into the tissues.

3. ***Cortisol decreases both migration of white blood cells** into the inflamed area and **phagocytosis** of the damaged cells.*

4. *Cortisol **suppresses the immune system**, causing lymphocyte reproduction todecrease markedly(especially T lymphocytes).*

5. *Cortisol **attenuates fever** mainly because it reduces the release of interleukin-1 from the white blood cells.*

In addition to that Cortisol causes resolution of inflammation, the rate of healing is enhanced. So it can be used in disease that are characterized by severe local inflammation like rheumatoid arthritis, rheumatic fever, and acute glomerulonephritis.

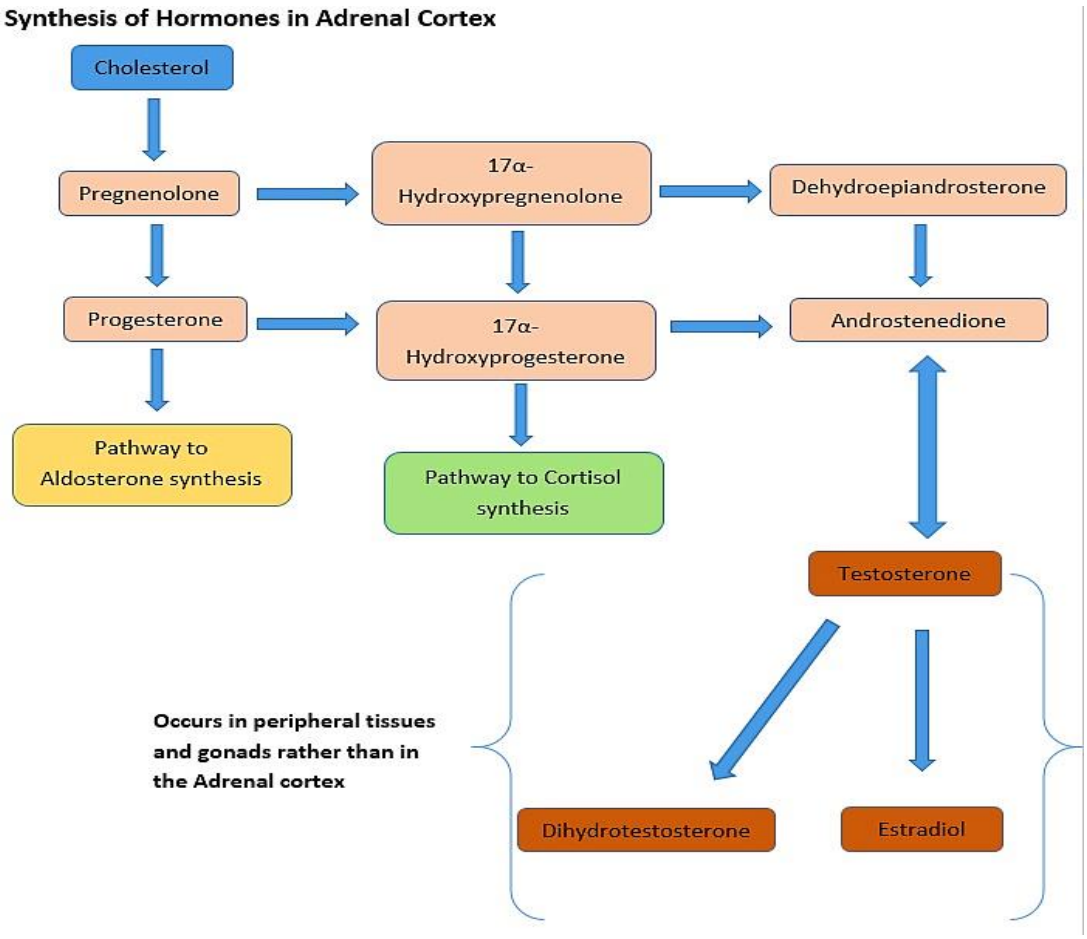
**8-Effect on allergy:**

It blocks the inflammatory response to allergic reactions in the same way that it blocks the other types of inflammatory response.

