HORMONAL REGULATION OF CALCIUM HOMEOSTASIS

*Calcium:

Functions of calcium in the body

Calcium is present in the body in two forms: salt and ionic Ca2+

I) Role of ionic Ca2+: (less than 1% of body calcium-non bony):

1. Blood clotting.
2. Second messenger: the cellular action of some hormones.
3. Membrane excitability: controls the excitability of nervous & muscular tissues.
4. Muscle contraction.
5. Cardiac function: maintains both contractility & rhythmicity of the heart.
6. Exocrine, endocrine & neurosecretion: exocytosis.

II) Role of calcium salts: more than 99% of total body calcium:

1. Constitution of tissues: hard tissues (bone & teeth) & fluid tissue (milk).
2. Storage function.

Calcium distribution in the body

The body contains 1000 – 1100 gm calcium.

1. Bony skeleton: 99% of the body calcium, it is present in two pools:

a. *Small calcium pool:* labile pool (1%): readily exchangeable: present in equilibrium with the plasma calcium.

b. *Large calcium pool:* stable pool (99%): calcium hydroxyapatite in mature bone. It is not readily exchangeable with plasma calcium.

2. Plasma: 10 mg/dl

a. Diffusible form (50%): most of it is ionized free Ca++ that can pass into & outside the intravascular space.

b. Non-diffusible form (50%): is bound to plasma proteins (albumin) so remains in intravascular space.

Absorption of calcium in the GIT

From 30-80% of the ingested calcium is absorbed, by the upper small intestine, through passive diffusion & active transport.

Factors that could affect Ca absorption:

1. *Local GIT factors:* affect the degree of calcium salts solubility. Salts in solution are absorbed readily, while in precipitate they are not.
2. *Acidity:* of the upper GIT secretions dissolve calcium salts.
3. *Protein meals:* make soluble complexes with calcium.
4. *Acidic food products:* lactic acid production from lactose, or from yogurt, or citrates facilitate solubility.
5. *Ingested phosphates & oxalates:* form insoluble calcium salts.
6. Active vitamin D3 stimulates the absorption of calcium.

*Phosphorous

- It is present in the body in an amount of 500 - 800gm
- 85 to 90% is in the skeleton.
- Its concentration in plasma is about 12 mg/dl.
- Many compounds contain phosphorous: ATP, cAMP, 2,3DPG as well as many proteins that play a very important role in cell phosphorylation and dephosphorylation reactions.

Physico-chemical characters of Ca2+ & PO4--

- A solution of an ionizable salt (electrolyte), below saturation, contains cations & anions in concentrations that are below a certain value: **the solubility product.**
- The solubility product is calculated by the multiplication of their concentrations.
- A rise in their concentrations will raise this value above the solubility product precipitation of the salt.
- Ca2+ and PO4-- exist in the ECF in concentrations **above** their solubility product, so they must exist in a salt form and precipitate in tissues.
- **Pyrophosphate (inhibitor of precipitation)** exists in tissues and no precipitation occurs.
- **Precipitation of calcium phosphate occurs if:**
  Physiologically: a cell (osteoblast) secretes an inhibitor to pyrophosphate.
- ***Pathologically:*** subendothelial in the wall of blood vessels (atherosclerosis) or degenerated cells and metastatic calcification.

Bone Physiology

Bone tissue is formed of:
1. **Matrix:** type I collagen protein
2. **Crystals:** mostly hydroxyapatite.
3. **Cells**:
a. ***Osteoblasts:*** bone-building cells: Secrete collagen and other bone proteins.
Secrete alkaline phosphatase enzyme which hydrolyzes plasma phosphate esters to phosphate ions needed for calcium phosphate formation. Secrete pyrophosphate inhibitor needed for precipitation of calcium.
b. ***Osteoclasts:*** bone-eating cells:
Secrete H+ ions by H+-ATPase pump that dissolve hydroxyapatite
Secrete acid protease: that dissolves collagen.
c***. Osteocyte:*** responsible for Ca exchange with ECF.

Bone remodeling:

- Bone is continuously remodeled (4% for compact bone and 20% for trabecular bone/year).
- There are about 2 million remodeling units in the human skeleton.
- The remodeling unit is formed of a group of osteoclasts that absorb bone and a group of osteoblasts that lay new bone

Control of plasma Calcium:

- Plasma calcium must be maintained constant within a very narrow range (9.4-10 mg/dl) because it will be reflected seriously on various body functions.
- Extracellular calcium is liable to a rapid decrease in cases of diarrhea or to a rapid increase in cases of excessive calcium absorption with an overdose of vitamin D by about 20-30%.