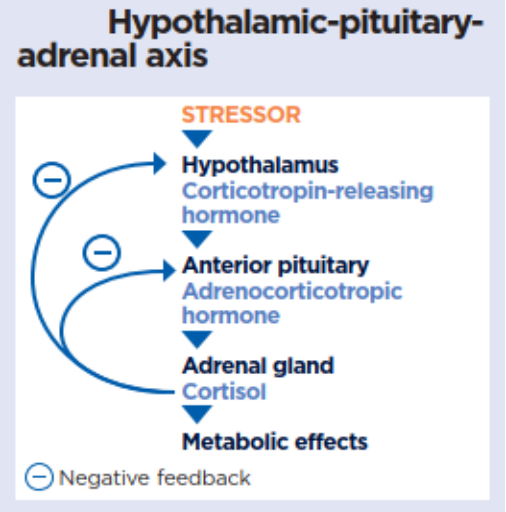
**9-Effect on blood:**

It decreases the number of eosinophils and lymphocytes in the blood. It also increases the production of red blood cells (mechanisms unclear).When excess cortisol is secreted by the adrenal glands, polycythemia often results, and conversely, when the adrenal glands secrete no cortisol, anemia often results.

The synthesis pathway of the steroids secreted by the Zonas of the adrenal gland is complex. **Cholesterol** is the major precursor for all steroids secreted. The first step is initiated by the actions of ACTH and Angiotensin II activating **adenylyl cyclase** and **phospholipase C** respectively. Cholesterol can then be converted to a steroid called Pregnenolone via an enzyme of the cytochrome P450 superfamily called cholesterol desmolase. From Pregnenolone, all the major secreted **mineralocorticoids,** glucocorticoids and androgens can be synthesised in a multi-step enzyme-assisted pathway. The metabolites of the synthesis pathway are moved in and out of the mitochondria, the smooth endoplasmic reticulum and the cytoplasm. It is the presence or lack of specific enzymes in each Zona that determines which hormones are secreted. In the Zona Fasciculata, the enzyme **11β-hydroxylase** catalyses the final step of the reaction that forms Cortisol and Corticosterone. Additionally the secretion of cortisol follows a **diurnal pattern** with more being secreted in the mornings.




**HPA axis** : Cortisol release is tightly regulated by homeostatic mechanisms that rely on negative feedback. The hypothalamus is a vital region of the brain that acts as a crossover point between the nervous system and the endocrine system. During periods of chronic stress (both physical and emotional), the hypothalamus releases corticotrophin- releasing hormone (CRH). CRH is delivered to the anterior pituitary in the hypothalamic-pituitary portal circulation, where it initiates the release of adrenocorticotropic hormone (ACTH). ACTH circulates systemically and stimulates the release of cortisol from the adrenal cortex. As cortisol is important in regulating metabolism and influences a variety of immune and behavioral responses, the hypothalamus continually monitors the plasma cortisol concentration. When levels of cortisol rise, the hypothalamus responds by reducing CRH secretion; this decreases the release of ACTH and, ultimately, cortisol secretion. Long-term stressors, such as physical injury, starvation or emotional stress, activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of cortisol. Cortisol also influences the sleep/wake cycle, mood and behaviour, and has a variety of immunosuppressant properties. In terms of immune modulation, it is a powerful natural anti- inflammatory molecule that helps limit and control the inflammatory response. Powerful steroidal anti-inflammatory medications, such as hydrocortisone creams commonly used to treat inflammatory skin conditions, mimic the effects of cortisol.




**Cushing's Syndrome**

In a steroid-producing adrenal tumour (or Anterior Pituitary adenoma), large concentrations of **glucocorticoids** are secreted in the body. When in high concentrations, glucocorticoid steroids activate mineralacorticoid receptors due to the similarity in shape of the receptors. Therefore, a patient with Cushing's Syndrome will have symptoms of high **glucocorticoid** secretion (fat build-up on back of neck and around face, wasting of limb muscles with central obesity, purple striae, hyperpigmentation) as well as show effects of high **mineralocorticoid** concentrations (hypertension, hypokalaemia). Treatment of Cushing's depends on the underlying cause, for example a **pituitary adenoma** may be surgically removed, as can a metastatic lung tumour secreting ACTH.

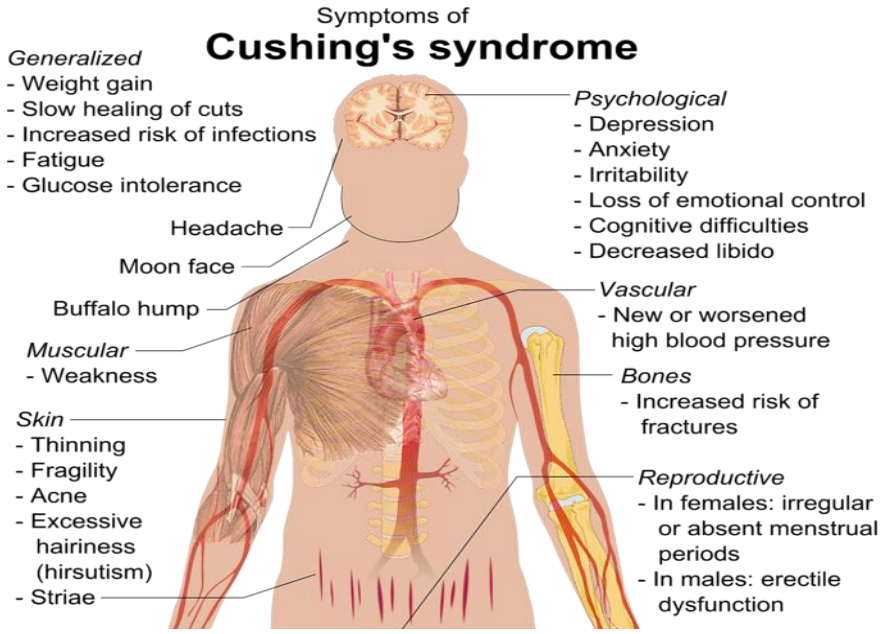



**Diagram showing the symptoms of Cushing's syndrome**

**Addison's disease :** is the opposite disease to Cushing's disease in many ways. Whereas Cushing's disease is due to an excess of cortisol, Addison's disease is due to a lack of cortisol, commonly due to autoimmune destruction of the adrenal cortex. This in turn causes hypotension and anorexia, in contrast to hypertension and truncal obesity in Cushing's disease. A unique symptom of Addison's disease is hyperpigmentation, particularly in the creases of the hand and in the mouth. A very serious complication of Addison's disease is an Addisonian crisis. As discussed above, cortisol is linked to the "fight or flight" response and is released in times of stress to the body.Therefore, in patients suffering from Addison's disease, they are unable to mount an adequate response to these stresses. This can result in numerous symptoms such as severe hypotension and electrolyte dysfunction.

### The zona reticularis

is the innermost layer of the adrenal cortex, lying just above the adrenal medulla. It comprises of **cylindrical** masses of epithelia arranged in an irregular, net-like pattern. In comparison to the zona fasciculata, the cells contain fewer **vacuoles** as well as appearing more irregular and smaller in size.

## Regulation of Adrenal Androgens

Adrenal androgens are regulated by ACTH (adrenocorticotropic hormone) secreted from the anterior pituitary gland which is stimulated by the release of CRH (corticotrophin releasing hormone) from the **hypothalamus.** However, the adrenal androgens along with their potent metabolites such as testosterone do not negatively feedback to ACTH or CRH. Therefore, in cases where there is a dramatic increase in ACTH, this leads to excess production of androgens which cannot be regulated.

## The parathyroid glands

are small endocrine glands located in the anterior neck. They are responsible for the production of parathyroid hormone (PTH). The parathyroid glands are located on the posterior, medial aspect of each lobe of the thyroid gland. Anatomically, the glands can be divided into two pairs:

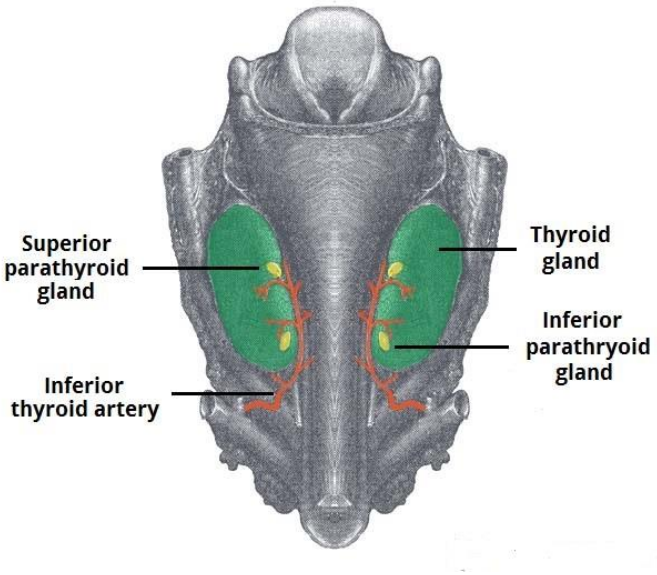
Superior parathyroid glands – Derived embryologically from the fourth pharyngeal pouch. They are usually located at the level of the inferior border of the cricoid cartilage.