Mechanisms to buffer the rapid changes of plasma calcium

I-The first line of defense:

a. Ca rapidly shifts from exchangeable Ca in bone (small or labile Ca pool) to plasma or the reverse. Rapid flow occurs because Ca crystals are small and dispersed on a big surface area.

b. Ca2+ rapidly flows from and to mitochondria of liver & intestinal cells.

II-The second line of defense: dependent on 3 hormones:

1) **Parathyroid hormone PTH;** secreted from the parathyroid gland.
2) **Thyrocalcitonin TCT:** secreted from the thyroid gland.
3) **Active vit.D3: 1, 25(OH)2 cholecalciforal** .

This line of defense starts immediately on a change in plasma Ca2+ and continues for a prolonged course to help the first line of defense.

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Origin and chemistry of Parathormone:

- The parathyroid hormone (Parathormone PTH or Parathrin) is secreted from the chief cells in 4 parathyroid glands, embedded in the four poles of the thyroid gland.
- PTH is a polypeptide (84 AA) hypercalcemic hormone

Mechanism of action of Parathormone

Types of parathyroid hormone receptors:

1.PTH/PTHrP receptors: in the osteoblasts, osteocytes.

PTHrP (parathyroid hormone-related protein) is a protein (140 AA). PTHrP binds to these receptors. In addition to its PTH activity, it acts as a growth factor in the skin, hair follicles, breasts, and chondrocytes.

2. PTH2- R: in the placenta, brain & pancreas.

3. CPTH-R: the C terminal of PTH molecule binds to it.

Mechanism of action of PTH:

PTH binds to membranous receptors coupled to the Gs & Gq proteins.

Gs: activates adenyl cyclase and increases the intracellular cAMP.

Gq : activates PLC and increases the intracellular Ca2+ & DAG that in turn activates the protein kinase C.

Physiological functions of Parathormone (Hypercalcemic hormone):

A. PTH actions on bone: Mobilization of Ca2+ from bone

PTH action on bone is composed of two phases:

1- Rapid phase 2- Slow phase

1- Rapid phase

- Begins within minutes and continues for hours.
- PTH binds to the receptors in osteocytes which form an osteocytic membrane. Activation increases the permeability of the osteocytic membrane to Ca2+ from the bone fluid.
- Raised intracellular Ca2+ is then pumped by the cell membrane calcium pumps into the extracellular fluid under the effect of 1,25 DHCC.

2- Slow phase

- It takes days or weeks to develop fully.
- PTH stimulates at first the osteoblasts' production of IL-6 and RANKL (receptor-activated NF-KB ligand), which in turn stimulates osteoclasts' proliferation (osteoclasts have no receptors for PTH).
- Activated osteoclasts resorb both the organic & inorganic bone matrix, releasing into the extracellular fluid, Ca2+, PO4-- & hydroxyproline.

B – PTH actions on Kidneys:

PTH decreases phosphate reabsorption from renal proximal convoluted tubules increases

- phosphate excretion (***phosphaturic action***) decreasing the phosphate in the blood (***hypophosphatemia***).
- PTH + decreased phosphate activates 1-α-hydroxylase enzyme in the proximal convoluted tubule to produce 1,25(OH)2D3.
- PTH & 1,25(OH)2D3: increases calcium reabsorption from distal parts of renal tubules (***hypocalciuria***) and increases calcium in the blood (***hypercalcemia***).
- PTH increases Mg2++ reabsorption & decreases H+ secretion.

C – PTH actions on the intestine

- PTH & 1,25(OH)2D3: increase calcium & phosphate absorption by the intestine.

***Collectively, the results of PTH are: Hypercalcemia, hyperphosphaturia, hypophosphatemia, and hypocalciuria.**

Regulation of secretion of Parathormone

Regulation of secretion of Parathormone

1- PTH secretion is **not** under pituitary control. It is directly related to feedback mechanisms depending on plasma Ca2+ concentration:

-Drop in plasma Ca2+ stimulates PTH secretion.

-Rise in plasma Ca2+ inhibits PTH secretion.

2- A rise in PO4-- will decrease extracellular Ca2+ causing an increase in PTH secretion.

In addition, a rise in PO4- increases the level of FGF23 in plasma that binds to FGF-receptor (FGFR) in renal proximal convoluted tubule → decreases PO4- reabsorption and also binds to FGFR in the parathyroid gland which respond by PTH secretion.

3- Conditions that increase the cAMP in the parathyroid gland as - adrenergic stimulation, increase PTH secretion.

4- 1,25(OH)2D3 inhibits the formation of PTH and so decreases its secretion.