Inferior parathyroid glands – Derived embryologically from the third pharyngeal pouch. They are usually located near the inferior poles of the thyroid gland. However in 1-5% of people they can be found deep in the superior mediastinum.

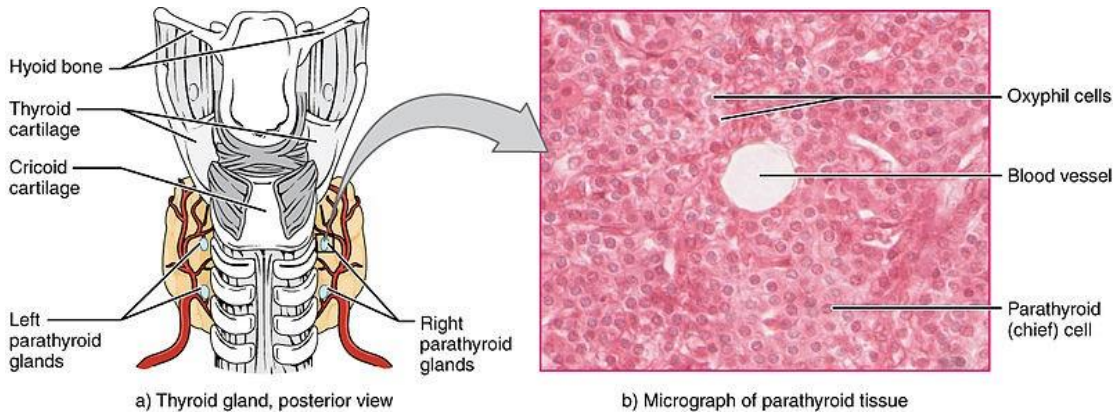
Parathyroid Gland Histology : There are two types of cells within the parathyroid gland, the chief cells and the oxyphil cells.

Chief cells– The role of this cell type is to secrete parathyroid hormone. They contain prominent Golgi apparatus and endoplasmic reticulum to allow for the synthesis and secretion of

parathyroid hormone. The chief cells are the smaller of the two cell types, however, they are more abundant. Oxyphil cells– These cells are much larger but less abundant than chief cells. Their purpose is unknown.Note that histologically fat cells (adipose cells) are also seen within the parathyroid gland**.**




**Anatomical location of the parathyroid gland**




**Anatomical location of the Parathyroid glands and their histology.**

## Parathyroid Hormone Actions

Parathyroid hormone (PTH) has three main actions, all of which act to increase calcium levels in the body;

Increased bone resorption– PTH acts directly on bone to increase bone resorption. It induces cytokine secretion from osteoblasts that act on osteoclast cells to increase their

activity. Osteoclasts are responsible for the breakdown of bone and thus an increase in their activity leads to increased bone break down. This leads to an increase in calcium in the extracellular fluid.

Increased reabsorption in the kidney- PTH increases the amount of calcium absorbed from the Loop of Henle and distal tubules, however, the mechanism is not fully understood. Additionally, PTH increases the rate of phosphate excretion which is very important to prevent to formation of calcium phosphate kidney stones.

Vitamin D synthesis- Although PTH does not actively increase the absorption of calcium from the gut it stimulates the formation of vitamin D, which subsequently increases absorption from the gut.

**Parathyroid Hormone Regulation**

Like most endocrine organs, the parathyroid gland is controlled by a negative feedback loop. Chief cells have a unique G-protein calcium receptor **(CaR)** on their surface, which regulates this. When calcium levels in the blood are elevated, PTH production must be stopped in order to prevent further elevation of calcium which could lead to **hypercalcaemia**. Calcium binds to the G protein CaR which subsequently leads to the prevention of PTH secretion thus calcium is deposited back into the bones. Furthermore, as mentioned above, PTH stimulates vitamin D synthesis. Vitamin D also acts directly on the parathyroid gland to decrease PTH synthesis.

When Calcium is reduced, the reverse occurs. Lowered calcium means reduced stimulation of CaR. Subsequently, PTH secretion is not inhibited. Decreased Vitamin D results in upregulation of PTH gene transcription thus more **PTH** is synthesised.

Note: Elevated phosphate lowers free Calcium in the blood and inhibits the formation of Vitamin D.

**Clinical Relevance – Hyperparathyroidism**

Hyperparathyroidism is the **over-activity** of the parathyroid glands and can be classed as primary, secondary, tertiary or malignant depending on the underlying cause. **Primary** hyperparathyroidism is a result of direct alterations to the parathyroid gland such as a benign tumour, hyperplasia or very rarely parathyroid cancer. The excess secretion of PTH leads to **elevated calcium** in the blood which can cause signs of hypercalcaemia, osteoporosis, osteitis fibrosa cystica and hypertension. **Secondary** hyperparathyroidism is a physiologically elevated PTH due to reduced calcium levels. This could be caused by **chronic renal failure** or **decreased vitamin D intake.**

**Tertiary** hyperparathyroidism occurs after prolonged secondary hyperparathyroidism. This is due to structural changes seen within the gland. To distinguish between secondary and tertiary hyperparathyroidism, a blood test will be carried out. **Elevated Calcium levels** indicate tertiary hyperparathyroidism.
**Malignant** hyperparathyroidism can be caused by some tumours, such as bronchial squamous cell carcinomas, as they produce a protein called Parathyroid related protein (**PTHrP**). PTHrP can mimic PTH due to the similarity in their structure which ultimately results in elevated calcium in the blood. However, PTH will be reduced due to negative feedback to the parathyroid gland itself.

**Hypoparathyroidism**

Hypoparathyroidism is the **underactivity** of the parathyroid gland and can be classed as primary or secondary depending on the cause.

**Primary** hypoparathyroidism is a result of decreased PTH secretion due to gland failure. This results in symptoms of hypocalcaemia and patients will often need Calcium supplementation.

**Secondary** hypoparathyroidism is commonly caused by surgical removal of the parathyroid glands. This is often accidental due to the fact that the inferior parathyroid glands are difficult to locate.

**Calcitonin**

It is a peptide hormone secreted by the thyroid gland , it decreases plasma calcium concentration &has effects opposite to those of PTH . Synthesis & secretion of calcitonin occur in the Para follicular cells or C cells , lying in the interstitial fluid between the follicles of the thyroid gland .The primary stimulus for calcitonin secretion is increased calcium ion concentration in plasma .

The reduction of Ca ions concentration caused by calcitonin leads within hours to a powerful stimulation of PTH secretion which over rides the calcitonin effect .

**Vitamin D**

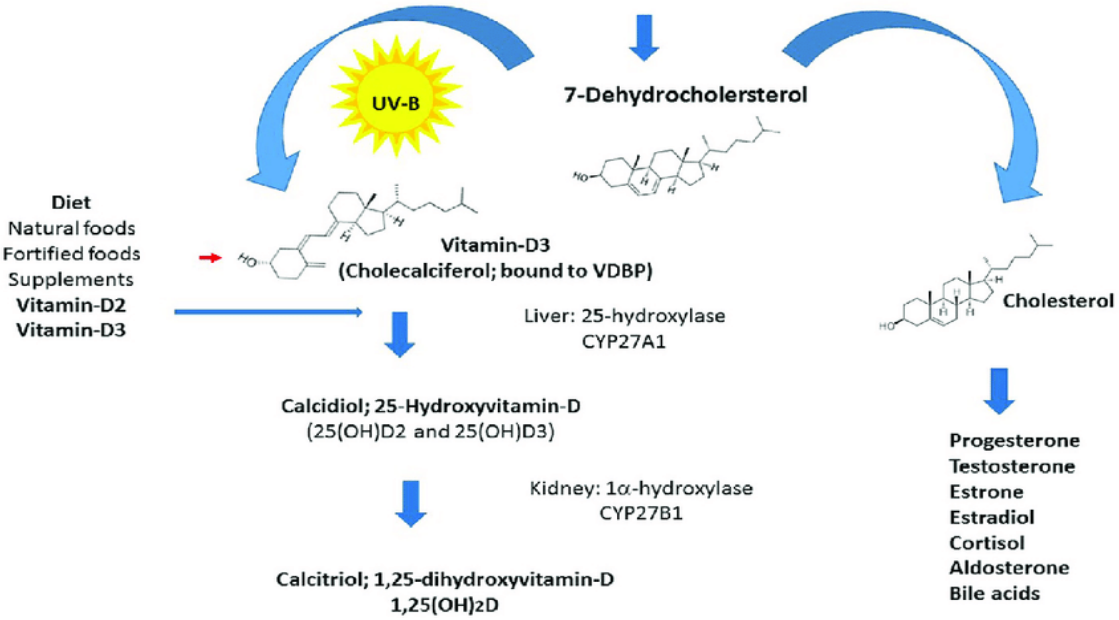
Vitamin D is a **long-term regulator** of serum calcium, with a half life of around 6 hours. Its main function is to **increase the intestinal absorption of calcium.** Vitamin D3 ( cholecalciferol ) is found in the skin .This is activated &converted to 25-hydroxycholecalciferol in the liver & this has a negative feedback effect on the conversion reactions. 25-hydroxycholecalciferol in the proximal tubules of the kidneys is converted to 1, 25-dihydroxycholecalciferol .this is the most active form of vitamin D .this conversion requires PTH .