The physiological role of Ca-sensing receptor (CaSR) and its clinical application:

- It is G protein-coupled receptor that is most highly expressed in the parathyroid glands, calcitonin-secreting C-cells of the thyroid gland, and kidneys
- A rise in extracellular ionized calcium activates the CaSR, which suppresses PTH expression.

- The CaSR serves as a 'calciostat' and plays a key role in calcium homeostasis.

Disturbance of Parathormone function

A. Hyperparathyroidism

1. ***Primary hyperparathyroidism (PHPT):***
   - Caused by a tumor of the parathyroid.
   - Characters: Hypercalcemia is the biochemical hallmark of PHPT. The rise of plasma calcium causes decreased neuromuscular excitability (weak contractions, decreased excitability of nerves).

2. Secondary hyperparathyroidism:

- *Caused by* hyperplasia of parathyroid glands in response to decreased serum calcium level due to:

a. Decreased intestinal calcium absorption (Vitamin D deficiency: serum 25-hydroxyvitamin D levels of < 20 ng/ml; Bariatric surgery; Malabsorption syndromes; Decreased calcium intake).

b. Renal insufficiency (Renal osteodystrophy): Phosphate retention in chronic renal diseases→ 2ry decrease in plasma Ca2+→ reactive hypersecretion of PTH

- *Characters:* elevated levels of PTH with normal or low levels of serum calcium.

3***. Tertiary Hyperparathyroidism:***

- *Caused by* an independent nodule secreting excessive parathyroid hormone after a long period of secondary hyperparathyroidism.

B- Hypoparathyroidism:

- *Cause:* usually secondary to thyroidectomy (by error, a surgeon may remove the parathyroid gland because it is deeply embedded)
- *Manifestations:* Tetany.

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1, 25 (OH)2 D3 : 1,25-DHCC

Origin:

In the skin keratinocytes, 7-dehydrocholesterol by the action of sunlight is converted to a provitamin, which is then spontaneously converted within three days to vitamin D3 (cholecalciferol), under the effect of sunshine thermal energy. Cholecalciferol is then converted in the liver to 25-HCC where it is stored. 25-HCC is then converted in the kidney to 1,25-DHCC (1,25(OH)2D3) by the effect of 1-α- hydroxylase enzyme

Chemistry: Vitamin D is a steroid hormone.

Mechanism of action of 1,25(OH)2D3

- Vitamin D3, 25HCC & 1,25-DHCC, all are carried on a plasma globulin: vitamin D binding protein (DBP). DBP possesses the highest affinity for vitamin D3, so its main function is the carriage of vitamin D3 from the skin.
- 1,25(OH)2D3 binds cytoplasmic receptors in target cells. Hormone-receptor complex enters the nucleus & stimulates transcription of mRNA for the formation of a Ca2+ binding protein: Calbindin D, responsible for Ca2+ transport.

- Receptors of 1,25-DHCC are present mainly in the intestine, kidney & bone, but they are present also in the anterior pituitary, skin, breast, skeletal & cardiac muscles, lymphocytes, monocytes.

Physiological functions of 1,25(OH)2D3

A - Action on the intestine

- Stimulates the formation of calbindin D in the intestinal epithelium that transports Ca2+ from the brush border to the basolateral membrane, to the interstitial fluid. The amount of Ca2+ absorbed is proportional to the amount of calbindin D.
- Also, it stimulates the Ca2+ ATPase pump at the basolateral border and the alkaline phosphatase enzyme.

B – Action on the kidney:

- Through calbindin D, it stimulates Ca2+ reabsorption by the renal distal tubules.
- It also stimulates phosphates reabsorption by the proximal tubule.

C –Action on bones:

- Its effect depends on prevailing Ca2+ & PO4-- concentrations:

-In the presence of a high Ca2+ & PO4--, it stimulates osteoblastic activity.
-In the presence of a low Ca2+ & PO4-- and under the effect of 1,25DHCC, PTH stimulates the osteolysis by an osteocytic membrane system. Also, PTH stimulates the osteoblasts to secrete IL-6 & RANKL that in a paracrine manner stimulates the osteoclastic activity.

Regulation of 1,25DHCC secretion

The amount of 1,25(OH)2D3 in plasma is inversely proportional to the Ca2+ concentration in plasma to maintain a constant plasma Ca2+

A drop of Ca2+ stimulates PTH secretion:

- Drop of Ca2+ & excess PTH stimulate 1α-hydroxylase enzyme →convert 25HCC into 1,25-DHCC →stimulates Ca2+ absorption from kidney & intestine.
- 1,25-DHCC→ negative feedback on 1α-hydroxylase enzyme → limit the formation of more 1,25- DHCC.
- 1,25-DHCC stimulates convertase enzyme →inactivation of 1,25-DHCC into 24,25–DHCC.