So it can be ingested, or synthesised from a cholesterol precursor as follows:

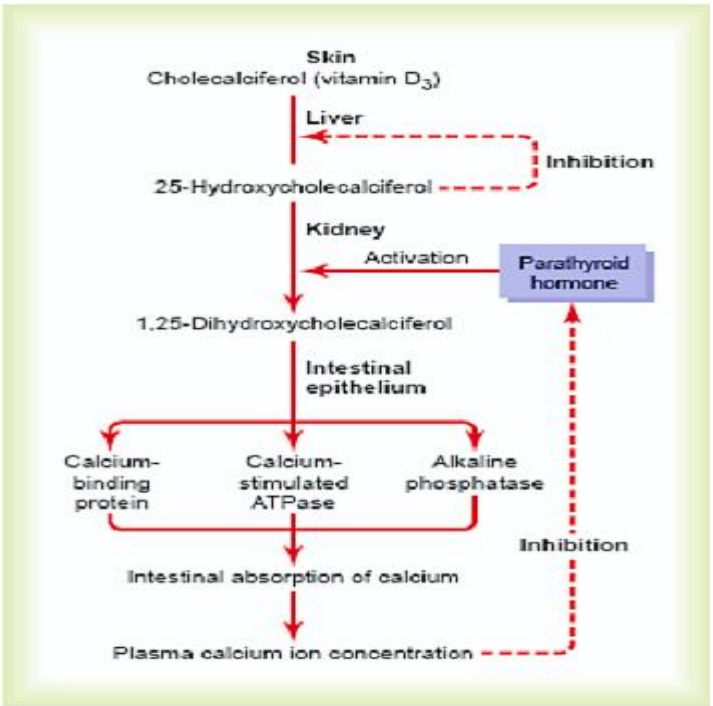
7-dehydrocholesterol is converted into vitamin-D3 under the influence of UV radiation.In the liver, vitamin-D3 is converted into 25-hydroxyvitamin-D.This is relatively inactive. In the kidney, convertion of 25-hydroxyvitamin-D into 1,25-dihydroxyvitamin-D, otherwise known as calcitriol. This is metabolically active.

Once synthesised, **calcitriol** is released into the bloodstream. It then stimulates intestinal epithelial cells to increase absorption of calcium.

If levels of calcitriol become excessive, it is converted to **24,25-dihydroxycholecalciferiol**, which is less active. This prevents toxicity.




**Schematic diagram of Vitamin D synthesis**




Activation of vitamin $D_3$ to form 1,25-dihydroxycholecalciferol and the role of vitamin D in controlling the plasma calcium concentration.

**Actions of vitamin D**

1. It promotes intestinal calcium absorption .
2. It promotes phosphate absorption by the intestines .
3. It decreases renal calcium and phosphate excretion .
4. It plays an important role in both bone absorption & bone deposition .

## Calcium & phosphate regulation in the extra cellular fluid & plasma

Calcium plays a key role in many physiological processes including :

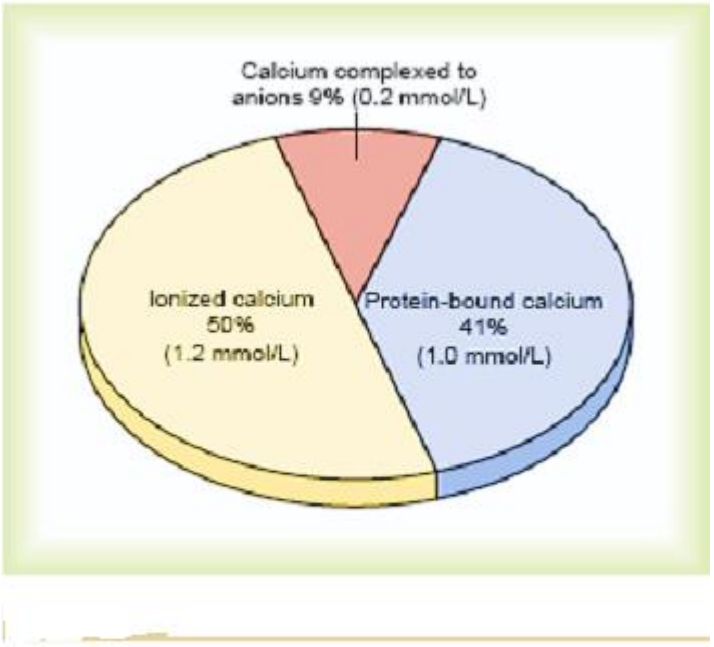
Contraction of skeletal ,cardiac and smooth muscle , Blood clotting , Transmission of nerve impulses . Only 0.1% of total body Ca is in the ECF , 1% is in the cells and the rest is stored in the bones.

About 85% of the body s phosphate is stored in bones , 14 – 15 %is in the cells and less than 1% is in the ECF. Calcium in the blood exists in three forms:

**Free-ionised** – diffusible, biologically active.

**Bound to anions** e.g. phosphate – diffusible, not biologically active.

**Bound to proteins** (mainly albumin) – not diffusible, not biologically active.




Distribution of ionized calcium ($Ca^{++}$), diffusible but un-ionized calcium complexed to anions, and nondiffusible protein-bound calcium in blood plasma.

**Non –bone physiologic effect of altered Ca & phosphate concentrations in the body fluids**.

Hypocalcemia causes nervous system excitement & tetany .Hypercalcemia decreases nervous system & muscle activity .When ECF concentration of Ca ions falls below normal the nervous system becomes more excitable , because this causes increased neural membrane permeability to Na ions allowing easy initiation of action potential .

At plasma Ca 50% below normal , the peripheral nerve fibers become so excitable that they discharge spontaneously initiating nerve impulses that pass to the peripheral skeletal muscles to cause tetanic muscle contraction .It also causes seizures because of its action of increasing excitability of the brain. this pic. Shows carpopedal spasm.

Hypocalcemic tetany in the hand, called carpopedal spasm.

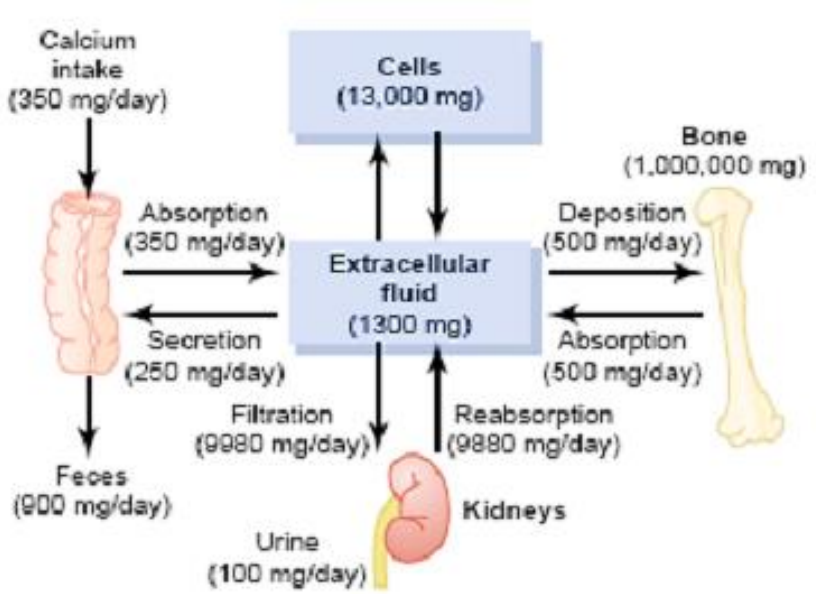
Tetany occurs when the blood concentration of Ca falls from 9.4 mg / dl to about 6 mg / dl , which is only 35% below normal & is usually lethal at about 4 mg / dl .

When calcium level in the body fluids rises above normal , the nervous system becomes depressed & reflex activities of the nervous system are sluggish , also decrease the QT interval of the heart ECG , constipation and lack of appetite.