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Calcitonin: Thyrocalcitonin: CT

Origin:

It is secreted by the parafollicular cells of the thyroid gland

Chemistry:

It is a polypeptide (32AA). It is a hypocalcemic hormone.

Functions of Calcitonin hormone:

It is generally antagonistic to PTH, as regards Ca2+, but with similar effects on PO4-

A – On bones: It decreases mobilization of Ca2+ from bone:

- It decreases the number & activity of osteoclasts.
- It stimulates osteoblasts and its alkaline phosphatase activity → decrease Ca2+ & PO4— release into plasma.

- It inhibits the Ca2+ pump of the osteocytic membrane system.

B – On kidneys:

- It inhibits the 1α hydroxylase activity of the proximal tubules.
- It stimulates the secretion of both Ca2+ & PO4- in urine.

Regulation of Calcitonin secretion:

1. A rise in plasma Ca2+ stimulates CT release.
2. B-adrenergic agonists, estrogen, prolactin & dopamine stimulate CT release.
3. GIT hormones: gastrin and CCK stimulate CT to release to prevent post-prandial hypercalcemia.
4. A decrease in plasma Ca2+ inhibits CT release.

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Tetany

Definition:

Increased neuromuscular excitability, caused by a slight decrease in the plasma level of ionized calcium.

Mechanism of tetany:

Decreased plasma Ca2+ causes a decrease in the threshold of voltage-gated sodium channels. Slight mechanical or electric stimuli, "and even spontaneously" initiate a train of nerve impulses that causes fibrillary twitches, then spasmodic contraction of supplied muscles. In severe cases, spasmodic contractions of the laryngeal and respiratory muscles may result in cyanosis, asphyxia, and death.

Causes of tetany:

1) Hypoparathyroidism: most commonly by accidental removal of the parathyroid during. thyroidectomy; less commonly by autoimmune destruction of the parathyroid.
2) Decreased calcium intake compared to body needs mainly in infants and pregnant women.
3) Decreased calcium absorption: 2ry to vitamin D deficiency, or alkalinity of the intestinal contents or presence of oxalates.
4) Alkalosis: decreases solubility product of Ca2+ and PO4--. Total plasma Ca may be normal but ionized Ca is reduced (e.g. hyperventilation and vomiting).
5) Phosphate retention: in advanced renal disease. This causes a secondary drop of Ca2+ if the bone stores of calcium are low.

Rickets is the softening and weakening of bones in children, usually because of an extreme and prolonged vitamin D deficiency that may be complicated by seizures and tetany.

Types of tetany:

A - Latent (hidden) tetany:

- Plasma calcium level is between 7-9.4 mg/dl.
- Its manifestations do not appear during rest but appear during exercise, stress or ischemia.
- It can be provoked to appear by certain provoking tests.

B - Manifest tetany:

- It occurs when the plasma Ca2+ drops below 7 mg/dl.
- Its manifestations appear during rest, the patient presents with carpopedal spasm or spasm of laryngeal muscles (laryngeal stridor) or spasm of respiratory muscles (cyanosis or asphyxia).

Provoking tests of latent Tetany

1- Chvostek's sign:

Test: Tapping the area of the face over the facial nerve in front of the ear.
Normal: the only feeling of a tap.
Tetany: Hyperexcitable facial nerve: the feeling of a tap with the appearance of involuntary reflex twitching of the ipsilateral facial muscles.

2- Trousseau's sign:

Test: occluding circulation of the arm for a few minutes with a blood pressure cuff above the systolic BP →Ischemia of the muscles of the upper limb
Normal: feeling ischemia pain in the upper limb.
Tetany: Hyperexcitable upper limb nerves: feeling ischemic pain, with the appearance of involuntary carpal spasm (accoucheur's hand) →flexion of the wrist and the metacarpophalangeal joints, with the extension of all inter-phalangeal joints and adduction of the thumb.

3- Erb's sign:

Test: Galvanic stimulation of the upper limb nerves by application of the two poles of an electric current over the medial side of the forearm.
Normally: Reflex contraction of the upper limb muscles at the make.
The muscles of the upper limb are relaxed during current flow.
Reflex contraction of the upper limb muscles at the break..
Tetany: Hyperexcitable upper limb nerves: involuntary reflex carpal spasm during the whole period of current flow.

Treatment of tetany:

1) Immediately: slow intravenous Injection of calcium gluconate.
2) Diet rich in calcium and vitamin D.
3) Vitamin D injections.
4) Treatment of the cause, e.g. renal failure, alkalosis, etc..