These effects occur when the level of calcium rises above 12 mg / dl, when the level of calcium rises above 17mg /dl in blood , calcium , phosphate crystals precipitate throughout the body.

**Absorption & excretion of calcium and phosphate**

Intestinal absorption & fecal excretion : the usual rates of intake are about 1000 mg / day for calcium & phosphate , Ca ions are poorly absorbed from the intestine , vitamin D promotes its absorption by the intestine. about 35%( 350 mg / day ) of ingested calcium is usually absorbed , the remaining is excreted in the feces, an additional 250 mg of calcium enters the intestine via secreted G.I.T. juices thus90% ( 900 mg / day ) of daily intake of calcium is excreted in feces.




Overview of calcium exchange between different tissue compartments in a person ingesting 1000 mg of calcium per day. Note that most of the ingested calcium is normally eliminated in the feces, although the kidneys have the capacity to excrete large amounts by reducing tubular reabsorption of calcium.

Intestinal absorption of phosphate occurs very easily. Except for the portion of phosphate that is excreted in the feces in combination with non-absorbed calcium, almost all the dietary phosphate is absorbed into the blood from the gut and later excreted in the urine.

**Renal excretion of calcium & phosphate**

About 10% ( 100 mg / day ) of ingested calcium is excreted in urine . About 41%of plasma calcium is bound to plasma proteins and therefore not filtered by the glomerular capillaries . The rest is combined with anions such as phosphate ( 9% ) or ionized 50% and is filtered through the glomeruli into the renal tubules .

Normally renal tubules absorb 99% of the filtered calcium & about 100mg / day is excreted in urine . About 90%of calcium in the glomerular filtrate is reabsorbed in the proximal tubules , loop of Henle and early distal tubules , then in the late distal tubular and early collecting ducts ,reabsorption of remaining 10% is very selective , depending on calcium ion concentration in blood .

When concentration is low , this reabsorption is great , so that almost , no calcium is lost in urine . Conversely , even a minute increase in blood calcium ion concentration above normal increases excretion markedly.

Renal phosphate excretion is controlled by an overflow mechanism that is when phosphate concentration in the plasma is below the critical value of about 1 mmol / L, all the phosphate in the glomerular filtrate is reabsorbed & no phosphate is lost in the urine .

**Regulation**

There are three molecules which regulate the amount of calcium in blood and ensure it is maintained within the normal range. These are calcitriol (vitamin D), parathyroid hormone and calcitonin. The synthesis of **calcitriol** is completed in the kidneys, **parathyroid hormone** (PTH) is secreted by the parathyroid glands, and **calcitonin** is secreted by the thyroid glands.

## Clinical Relevance : Hypocalcaemia

Hypocalcaemia is defined as an adjusted calcium level of **<2.20mmol/L**.

Patients who develop hypocalcaemia acutely tend to be **more symptomatic** compared to patients who develop hypocalcaemia over a long period of time (chronic hypocalcaemia). The symptoms of hypocalcaemia include peri-oral and peripheral numbness or tingling, cardiac arrythmias (**prolonged QT interval** on ECG), muscle spasms, and seizures. This is due to a reduction in the resting membrane potential, rendering the cell **hyper-excitable**.

Causes of hypocalcaemia include:

- **Hypoparathyroidism**
- **Vitamin D deficiency**
- **Hyperphosphatemia:** Phosphate binds to calcium to form calcium phosphate, reducing free calcium.
- **Renal disease:** Reduced calcitriol synthesis.
- **Acute pancreatitis:** Free fatty acids bind calcium, reducing levels of free calcium.
- **Respiratory alkalosis:** In alkalosis, calcium ions associate with albumin with greater affinity, thus reducing free and active calcium.

## Hypercalcaemia

Hypercalcaemia is defined as an adjusted calcium level of **>2.60mmol/L**.

Patients with mild hypercalcaemia tend to be asymptomatic, but when levels exceed 3mmol/L, symptoms include muscle weakness, cardiac arrhythmias (**short QT interval**), constipation, kidney stones and depression.

Causes of hypercalcaemia include:

- **Hyperparathyroidism**
- **Malignant tumour** – Some tumours secrete parathyroid-hormone related peptide (PTHrP). This mimics PTH, leading to hypercalcaemia.
- **Vitamin D intoxication** – excess vitamin D causing increased intestinal absorption of calcium.
- **Thiazide diuretics** – increase renal reabsorption of calcium causing excess calcium in blood.

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